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TBM 优秀论文

1. SLC44A4 在乳腺癌中的生物信息学分析

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目的：通过生物信息学方法分析 SLC44A4 在乳腺癌中的表达及预测其潜在生物学功能机制。

方法：利用公共数据库 ualcan、The human protein atlas、GEPIA 等在 TCGA、GEO 中收集 SLC44A4 乳腺癌中的表达数据，分析 SLC44A4 基因的表达水平、免疫组化、生存分析及临床病理特征情况。

结果：与正常乳腺组织相比，乳腺癌组织中 SLC44A4 基因 mRNA 水平呈高表达（P＜0.01）。ER 或 PR 阳性患者的 SLC44A4 表达高于 ER 或 PR 阴性患者（P＜0.01），I、II、III、IV 期乳腺癌患者表达水平均高于正常乳腺组织。SLC44A4 高表达的淋巴结阳性乳腺癌患者总体生存时间较好（HR=0.61,P＜0.01）。免疫组化显示乳腺浸润性导管癌组织中 SLC44A4 蛋白表达水平高于癌旁组织。基因功能分析提示与 SLC44A4 表达相关 20 个基因主要位于细胞膜、胞外间隙、内膜系统中，通过相关蛋白质、转运体活动、水解酶活性等参与代谢、生物调控、定位等过程。

讨论:SLC44A4 在乳腺癌中明显高表达，并且表达与乳腺癌患者不良预后相关，可能成为乳腺癌标志物及治疗干预的靶点。

2. 基于 γ-GT/前白蛋白比值的预测肝癌消融预后的新指标

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目的：评估 γ-GT 和前白蛋白比值（GPR）对于接受 TACE 联合消融治疗的肝癌患者预后的预测价值，以及该比值和其他指标联合是否能提高其预测效能。

方法：回顾性分析 235 例采用联合治疗的原发性肝癌患者，收集人口学资料和临床病理资料。单因素、多因素 COX 回归模型筛选独立危险因素。K-M 曲线计算 RFS 和 OS。ROC 曲线和约登指数来计算最佳 cut-off 值。高纤维蛋白原（Fib）和高 GPR 计 2 分；低 Fib 和低 GPR 计 0 分；否则计 1 分。 低中性粒细胞（N）和高 GPR 计 2 分；高 N 和低 GPR 计 0 分；否则计 1 分。分别计算和比较不同评分患者的预后是否存在差异。

结果：多发肿瘤、AFP、Fib 和 GPR 是复发的独立危险因素。多发肿瘤、低 N 和 GPR 是长期生存的独立危险因素。Fib-GPR 评分为 2 分和 N-GPR 评分为 2 分的患者 RFS 和 OS 均最差。

结论：Fib-GPR 和 N-GPR 可以有效预测接受联合治疗肝癌患者的早期复发和长期预后。能够帮助帮助肝癌患者优化治疗方案，帮助临床医生做出最佳临床决策。

3. 基于细胞-SELEX 技术的肿瘤标志物的发现和循环肿瘤相关物质的检测研究

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细胞-SELEX 技术是以细胞为靶标的快速体外筛选/进化技术，筛选获得的核酸适体可用于疾病的诊断、成像及靶向治疗等，亦可发现新的生物标志物或分子事件。利用该策略，我们发现了一系列潜在肿瘤生物标志物和新的分子事件。在细胞分析中死细胞往往严重干扰结果的判别，为了有效甄别死细胞的干扰，通过细胞-SELEX 筛选技术得到了一个高特异性识别死细胞的核酸适体（Ch4-1），成功用于细胞流式分析及组织切片染色。用细胞-SELEX 技术发现了朊蛋白在前列腺癌细胞 PC-3 和耐药乳腺癌细胞 MCF-7R 中高表达，组织切片染色发现朊蛋白可能是前列腺癌和乳腺癌潜在的肿瘤标志物。基于细胞-SELEX 技术发现了识别碱性磷酸酶异源二聚体蛋白的核酸适体，利用该核酸适体发现碱性磷酸酶异源二聚体在结直肠癌、肝癌、乳腺癌等数种肿瘤细胞系中高表达，并实现了碱性磷酸酶异源二聚体的体内原位检测；利用核酸适配体 BG2 对碱性磷酸酶异源二聚体特异性的识别作用，以及内源性碱性磷酸酶的信号放大策略，建立了循环肿瘤相关物质的高灵敏度、高特异性的检测方法，结果表明在癌症患者(50 例)和健康个体(39 例)中存在显著性差异（$p<0.0001$），通过 ROC 分析，AUC 值为 0.93、灵敏度为 92%、特异性为 82%，说明该方法具有用于临床结直肠癌诊断和疗效预测的潜力。

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4. 基于性别的肝癌患者的预后差异

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目的：尽管男性较女性罹患肝细胞癌的风险更高，但其是否有较差的预后目前仍存在争议。该研究旨在探究在接受导管联合消融治疗的肝癌患者中，基于性别的预后是否存在差异。

方法：回顾性分析 2012 年 1 月 1 日-2016 年 12 月 31 日就诊于首都医科大学附属北京佑安医院的 806 例接受 TACE 联合局部消融治疗的原发性肝癌患者。基于临床资料进行分组，分析预后并绘制森林图；使用 Kaplan-Meier 计算基于性别的 RFS 和 OS；使用 Cox 回归分析筛选影响预后的独立危险因素。

结果：在基线时，女性患者的平均年龄较男性高，而在白细胞、淋巴细胞、BUN、ALP、

GGT、前白蛋白、APTT 等方面男性较女性高（P<0.05）。女性 135 年的 RFS 优于男性（79.0%，54.6%，49.6% vs 68.4%，40.4%，33.4%；P<0.001）；OS 也优于男性，P 值未达到统计学意义（100%，95.0%，85.7% vs 98.6%，88.0%，81.2%，P=0.092）。性别、年龄、肿瘤个数、肿瘤大小以及中性粒细胞、BUN、球蛋白、GGT 以及 AFP 是影响肝癌患者复发的独立危险因素。而年龄，病因、肿瘤大小、AST 是影响肝癌长期生存的独立危险因素。年龄小的女性明显优于年龄大的男性（P<0.05）。

结论：女性较男性有较高的 RFS。虽然基于性别的 OS 尚未达到统计学差异，但年龄较高，Child-PughB 级，高 AST 水平，低白蛋白水平，以及 AFP7-400 的患者，女性较男性有较好的 OS。若结合年龄，基于性别的预后差异更加明显。性别差异可以支持更进一步的研究以验证基于性别的分层对于肝癌预后管理的重要性。

5. Association between serum pepsinogen and atherosclerotic cardiovascular disease

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Background Serum pepsinogens (PGs) are biomarkers for gastric mucosal damage and have been reported to be associated with atherosclerosis. Its correlation with atherosclerotic cardiovascular disease (ASCVD) is still unknown.Objective This study was to explore the association between serum PGs and ASCVD for providing physicians with an integrative picture to make rational plans in the diagnosis and treatment of ASCVD.

Methods Serum PGs concentration and their distributions between ASCVD and non-ASCVD were compared by non-parametric test and Chi-squared test or Fisher exact test. The correlation between variables was analyzed by Spearman's correlation test. The association of serum PGs with ASCVD was analyzed by the binary logistic regression and two-piecewise linear regression.

Results A total of 8,355 recruited cases were eligible for the study. The concentrations of serum PGs were significantly different between the ASCVD and non-ASCVD groups (P=0.025, P <0.001). The lower PGI and PGR levels were significantly correlated with a high risk of ASCVD presence after adjustment for 26 potential covariates. Moreover, there was a linear relationship between the higher PGII and the high risk of ASCVD [adjusted OR=1.16(1.00,1.37), P=0.07]. A nonlinear relationship of PGI/PGR and ASCVD (P=0.08/<0.001)was also revealed. The risk of ASCVD presence increased with a log PGI ≥2.13(PGI≥131 ng/ml)[adjusted OR=4.67(1.00, 23.17)], and decreased with a log PGR ≥0.22 (1.65) [adjusted OR=0.59(0.48, 0.74), P<0.001].

Conclusions Serum PGI and PGR are nonlinearly correlated with ASCVD, while PGII is linearly correlated with ASCVD. PGR may serve as the most reliable biomarker for ASCVD.

6. Identification of Clonal Neoantigens Derived From Driver Mutations in an EGFR-Mutated Lung Cancer Patient Benefitting From Anti-PD-1

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been recommended as the first-line therapy for non-small cell lung cancer (NSCLC) patients harboring EGFR mutations. However, acquired resistance to EGFR-TKIs is inevitable. Although immune checkpoint blockades (ICBs) targeting the programmed cell death 1 (PD-1)/PD-ligand (L)1 axis have achieved clinical success for many cancer types, the clinical efficacy of anti-PD-1/PD-L1 blockades in EGFR mutated NSCLC patients has been demonstrated to be lower than those without EGFR mutations. Here, we reported an advanced NSCLC patient with EGFR driver mutations benefitting from anti-PD-1 blockade therapy after acquiring resistance to EGFR-TKI. We characterized the mutational landscape of the patient with next-generation sequencing (NGS) and successfully identified specific T-cell responses to clonal neoantigens encoded by EGFR exon 19 deletion, TP53 A116T and DENND6B R398Q mutations. Our findings support the potential application of immune checkpoint blockades in NSCLC patients with acquired resistance to EGFR-TKIs in the context of specific clonal neoantigens with high immunogenicity. Personalized immunomodulatory therapy targeting these neoantigens should be explored for better clinical outcomes in EGFR mutated NSCLC patients.

7. 联合检测 FOXP3 mRNA 和 SCCA 对宫颈癌诊断价值的研究

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摘要：目的 分析宫颈癌患者外周血中 Foxp3 mRNA、SCCA、CA50、CA125 变化,探讨其相关性及 Foxp3 mRNA 联合 SCCA 诊断宫颈癌的价值。**方法** 检测 92 例宫颈癌患者、同期 87 例体检健康女性 Foxp3 mRNA、SCCA、 CA50 和 CA125 水平;分析 Foxp3 mRNA 水平与宫颈癌临床特征的关系;Pearson 法分析 Foxp3 mRNA 与 SCCA、CA19-9 和 CA125 的相关性;绘制 ROC 曲线,分析 Foxp3 mRNA 联合 SCCA 诊断宫颈癌的价值。**结果** 宫颈癌组 Foxp3 mRNA 相对表达

水平（13.71±5.27）、SCCA[(13.07±1.82)ng/ml]、CA50[(49.2±13.29)IU/ml]和CA125[(51.72±15.26)u/mL]水平均高于对照组(2.09±1.51)、(2.85±0.08）ng/ml、(15.61±6.94)IU/ml、(11.57±7.64)u/mL，(P＜0.05)；Foxp3 mRNA 相对表达水平在I～IV 期升高（12.37±1.77）、（13.25±2.19）、（13.98±3.02）、（15.25±2.32），(P＜0.05)；在高、中、低分化患者升高（12.98±2.60）、（14.02±1.75）、（16.87±2.94），(P＜0.05)；在鳞癌患者、腺癌患者、腺鳞癌患者中的相对表达水平比较差异无统计学意义；宫颈癌患者 Foxp3mRNA 的相对表达水平与 SCCA 呈正相关性（r=0.577,P=0.019）,与 CA50、CA125 无线性相关。ROC 曲线分析结果显示,Foxp3 mRNA 以 12.325 为最佳截断值,诊断宫颈癌的 AUC 为 0.839（95%CI：0.707～0.907，P＜0.05），灵敏度为 84.7%，特异度为 74.5%；血清 SCCA 以 11.72ng/mL 为最佳截断值,诊断宫颈癌的 AUC 为 0.745，灵敏度为 84.1%，特异度为 78.5%；Foxp3 mRNA 联合 SCCA 诊断宫颈癌的 AUC 为 0.911，灵敏度为 93.1%，特异度为 84.7%。**结论** 宫颈癌患者 Foxp3 mRNA、SCCA、CA50 和 CA125 水平增高，Foxp3 mRNA 的表达水平与肿瘤临床分期、分化程度有关，与 SCCA 表达呈正相关，Foxp3 mRNA 与 SCCA 联合检测对宫颈癌有较高的诊断价值。

8. 6 种化学发光系统检测肿瘤标志物的应用评估分析

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摘要：目的 探讨 6 种化学发光系统检测甲胎蛋白(AFP)、癌胚抗原(CEA)、总前列腺特异抗原(tPSA)、游离前列腺特异性抗原(fPSA)、糖类抗原 CAl99(CAl99)、糖类抗原 CAl53(CAl53)和糖类抗原 CAl25(CAl25)仪器参数、西格玛值 δ)、可比性及临床可接受程度。**方法** 收集 6 种系统的检测速度，试剂仓位，开展项目数等硬件参数，使用单位半年质控数据，计算各系统检测项目的精密度及 δ 值。以 Roche E602 电化学发光系统为参考系统，根据 EP9-A2 文件的要求，对检测结果进行方法比对和偏倚评估。**结果** ①比较 6 种检测系统的检测速度，试剂仓位，软件功能等参数，6 种检测系统基本满足临床需求。②RocheE602 与 A 厂家比较，多数检测项目盯值多数高于 6δ 水平；B，D 和 E 三家厂家检测项目盯值基本处于优秀水平(5-6δ)；C 厂家多个项目小于 4δ 水平，存在较大差距。(除 B 厂家外，其它厂家与 RocheE602 多数项目偏移超过 1／2TEa，临床不可接受。**结论** 实验室同时存在多种不同品牌化学发光检测系统检测同一检验项目时，应进行方法比对和偏倚评估，判断其临床可接受性能，以保证检验结果的可比性。

9. In-depth mapping carboxylic acid metabolome reveals the potential biomarkers in colorectal cancer using polarity-tuning derivatization-LC-MS approach

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Carboxylic acids widely exist in living systems and are the essential components for life. Global characteristics of carboxylic acids in biological samples are critical for the understanding of physiological processes and the discovery for the onset of relevant diseases. However, their determination represents a challenge due to enormous polarity differences, structural diversity, high structural similarity, and poor ionization efficiency. Herein, 5-(diisopropylamino)-amylamine (DIAAA) derivatization coupled with liquid chromatography−mass spectrometry (LC-MS) was developed for mapping carboxylic acids. With this methodology, the sensitivity was significantly enhanced. More importantly, the hydrophobicity of polar carboxylic acids and the hydrophilicity of low-polar carboxylic acids were significantly increased, resulting in a remarkable separation efficiency. In addition, after derivatization, the characteristic MS/MS fragments ions of m/z 86.09, 128.14, and 187.21 could be performed for carboxylic acid metabolomics analysis in CRC serum samples. Finally, 1054 carboxylic acids were quickly and selectively identified after extraction using the characteristic fragment ions. Among them, 605 carboxylic acids exhibit discriminating levels between healthy and CRC patients in training cohort. Furthermore, the differential metabolites were found to be mainly enriched in amino acid metabolism, fatty acid biosynthesis and TCA cycle by MetaboAnalyst and iPath analysis. Serine, glycine, and methionine were determined as the potential biomarkers after further confirmation using validation cohort and in vitro metabolic flux analysis. The above results collectively demonstrated that a new set of carboxylic acids can be quickly and selectively discovered using characteristic fragment ions.

10. Identification of key genes controlling breast cancer stem cell characteristics via stemness indices analysis

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Abstract

Background: With the gradual unveiling of tumour heterogeneity, cancer stem cells (CSCs) are now being considered the initial component of tumour initiation. However, the mechanisms of the growth and maintenance of breast cancer (BRCA) stem cells are still unknown.

Methods: To explore the crucial genes modulating BRCA stemness characteristics, we combined the gene expression value and mRNA expression-based stemness index (mRNAsi) of samples from The

Cancer Genome Atlas (TCGA),and the mRNAsi was corrected using the tumour purity (corrected mRNAsi). mRNAsi and corrected mRNAsi were analysed and showed a close relationship with BRCA clinical characteristics, including tumour depth, pathological staging and survival status. Next, weighted gene co-expression network analysis (WGCNA) was applied to distinguish crucial gene modules and key genes. A series of functional analyses and expression validation of key genes were conducted using multiple databases, including Oncomine, Gene Expression Omnibus (GEO) and Gene Expression Profiling Integrative Analysis (GEPIA).

Results: This study found that mRNAsi and corrected mRNAsi scores were higher in BRCA tissues than that in normal tissues, and both of them increased with tumour stage. Higher corrected mRNAsi scores showed worse overall survival outcomes. We screened 3 modules and 32 key genes, and those key genes were found to be strongly correlated with each other. Functional analysis revealed that the key genes were related to cell fate decision events such as the cell cycle, cellular senescence, chromosome segregation and mitotic nuclear division. Among 32 key genes, we identified 12 genes that strongly correlated with BRCA survival.

Conclusions: Thirty-two genes were found to be closely related to BRCA stem cell characteristics; among them,12 genes showed prognosis-oriented effects in BRCA patients. The most significant signalling pathway related to stemness in BRCA was the cell cycle pathway, which may support new ideas for screening therapeutic targets to inhibit BRCA stem characteristics. These findings may highlight some therapeutic targets for inhibiting BRCA stem cells.

11. Regulation of Integrin subunit alpha 2 by miR-135b-5p Modulates Chemoresistance in Gastric Cancer

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Chemotherapy has substantially improved gastric cancer (GC) patient outcomes in the past decades. However, the development of chemotherapy resistance has become the major cause of treatment failure. Although numerous molecules have been implicated in GC chemoresistance, its pathological mechanisms are still unclear. Here, we found that integrin subunit alpha 2 (ITGA2) is upregulated in chemoresistant GC cells and that increased ITGA2 levels correlated with the poor prognosis of GC patients who received chemotherapy. ITGA2 overexpression led to elevated chemotherapy resistance and drug-induced apoptosis inhibition in GC cells. ITGA2 knockdown resulted in restored chemosensitivity and increased apoptosis in chemoresistant GC cells both in vitro and in vivo. NanoString analysis revealed a unique signature of deregulated pathway expression in GC cells after ITGA2 silencing. The MAPK/ERK pathway and epithelial-mesenchymal transition (EMT) were

found to be downregulated after ITGA2 knockdown. miR-135b-5p was identified as a direct upstream regulator of ITGA2. miR-135b-5p overexpression reduced chemoresistance and induced apoptosis in GC cells and attenuated ITGA2-induced chemoresistance and antiapoptotic effects by inhibiting MAPK signaling and EMT. In conclusion, this study underscored the role and mechanism of ITGA2 in GC and suggested the novel miR-135b-5p/ITGA2 axis as an epigenetic cause of chemoresistance with diagnostic and therapeutic implications.

12. Identification of SOCS family members with prognostic values in human ovarian cancer

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Background: Suppressor of cytokine signaling (SOCS) family proteins regulate cytokine responses through inhibition of multiple signaling pathways. The expression profiles and prognostic significance of SOCS members in ovarian cancer (OC) patients still remains unclear. Here, we aimed to provide a comprehensive understanding of the prognostic values of SOCS family members in OC and to discover promising therapeutic targets for OC.

Methods: We firstly analyzed the KEGG pathway enrichment to reveal the possible pathways associated with SOCS family. Next, we used public databases including cBioPortal, Human Protein Atlas and Oncomine to investigate genetic alterations and mRNA expression of SOCS family in OC patients. More importantly, we explored the prognostic value of each individual SOCS members in OC patients using Kaplan Meier plotter database.

Results: SOCS family was markedly enriched in JAK-STAT signaling pathway. A high mutation rate in SOCSs was observed in patients with ovarian serous cancer (OSC). An increased mRNA expression of SOCS1 indicated a favorable overall survival (OS) in both OC and OSC patients, while increased SOCS5 and SOCS7 expressions were significantly associated with poorer OS. We also explored the diverse roles of SOCS members in OC patients with different clinicopathological features including grades, stages and therapies employed.

Conclusion: SOCS1, SOCS5 and SOCS7 may serve as prognostic biomarkers for OC patients. SOCS5 and SOCS7 may be potential therapeutic targets for OC treatment. Our results render novel insights into the association between SOCS family genes and OC development, and may highlight promising molecular targets for therapeutic interventions in OC patients.

13. Targeting TIGIT in MDS

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Objective: Targeting immune checkpoints, such as PD-1, represents a promising approach for cancer immunotherapy, achieving long-term disease remission rates in numerous types of cancer. T cell immunoglobulin and ITIM domain (TIGIT) is a checkpoint receptor associated with the antitumor roles of NK and T cells. Notably, the blockade of TIGIT has been revealed as a potential promising approach in cancer immunotherapy. However, the therapeutic potential of blocking TIGIT in myelodysplastic syndrome (MDS) remains unclear and further research is required to reveal their role.

Methods: Fresh peripheral blood (PB) and bone marrow (BM) were obtained from patients with MDS and healthy donors (HDs) at the Tianjin Medical University General Hospital between January 21 2018 and March 22 2019. The present study investigated the expression levels of TIGIT on NK and T cells using flow cytometry (FCM) and PCR. In addition, other checkpoint receptors, such as CD226 and PD-1, were also investigated.To determine the mechanisms of antitumor immunity, the functions of NK and T cells expressing TIGIT were determined.

Results: TIGIT was found to be highly expressed on NK and T cells of the PB, where it was involved in disease progression and the immune escape of MDS. The high expression levels of TIGIT were associated with decreased NK and T cell function, and significantly lower secretions of activation factors, such as CD107a, IFN-g and TNF-a.Notably, blocking TIGIT enhanced the antitumor effects of NK and T cells.

Conclusion: The results of the present study suggested that targeting TIGIT alone or in combination with PD-1 may be a promising anticancer therapeutic strategy in MDS.

14. m6A Regulator-based Methylation Modification Patterns Characterized by Distinct Tumor Microenvironment Immune Profiles in Colon Cancer

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Background: Recent studies have highlighted the biological importance of RNA N6-methyladenosine (m6A) modification in tumorigenicity. However, the potential roles of m6A modification in tumor immune infiltration remain unclear.

Method: In this investigation, we performed consensus molecular subtyping with nonnegative matrix factorization (NMF) based on 23 m6A regulators to determine the m6A modification patterns and m6A-related gene signature. Marker gene-based approaches(ssGSEA) and deconvolution

methods(CIBERSORT) were employed to quantify the infiltration level of various immune cell subsets. An m6A scoring scheme with principal component analysis was developed to evaluate the m6A modification patterns of individual tumors with an immune response.

Results: Three distinct m6A modification patterns represented by different survival outcomes and tumor microenvironment characteristics were identified in 1307 colon cancer samples. The immune profile characterization revealed that these three m6A patterns were highly consistent with the three known immune phenotypes: immune-inflamed, immune-excluded, and immune-desert. The m6A score extracted from the principal components of m6A-related signature genes divided CC patients into high- and low-score subgroups; a low score was significantly associated with prolonged survival and enhanced immune infiltration. Further analysis indicated that patients with low m6A scores harbored stronger tumor mutation loads and higher mutation rates in SMGs (e.g., PIK3CA and SMAD4). In addition, patients with low m6A scores demonstrated marked immune responses and durable clinical benefits in two independent immunotherapy cohorts.

Conclusions: This study highlights that m6A modification is significantly associated with TME diversity and complexity. Quantitatively evaluating the m6A modification pattern of individual tumors will strengthen our understanding of TME characterization and promote more effective immunotherapy strategies.

15. 肺癌组织中本底和去糖基化 PD-L1 检测的比较研究

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目的：PD-1/PD-L1 免疫检查点抑制剂（ICIs）是目前临床上研究和应用最广泛的免疫检查点抑制剂之一，可以阻断 PD-1 与 PD-L1 的结合，使 T 细胞恢复肿瘤杀伤活性，在包括肺癌在内的多种肿瘤治疗过程中显示出卓越的疗效。FDA 在批准 PD-1/PD-L1 ICIs 的同时，也分别批准了相应的伴随/补充诊断抗体，用于 PD-L1 表达水平的免疫组化检测。然而临床实践表明，相当一部分 PD-L1 表达阴性的患者仍可从 PD-1/PD-L1 ICIs 治疗中获益。近期研究表明通过对组织切片进行去糖基化处理，可以显著提高 PD-L1 的检出率，去糖基化 PD-L1 的检测可能是 ICIs 更好的用药标志物。本研究探讨不同去糖基化方法对 PD-L1 检出率的影响及不同克隆编号的 PD-L1 抗体对去糖基化检测的反应程度。

方法：在常规免疫组化过程中，分别添加有、无热变性的去糖基化步骤对 PD-L1 进行检测；使用 4 个不同克隆号的 PD-L1 抗体（28-8，CAL10，73-10，SP142）对本底和去糖基化 PD-L1 进行检测；使用 HALO 数字病理系统评价 PD-L1 的肿瘤细胞阳性百分率（TPS）和免疫组化 H 得分（H-score）。

结果：相对于无热变性的去糖基化检测方法，对组织切片进行热变性介导的去糖基化处理可以

显著提高 PD-L1（28-8）的检出率；不添加去糖基化步骤时，4 个 PD-L1 抗体对本底 PD-L1 呈现相似的检出率；热变性介导的去糖基化检测可以显著提高应用 28-8、CAL10 和 SP142 抗体的 PD-L1 检出率，然而当使用 73-10 抗体时，去糖基化处理则轻度抑制 PD-L1 的检测效率；此外，相较于本底 PD-L1 信号强的样本，本底信号低的样本在去糖基化处理后其 PD-L1 信号强度增强更明显。

结论：本研究对去糖基化方法和不同 PD-L1 抗体对糖基化的反应程度进行了全面探讨。热变性介导的去糖基化可以提高应用 28-8、CAL10 和 SP142 抗体的 PD-L1 检出率，或可成为确定 PD-1/PD-L1 ICIs 治疗获益患者的重要方法。

16. FZR1 可作为乳腺癌新辅助化疗疗效的预测标志物

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新辅助化疗在乳腺癌治疗中的地位已被广泛肯定，它不仅可以降低肿瘤分期，提高手术切除率和增加保乳机会，而且对于新辅助化疗后达到病理完全缓解的患者，可获得更高的生存期。在临床应用中，若手术前可对新辅助化疗疗效作出准确的评价，不仅有助于治疗方案的调整，对患者获得病理完全缓解的可能性也会大大提高。目前，预测新辅助化疗效果的生物标志物非常缺乏。在本研究中，我们通过临床患者队列评估和分子机制研究，确定 FZR1 可作为乳腺癌新辅助化疗疗效的新型标志物。转录组数据分析表明 FZR1 在化疗药物诱导细胞凋亡和细胞周期阻滞中起关键作用，FZR1 通过破坏 ser15 位点的磷酸化而参与 p53 的稳定性，此外，FZR1 结合 KIF11 调控 p53 的稳定性。研究证明通过免疫组化（IHC）定量检测 FZR1 的表达可以作为新辅助化疗疗效的有效预测因子，我们建议在临床上用 FZR1 IHC 评分来预测新辅助化疗的疗效，使患者得到更多的获益。

17. Molecular characterization of advanced colorectal cancer using serum proteomics and metabolomics

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Colorectal cancer (CRC) is a growing public health concern with high mortality rate. However, there are no valid diagnostic biomarkers and few therapeutic strategies available for CRC, especially advanced CRC, since the pathogenic mechanisms remain poorly understood. In the present study,

taking advantage of nanoscale liquid chromatography and quadrupole time-of-flight tandem mass spectrometry (nanoLC/Q-TOF-MS/MS) and ultraperformance LC/Q-TOF-MS/MS technologies, we applied integrated proteomic and metabolomic analyses on serum samples from 20 patients with CRC at stage III or IV to comprehensively reveal molecular characterization of advanced CRC. Overall, 551 proteins and 719 metabolites were identified in those serum samples, respectively. Hierarchical clustering analysis indicated much more remarkable diversity in proteomic profiles than metabolomic profiles. Further functional analysis suggested that ten key pathways associated with cancer cell metabolism were dissected including glycolysis/gluconeogenesis, biosynthesis of amino acids, glutathione metabolism, and arachidonic acid metabolism, based on which protein-protein interaction network analysis was thus constructed with 80 proteins and 21 metabolites. Moreover, the regulatory network in advanced CRC was established according to correlation analysis, indicating conserved roles of metabolome and lipids & lipid like molecules in human serum. Nevertheless, three metabolites and two proteins including hydroquinone, leucenol and sphingomyelin were supposed to be potential biomarkers, which were determined to be positively and significantly correlated with CEA and/or CA 19-9. Altogether, our work not only extended our understanding on the physiopathology of advanced CRC, but provided potential biomarkers to improve the accuracy of the diagnosis and monitoring of the syndrome.

18. MMP14: a candidate prognostic biomarker for Diffuse Large B-cell Lymphoma

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Background: Matrix metallopeptidase 14 (MMP14) is an important gene in the regulation of T cell function. However, the correlation between MMP14 expression, and prognosis, and immune cell infiltration in Diffuse Large B-cell Lymphoma (DLBCL) remains unclear.

Methods: We investigated the influence of MMP14 on clinical prognosis using data obtained from three Gene Expression Omnibus (GEO) database sets (GSE98588, GSE10846, and GSE4475). The expression of MMP14 was analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA). The correlation between MMP14 and immune cell infiltration was investigated using the Cell-type Identification By Estimating Relative Subsets Of RNA Transcripts (CIBERSORT) and Tumor Immune Estimation Resource (TIMER) tools. In addition, the correlation between MMP14 expression and immune gene markers was analyzed by TIMER and GEPIA.

Results: MMP14 expression positively correlated with favorable progression-free survival (PFS) (GSE98588, P = 0.02) and overall survival (OS) (GSE98588, P = 0.003; GSE10846, P = 5.517e-05; GSE4475, P = 9.85e-04). Moreover, MMP14 expression was higher in DLBCL tumors

than normal tissues. Regarding clinical characteristics, we found that high MMP14 expression was correlated with race. MMP14 expression was also correlated with immune cell infiltration and had a remarkable correlation with various immune marker sets. We found that M0 macrophages were the immune cells most related to survival, decreasing with the increase of Ann Arbor clinical stage. Especially, we showed that MMP14 was a prognostic biomarker and related to the macrophages M0.

Conclusion: Our results suggest that MMP14 is a novel prognostic molecular marker for DLBCL, and is related to the immune cell infiltration, especially related to the macrophages M0. Our study provides insights for understanding the potential roles of MMP14 in tumor immunology and its suitability as a prognosis biomarker in DLBCL.

19. 对非吸烟女性肺腺癌患者中关键基因的综合生物信息学分析

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背景:近年来，非吸烟女性肺腺癌的发病率和死亡率急剧上升。尽管已经有许多相关研究，并且取得了一些进展，但其分子机制仍不清楚。在这项研究中，我们旨在评估非吸烟女性肺腺癌患者的关键基因。

材料和方法:首先，基于 GSE10072、GSE31547 和 GSE32863 三个独立的基因芯片数据集，我们通过 GEO2R 分析获得差异表达基因，用 DAVID 数据库进行差异表达基因的功能富集分析。此外，我们通过 STRING、Cytoscape 和 Kaplan Meier 鉴定了具有预后价值的关键基因。随后，这些基因通过 GEPIA、Oncomine 和人类蛋白质图谱进行进一步分析。

结果:我们发现了 315 个差异表达基因，它们富集在细胞外基质组织、细胞粘附、整合素结合、血管生成和缺氧反应中。在这些差异表达基因中，我们鉴定了 10 个具有重要预后价值的关键基因(SPP1、ENG、ATF3、TOP2A、COL1A1、PAICS、CAV1、CAT、TGFBR2 和 ANGPT1)。

结论:这 10 个关键基因可能是非吸烟女性肺腺癌的生物标志物，这一发现仍需要进一步评估。

20. Ribosomal S6 protein kinase 4 promotes radioresistance in esophageal squamous cell carcinoma

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Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive cancers and is highly resistant to current treatments. ESCC harbors a subpopulation of cells exhibiting cancer stem-like cell

(CSC) properties that contribute to therapeutic resistance including radioresistance, but the molecular mechanisms in ESCC CSCs are currently unknown. Here, we report that ribosomal S6 protein kinase 4 (RSK4) plays a pivotal role in promoting CSC properties and radioresistance in ESCC. RSK4 was highly expressed in ESCC CSCs and associated with radioresistance and poor survival in patients with ESCC. RSK4 was found to be a direct downstream transcriptional target of ΔNp63α, the main p63 isoform, which is frequently amplified in ESCC. RSK4 activated the β-catenin signaling pathway through direct phosphorylation of GSK-3β at Ser9. Pharmacologic inhibition of RSK4 effectively reduced CSC properties and improved radiosensitivity in both nude mouse and patient-derived xenograft models. Collectively, our results strongly suggest that the ΔNp63α/RSK4/GSK-3β axis plays a key role in driving CSC properties and radioresistance in ESCC, indicating that RSK4 is a promising therapeutic target for ESCC treatment.

21. 乳腺巨球蛋白 B（Mammaglobin B）可能是子宫内膜癌潜在的预后标志物

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乳腺巨球蛋白 B（Mammaglobin B），又称分泌型珠蛋白 2A 家族成员 1(SCGB2A1)，其在子宫内膜癌(UCEC)中的表达高于在正常子宫内膜中的表达。然而，SCGB2A1 在 UCEC 中的预后价值尚不清楚。我们利用 Oncomine、TCGA 和临床蛋白质肿瘤分析联盟数据库研究 SCGB2A1 的差异表达。从 TCGA 下载 UCEC 患者资料，进行 Logistic 回归分析、生存分析、单因素和多因素分析，以确定其对 UCEC 的预后价值。此外，我们还利用基因集富集分析(GSEA)对 SCGB2A1 在 UCEC 中的作用机制进行了初步探讨。SCGB2A1mRNA 和蛋白表达水平降低与预后不良的临床病理特征显著相关(均 $P<0.05$)。同时，与 SCGB2A1 高表达相比，SCGB2A1 低表达水平与 UCEC 患者的存活率降低有关。接着，我们通过单因素和多因素分析确定 SCGB2A1 在 UCEC 中的独立预后价值。此外，GSEA 结果显示，血管内皮生长因子、PTEN、血小板衍生生长因子、DNA 修复、KRAS 信号通路和 PI3K-AKT-mTOR 信号通路在 SCGB2A1 低表达表型中存在差异富集。以上结果提示 SCGB2A1 可能是 UCEC 中一个潜在独立预后因子，同时这些信号通路可能对通过 SCGB2A1 调控 UCEC 起关键作用。

22. MET mutations predict survival in multiple cancer patients with immunotherapy

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Purpose: MET is a well-known protooncogene, and MET signaling dysregulation has been reported in various human cancers. As a whole, targeted therapies for MET mutations have been less successful than other genes like EGFR and ALK. Recently, numerous studies have focused on MET exon 14 (METex14) alterations, defining a distinct subset that is sensitive to MET-tyrosine kinase inhibitors (TKIs) such as crizotinib. However, resistance to MET-TKIs is inevitable, and several MET kinase domain mutations have been found to be associated with resistance to METex14-targeted therapy. Moreover, therapeutic strategies for cancers with MET non-ex14 mutations, such as MET kinase domain or semaphorin domain mutations, are still largely unknown. Therefore, finding novel strategies to improve the prognosis of MET-mutant cancer is necessary and urgently needed. Recently, immunotherapy has revolutionized the treatment of various cancers, however, whether patients with MET mutations can benefit from immunotherapy is still undetermined.

Methods: Using tumor mutational burden (TMB) and immunotherapy database, we evaluated the relationship between MET mutations and the responses of cancer patients who received immune checkpoint inhibitors (ICIs) treatment. Genomic and survival data from 1661 tumor-normal pairs from 1661 patients with various cancer types that were sequenced with the MSK-IMPACT assay were included in this database.

Results: MET mutations were identified in 60 (60/1661, 4%) of the patients with various cancer types. And we identified 11 METex14 mutations were identified in the entire cohort in nine patients with NSCLC, one patient with melanoma and one patient with glioma. we found that the TMB was significantly higher in patients harboring MET mutations than in the counterpart patients with wild-type MET ($p < 0.001$). Corresponding to the TMB results, we found taht patients who harbored MET mutations had significantly better overall survival in the entire group ($p = 0.006$). Furthermore, we performed a NSCLC subgroup analysis in this database. The results indicated that 14 (14/350, 4%) patients in the NSCLC subgroup harbored MET mutations, most of which were METex14 mutations (9/14, 64%). The NSCLC patients with MET mutations had comparable TMB contrast to their wild-type counterparts ($p = 0.556$). Interestingly, although MET mutations were not correlated with a higher TMB in NSCLC patients, they were still associated with a significantly longer overall survival time ($p = 0.023$).

Conclusion: The present study demonstrated that MET mutations were associated with higher TMB and could act as a favorable prognostic biomarker in various human cancers received ICIs treatment.

To the best of our knowledge, this is the first study to evaluate the efficacy of ICIs in different cancer patients with various MET mutations. Considering that METex14-mutant patients were sensitive to MET-TKIs, we suggested that ICIs could be considered an option for patients who harbor MET mutations and acquire resistance to MET-TKIs in our clinical practice. Of note, only 14 patients harbored MET mutations in our NSCLC subgroup, and the relationship between MET mutations and the efficacy of ICIs in NSCLC deserves further investigation.

23. Circulating tumor cells signatures for thyroid cancer diagnosis: A prospective, blinded, multicenter study

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Background: Fine needle aspiration (FNA) for ultrasound-selected thyroid nodules is the current standard management for screening individuals with thyroid cancer. However, it is still an invasive examination and may be undetermined in 15%-20% of cases. The study aimed to develop a reliable diagnostic model based on circulating tumor cells (CTCs) in patients with suspicious thyroid nodules.

Methods: This prospective, blinded cohort study was carried out in two parts. First, we examined potential CTCs markers in the test group and established an effective combination. Then, validation was performed in a multicenter cohort. Totally, 532 subjects were clinically evaluated, 274 of which have drawn peripheral blood samples for CTCs test.

Results: In the test group (20 healthy subjects and 50 patients with papillary thyroid cancer (PTC)), a combination of CK19, Survivin and Tg signatures was established as a diagnostic model, which correctly classified 85.7% of patients with a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 80.0%, 100.0%, 100.0%, 66.7%, respectively. In the validation group (150 patients with suspicious thyroid nodules), the established model demonstrated a diagnostic accuracy of 82.0%, with a sensitivity of 82.3% and a specificity of 81.1% (PPV=93.0%; NPV=60.0%). Detailed analysis showed that Survivin positivity was found in 41 patients, all of whom were PTC. Of the 163 patients with PTC, gross extrathyroidal extension (gETE) was associated with decreased Tg mRNA expression.

Conclusions: Combined CTCs signatures could accurately classify 80% of patients and would be a promising biomarker for diagnosis of thyroid cancer

24. 肺小细胞癌相关的肿瘤分子标志物的研究进展

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肺癌是临床中最常见的肿瘤之一，其中以肺小细胞癌（Smal cell lung cancer，SCLC）的恶性程度最高，治疗最为棘手，预后情况差，这就对 SCLC 的早期诊断和治疗提出了很大的挑战。传统的病理学诊断方法和化疗已经无法满足实际临床需要，所以从分子水平上来研究 SCLC 的发病机制，寻找更多的 SCLC 标志物就显得尤其重要。近年来对于肿瘤分子标志物的研究不仅让我们对一些在临床上广泛应用的标志物有了新的认识，还发掘出很多极具应用潜力的标志物用于未来 SCLC 的诊断和治疗效果的评价，同时也发现了不少针对于 SCLC 分子治疗的特异性靶点。肿瘤分子标志物的相关研究将会大大的提高 SCLC 诊断和治疗效率，减少患者的痛苦，有效提高患者生存几率。

25. SEC61G overexpression and amplification correlates with prognosis and immune cell infiltration in head and neck squamous cell carcinoma

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Purposes: The SEC61 translocon gamma subunit (SEC61G) is a component of the SEC61 complex, which mediates protein degradation. However, the correlation between SEC61G and disease prognosis in head and neck squamous cell carcinoma (HNSCC) remains unclear.

Methods: SEC61G expression was analyzed using publicly-available datasets. The association between SEC61G and disease prognosis was evaluated. SEC61G methylation and copy number variation were investigated and gene set enrichment analysis (GSEA) and gene ontology (GO) analyses identified SEC61G-associated functions. We also investigated the correlation between SEC61G and immune cell infiltration. Finally, immunohistochemistry (IHC) was used to detect SEC61G expression in oropharyngeal carcinoma.

Results: SEC61G was overexpressed in pan-cancers, including HNSCC, and negatively correlated with overall survival ($p<0.001$ for TCGA-HNSCC and $p=0.019$ for GSE65858). Moreover, SEC61G was an independent prognostic factor for overall survival (OS) in TCGA and GSE65858 [hazard ratio (HR)=1.80, 95% CI: 1.35-2.39, $p<0.001$; HR = 1.87, 95% CI: 1.14-3.07, $p=0.013$, respectively) SEC61G amplification (9.66% of patients) was significantly associated with poor OS ($p=0.034$). SEC61G overexpression and amplification negatively correlated with B cell, $CD8^+$ T cell, $CD4^+$ T cell,

macrophage, neutrophil, and dendritic cell infiltration (all p<0.05). Among metastatic urothelial cancer patients received atezolizumab, high SEC61G expression had an inferior OS (p=0.006). Furthermore, SEC61G protein expression was also an independent prognostic factor of OS (HR=2.49, 95% CI: 1.15-5.30, p=0.020) and progression-free survival (HR=2.82, 95% CI: 1.36-5.84, p=0.005) for oropharyngeal cancer.

Conclusions: SEC61G is overexpressed in HNSCC and is an independent prognostic factor for OS. SEC61G amplification contributes to overexpression and poor outcome. Interestingly, SEC61G correlates with immune cell infiltration in HNSCC, and can predict response to immune checkpoint inhibitors. These findings suggest that SEC61G is a potential broad-spectrum biomarker for prognosis in HNSCC and predicting response to immune checkpoint inhibitors.

26. High Expression of Hyaluronan-Mediated Motility Receptor Predicts Adverse Outcomes: A Potential Therapeutic Target for Head and Neck Squamous Cell Carcinoma

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Background: Several studies have shown that the hyaluronan-mediated motility receptor (HMMR)is overexpressed in various cancers and could be a potential prognostic factor. However, further research is still required to determine the prognostic value and potential function of HMMR in head and neck squamous cell carcinoma (HNSCC). Therefore, we investigated the prognostic value and potential function of the HMMR gene in HNSCC.

Materials and Methods: Transcriptomic expression data were collected from the Cancer Genome Atlas database (TCGA) and Gene Expression Omnibus and the differences in HMMR expression between normal and tumor tissues were analyzed. The prognostic value of HMMR in HNSCC was investigated using the Kaplan–Meier survival and Cox analyses. The correlation between the methylation level of HMMR and its mRNA expression was analyzed via cBioPortal. Additionally, the data obtained from TCGA was analyzed with MethSurv to determine the prognostic value of the HMMR methylation levels in HNSCC. Gene set enrichment analysis (GSEA) and single sample GSEA (ssGSEA) were used to explore the potential biological functions of HMMR.

Results: HMMR was highly expressed in HNSCC tumor tissue compared to normal tissue (p < 0.001). Multivariate analysis showed that high HMMR expression was an independent prognostic factor in TCGA (HR = 1.628 95% CI: 1.169–2.266, p = 0.004) and GSE41613 data (HR = 2.238, 95% CI:

1.187–4.221, p = 0.013). The methylation level of HMMR negatively correlated with the HMMR expression (R = −0.12, p < 0.001), and patients with low HMMR methylation had worse overall survival than patients with high methylation (p < 0.001). GSEA found that HMMR expression was associated with the KARS, EMT, and G2M checkpoint pathways, as well as the interferon-gamma and interferon-alpha responses, whereas ssGSEA showed that HMMR expression positively correlated with the infiltration level of Th2 cells.

Conclusions: This study demonstrated that the upregulation of HMMR in HNSCC is a biomarker for poor prognosis. The biological functions of HMMR is potentially related to the KARS, EMT, and G2M checkpoint pathways, as well as the interferon-gamma and interferon-alpha responses. These findings help to elucidate the role of HMMR in carcinogenesis and lay a foundation for further study.

27. Integrative Proteomic Characterization of Human Lung Adenocarcinoma

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Genomic studies of lung adenocarcinoma (LUAD) have advanced our understanding of the disease's biology and accelerated targeted therapy. However, the proteomic characteristics of LUAD remain poorly understood. We carried out a comprehensive proteomics analysis of 103 cases of LUAD in

Chinese patients. Integrative analysis of proteome, phosphoproteome, transcriptome, and whole-exome sequencing data revealed cancer-associated characteristics, such as tumor-associated protein variants, distinct proteomics features, and clinical outcomes in patients at an early stage or with EGFR and TP53 mutations. Proteome-based stratification of LUAD revealed three subtypes (S-I, S-II, and S-III) related to different clinical and molecular features. Further, we nominated potential drug targets and validated the plasma protein level of HSP 90ß as a potential prognostic biomarker for LUAD in an independent cohort. Our integrative proteomics analysis enables a more comprehensive understanding of the molecular landscape of LUAD and offers an opportunity for more precise diagnosis and treatment.

28. Enhanced B7-H4 expression in gliomas with low PD-L1 expression identifies super-cold tumors

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Background: Characterizing expression profiles of different immune checkpoint molecules are promising for personalized checkpoint inhibitory immunotherapy. Gliomas have been shown as potential targets for immune checkpoint inhibitors recently. Our study was performed to determine co-expression levels of two major B7 immune regulatory molecules PD-L1 and B7-H4, both of which have been demonstrated to inhibit anti-tumor host immunity in gliomas.

Methods: We assessed tumor tissues from stage II–IV primary gliomas (n=505) by immunohistochemistry (IHC) for protein levels of both PD-L1 and B7-H4. Gene co-expression analysis assessing clusters based on extent of PD-L1/B7-H4 classifier genes expression were investigated in two transcriptome datasets (TCGA and CGGA). In addition, levels of immune cell infiltrates were estimated with IHC and RNA-seq data for assessing the tumor immune microenvironment of PD-L1/B7-H4 subgroups.

Results: High-expression of PD-L1 and B7-H4 in gliomas was 23% and 20% respectively, whereas co-expression of two proteins at high levels was limited to 2% of the cases. Comparable results were seen in RNA-seq datasets where PD-L1 mRNA expression levels negatively correlated with that of

B7-H4. Gene co-expression modules clustered within each grade of gliomas demonstrated lack of Double-High modules (cluster with high expression of both PD-L1 and B7-H4 classifier genes). B7-H4 mRNA expression levels showed negative correlation with extent of immune cell infiltration and High-B7-H4 module gliomas (high B7-H4 but low PD-L1 classifier genes expression) had less tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs). IHC assessment also showed few TILs and TAMs in High-B7-H4 subgroup gliomas.

Conclusions: The majority of gliomas express PD-L1 or B7-H4, however, co-expression of both at high levels is minimal. The High-B7-H4 patients could be considered as “super-cold” gliomas with significantly deficient in TILs, suggesting that B7-H4 might inhibit T-cell trafficking into the central nervous system. This study demonstrated that PD-L1 and B7-H4 may serve as mutually compensatory immune checkpoint molecules in gliomas for immune targeted or active-specific immunotherapy. The distinct B7-H4 pathways modulating T-cell function and immune evasion in glioma patients deserved to be further explored in the future during immunotherapy.

29. 软骨肉瘤生物标记物的研究进展

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临床预后是癌症患者最关心的问题。在过去的几十年中，各种癌症中的分子标记物已经逐步确定。虽然软骨肉瘤是骨肉瘤之后第二常见的原发性骨肿瘤，但用于准确判断软骨肉瘤预后的分子生物标记物尚存在争议。软骨肉瘤是软骨细胞起源的一种恶性肿瘤，大多数软骨肉瘤生长缓慢，很少转移，适当的手术后患者预后良好。该肿瘤对化学疗法和放射疗法不敏感，因此在高级别软骨肉瘤中需要进行广泛的手术切除。为了决定最佳治疗方法，软骨肉瘤中需要开展早期准确的生物标记物来诊断。这篇综述通过总结近几年研究报道的软骨肉瘤生物标记物，希望对该疾病的诊疗实践提供一定的帮助。

30. Genome-wide mapping of 5-hydroxymethylcytosines in circulating cell-free DNA as a non-invasive approach for early detection of hepatocellular carcinoma

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Objective: The lack of highly sensitive and specific diagnostic biomarkers is a major contributor to the poor outcomes of patients with hepatocellular carcinoma (HCC). We sought to develop a non-invasive diagnostic approach using circulating cell-free DNA (cfDNA) for the early detection of HCC.

Design: Applying the 5hmC-Seal technique, we obtained genome-wide 5-hydroxymethylcytosines (5hmC) in cfDNA samples from 2554 Chinese subjects: 1204 patients with HCC, 392 patients with chronic hepatitis B virus infection (CHB) or liver cirrhosis (LC) and 958 healthy individuals and patients with benign liver lesions. A diagnostic model for early HCC was developed through case-control analyses using the elastic net regularisation for feature selection.

Results: The 5hmC-Seal data from patients with HCC showed a genome-wide distribution enriched with liver-derived enhancer marks. We developed a 32-gene diagnostic model that accurately distinguished early HCC (stage 0/A) based on the Barcelona Clinic Liver Cancer staging system from non-HCC (validation set: area under curve (AUC)=88.4%; (95% CI 85.8% to 91.1%)), showing superior performance over α-fetoprotein (AFP). Besides detecting patients with early stage or small tumours (eg, ≤2.0 cm) from non-HCC, the 5hmC model showed high capacity for distinguishing early HCC from high risk subjects with CHB or LC history (validation set: AUC=84.6%; (95% CI 80.6% to 88.7%)), also significantly outperforming AFP. Furthermore, the 5hmC diagnostic model appeared to be independent from potential confounders (eg, smoking/alcohol intake history).

Conclusion: We have developed and validated a non-invasive approach with clinical application potential for the early detection of HCC that are still surgically resectable in high risk individuals.

31. ERO1L promotes IL6/sIL6R signaling and regulates MUC16 expression to 1 promote CA125 secretion and the metastasis of lung cancer cells

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The abnormal secretion of CA125, a classic tumor marker, is usually related to a poor prognosis in various tumors. Thus, this study aimed to explore the potential mechanisms that promote CA125 secretion in lung cancer. By querying the database, the gene endoplasmic reticulum oxidoreductase 1L (ERO1L) was identified and chosen as the research subject. The antibody chips were used to screen the lung cancer cell supernatant and found that the most obvious secreted protein was CA125. ERO1L was found to promote the secretion of IL6R by affecting the formation of disulfide bonds. IL6R bound to IL6 and triggered the activation of the NF-κB signaling pathway. Then, NF-κB bound to the promoter of MUC16, resulting in overexpression of MUC16. The extracellular segment of MUC16 was cleaved to form CA125, while the C-terminus of MUC16 promoted the EMT phenotype and the release of IL6, forming a positive feedback pathway. In conclusion, ERO1L might affect the secretion of CA125 through the IL6 signaling pathway and form

a positive feedback loop to further promote the development of lung cancer. This might expand the application scope of CA125 in lung cancer.

32. NAT10 promotes gastric cancer metastasis via N4-acetylated COL5A1

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Background: Gastric cancer (GC) is among the most prevalent gastrointestinal malignancies. The occurrence of local deep infiltration or distant metastasis in GC is commonly associated with weak treatment and poor prognosis. Although, N4-Acetylcytidine (ac4C) represents one of the extensive chemical modifications in mRNAs that plays a pivotal role in modulating mRNA stability and the mRNA translation process. However, the role of mRNA ac4C modification in disease remains unclear. As the only known ac4C “writer” protein, NAT10 is thought to have critical effects in tumor metastasis and tumor cell epithelial-to-mesenchymal transition (EMT). Here, we report a novel mechanism of NAT10-mediated mRNA ac4C modification regulating gastric cancer metastasis and EMT.

Method: We performed immunohistochemical (IHC) and bioinformatics analysis to evaluate the correlation between the expression levels of NAT10 and clinical information. In vitro and in vivo experiments were conducted to investigate the effect of NAT10 on GC metastasis. RIP-seq, acRIP-seq, a luciferase reporter assay, RNA stability assay, RNA translation efficiency assay, and other techniques were utilized to elucidate the regulatory mechanism of NAT10 in GC metastasis.

Result: NAT10 was significantly up-regulated in GC. Clinically, NAT10 up-regulation was associated with poor prognosis and lymph node metastasis. The cell and animal experiment findings showed that NAT10 enhanced the EMT and metastasis of cancer cells in vivo. Mechanistically, we established that NAT10 up-regulated the modification levels of COL5A1 mRNA ac4C, maintained the stability of COL5A1, and up-regulated the expression of COL5A1, further promoting GC cell EMT, which led to GC metastasis.

Conclusion: Herein, we propose a novel mechanism through which mRNA ac4C modification regulates cancer metastasis. Besides, we demonstrate the regulation effect of NAT10-COL5A1 on GC cell EMT and GC metastasis. Therefore, we provide a potential therapeutic strategy for GC.

33. 干细胞和母细胞在软骨肉瘤血管形成中的作用

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摘要：软骨肉瘤和去分化软骨肉瘤主要发生在 40-70 岁的人群中。关于软骨肉瘤的起源细胞类型说法很多，但至今还没有明确定论，其中较多的人认为骨髓中的间充质干细胞和母细胞（mesenchymal stem and progenitor cells, MSPC）是软骨肉瘤发生的来源。研究显示软骨肉瘤在极低的概率下逃脱了衰老和凋亡的命运开始恶性增殖，并且诱导新生血管形成和局部转移发生。在这篇文章中，我们将介绍和讨论软骨肉瘤血管形成中信号转导通路和细胞因子，其中 MSPC 参与的部分是重点。

34. TXNDC12 promotes EMT and metastasis of hepatocellular carcinoma cells via activation of β-catenin

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Metastasis is one of the main contributors to the poor prognosis of hepatocellular carcinoma (HCC). However, the underlying mechanism of HCC metastasis remains largely unknown. Here, we showed that TXNDC12, a thioredoxin-like protein, was upregulated in highly metastatic HCC cell lines as well as in portal vein tumor thrombus and lung metastasis tissues of HCC patients. We found that enforced expression of TXNDC12 promoted metastasis both in vitro and in vivo. Subsequent mechanistic investigations revealed that TXNDC12 promoted metastasis through upregulation of the ZEB1-mediated epithelial-mesenchymal transition (EMT) process. We subsequently showed that TXNDC12 overexpression stimulated the nuclear translocation and activation of β-catenin, a positive transcriptional regulator of ZEB1. Accordingly, we found that TXNDC12 interacted with β-catenin and that the thioredoxin-like domain of TXNDC12 was essential for the interaction between TXNDC12 and β-catenin as well as for TXNDC12-mediated β-catenin activation. Moreover, high levels of TXNDC12 in clinical HCC tissues correlated with elevated nuclear β-catenin levels and predicted worse overall and disease-free survival. In summary, our study demonstrated that TXNDC12

could activate β-catenin via protein-protein interaction and promote ZEB1-mediated EMT and HCC metastasis.

35. Identification of a 6-lncRNA prognostic signature based on microarray re-annotation in gastric cancer

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Gastric cancer (GC) remains an important malignancy worldwide with poor prognosis. Long noncoding RNAs (lncRNAs) can markedly affect cancer progression. Moreover, lncRNAs have been proposed as diagnostic or prognostic biomarkers of GC. Therefore, the current study aimed to explore lncRNA-based prognostic biomarkers for GC. LncRNA expression profiles from the Gene Expression Omnibus (GEO) database were first downloaded. After re-annotation of lncRNAs, a univariate Cox analysis identified 177 prognostic lncRNA probes in the training set GSE62254 (n = 225). Multivariate Cox analysis of each lncRNA with clinical characteristics as covariates identified a total of 46 prognostic lncRNA probes. Robust likelihoodbased survival and least absolute shrinkage and selection operator (LASSO) models were used to establish a 6-lncRNA signature with prognostic value. Receiver operating characteristic (ROC) curve analyses were employed to compare survival prediction in terms of specificity and sensitivity. Patients with high-risk scores exhibited a significantly worse overall survival (OS) than patients with low-risk scores (log-rank test P value <.0001), and the area under the ROC curve (AUC) for 5-year survival was 0.77. A nomogram and forest plot were constructed to compare the clinical characteristics and risk scores by a multivariable Cox regression analysis, which suggested that the 6-lncRNA signature can independently make the prognosis evaluation of patients. Single-sample GSEA (ssGSEA) was used to determine the relationships between the 6-lncRNA signature and biological functions. The internal validation set GSE62254 (n = 75) and the external validation set GSE57303 (n = 70) were successfully used to validate the robustness of our 6-lncRNA signature. In conclusion, based on the above results, the 6-lncRNA signature can effectively make the prognosis evaluation of GC patients.

36. SLCA6A6 as a novel biomarker for multidrug resistance and a target for chemotherapy

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Background: Stomach cancer ranks as the fifth most frequently diagnosed cancer and the third leading cause of cancer death. For gastric cancer treatment, perioperative chemotherapy is the

recommended regimen for stage II–III gastric cancer, and the standard care of stage IV gastric cancer is palliative chemotherapy that brings better survival and quality-of-life (QoL) outcomes. Although chemotherapy is considered the essential method for gastric cancer, 5-year survival of patients with advanced or metastatic gastric cancer failed reach 10%. One of the most important reasons for the limited effectiveness of chemotherapy is multidrug resistance (MDR), which is a fairly common phenomenon in gastric cancer treatment. A massive amount of research has specialized in MDR, and the mechanism of MDR has been partially uncovered that changed drug uptake, accelerated drug efflux, target molecules alterations led to MDR. However, few studies focused on the biomarkers that could Identify patients who benefit most from chemotherapy. **Methods:** Transcriptome sequencing was used to detect differentially expressed genes between 5-FU-resistant gastric cancer cells and their parental cells. Tissue chip assay was performed to explore the expression profile and prognosis prediction of SLC6A6 in gastric cancer. Western blotting and qPCR were carried out to examine the expression of SLC6A6 in gastric cancer cells and stable cells infected with lentivirus. Dual-luciferase reporter system was employed to verify the transcriptional regulation of SLC6A6 by SP1. **Results:** SLC6A6 wad remarkably increased in SGC7901/5-FU cells compared to SGC7901 cells through transcriptome sequencing, indicating that SLC6A6 was correlated to chemotherapeutic resistance. In clinic tissue chip, high expression of SLC6A6 extremely implied a poor prognosis, which was same as the results from TCGA database of gastric cancer cases. It reminded the role of SLC6A6 as a biomarker of MDR that SLC6A6 has a high correlation with IC50 of gastric cancer cells against chemotherapy drugs in cancer cell line Encyclopedia (CCLE). Furthermore, SLC6A6 was confirmed to mediate chemotherapeutic resistance in vitro and in vivo. In terms of mechanism, SP1 was screened and demonstrated as a transcription factor of SLC6A6 through jasper database and dual-luciferase reporter system. Interestingly, SP1 and SLC6A6 was gradually elevated along with time in SGC7901 cells when treated with 5-FU. And SP1 was increased on the first day with 5-FU treatment while SLC6A6 did on the third day, indicating SP1 was an initiator against the killing effect of chemotherapy drugs and SLC6A6 as executor. **Conclusion:** SLC6A6 expression was elevated in gastric cancer cells and high expression of it was correlated with poor prognosis of patients with gastric cancer. Furthermore, SLC6A6 could be served as a biomarker of MDR because of its prominent role in promoting chemotherapeutic resistance. SP1 was a transcription factor of SLC6A6, initiated the resistance to chemotherapy. Therefore, SLC6A6 was highly likely to be a biomarker for predicting the effect of chemotherapy and a therapeutic target for overcoming MDR.

Keywords: SLC6A6, SP1, gastric cancer, biomarker, MDR

37. Overcoming Obstacles in Pathological Diagnosis of Pulmonary Nodules through Circulating Tumor Cell Enrichment

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With the increasing use of low-dose computed tomography (LDCT) in the clinical examination of the lung, the prevalence of pulmonary nodules has significantly increased. As pulmonary nodules may arise from multiple etiologies, not only tumor, but lung inflammation, tuberculosis or hemorrhage as well, an accurate diagnosis to determine the nature of an identified nodule is key for subsequent clinical decision-making and treatment planning. Peripheral blood containing a small number of tumor cells, known as circulating tumor cells (CTCs) have become increasingly studied as promising diagnostic or screening indicators for cancer, however, their enrichment and identification has been a technical barrier for clinical application due to the scarcity.

In this study, we developed a simple and easy-to-use enrichment protocol based on immunomagnetic beads to isolate and concentrate folate receptor (FR) – positive CTCs. The method was validated with 3798 patients recruited from the Department of Thoracic Surgery at Shanghai Pulmonary Hospital. The average CTC concentration of patients with lung disease is 11.97 functional unit (FU) in a 3 mL sample of peripheral blood. We next determined the correlation between the level of FR-positive CTCs and other tumor markers, genotypes, TNM stage and clinicopathological features. No correlation was found between CTC with expression of three major lung cancer driver genes (PIK3CA, ALK, BRAF), the TNM stage of the lung lesion or presence of pleura invasion. Finally, we analyzed the diagnostic potential of characterizing FR-positive CTC levels. Based on our previous CTC analysis in healthy population, patients with benign lung disease and lung cancer, we set the cutoff diagnostic threshold for lung cancer at 8.7 FU/3mL blood sample. In our cohort, 2835 samples had a CTC level above this diagnostic threshold; of those 2468 (87.05%) had subsequent pathological confirmation of lung cancer. These results indicated that the additional knowledge of FR-positive CTC levels strongly correlate with lung cancer diagnosis.

In conclusion, our findings in a large patient population demonstrate that the determination of FR-positive CTC concentration is a convenient and time-saving strategy to improve the pathological diagnosis of pulmonary nodules.

38. Clinical use of a machine learning histopathological image signature in diagnosis and survival prediction of clear cell renal cell carcinoma

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Background: Renal cell carcinoma is one of the most aggressive malignancies and represents 2%-3% of all cancers. Due to the complicated histopathological characteristics of renal neoplasms, traditional distinguishing of clear-cell renal-cell carcinoma (ccRCC) by naked eyes of experienced pathologist remains labor-intensive and time-consuming.

Methods: A total of 947 RCC patients from Shanghai General Hospital and The Cancer Genome Atlas were recruited in this study. We extracted quantitative features of hematoxylin-eosin stained images using CellProfiler and performed machine-learning method to develop and verify a novel computational recognition of digital pathology for diagnosis and prognosis of ccRCC patients in the training, test and external validation cohort. Integrated nomogram with clinicopathologic factors was carried out to improve survival prediction efficiency.

Results: The diagnostic model based on digital pathology could accurately distinguished ccRCC from normal renal tissues, with area under the curve (AUC) of 96.0%, 94.5% and 87.6% in the training, test and external validation cohorts, respectively. It could also accurately distinguished ccRCC from other pathological types of renal cancer, with AUC of 97.0% and 81.4% in the TCGA cohort and General cohort. We next developed and verified a computational recognition prognosis model with risk score. There was a significant difference in disease-free survival comparing patients with high versus low risk score in training cohort (hazard ratio = 2.72, $p < 0.0001$) and validation cohort (hazard ratio = 9.50, $p = 0.0091$). The integration nomogram based on our computational recognition risk score and clinicopathologic factors demonstrated excellent survival prediction for ccRCC patients, with increased accuracy by 6.6% in patients from Shanghai General Hospital and by 2.5% in patients from TCGA cohort when compared to current tumor stages/grades systems. These results indicate the potential clinical use of our machine learning histopathological image signature in diagnosis and survival prediction of ccRCC.

Conclusion: We developed and verified a computational recognition model for automatic diagnosis and prognostic prediction for ccRCC patients. Moreover, integrated with clinicopathologic factors, our prognostic model demonstrated excellent survival prediction of ccRCC patients, which can provide referential advice for clinical decision making.

39. The identification and potential mechanism of SET7/9 as a tumor biomarker in breast cancer

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Objective Although the deregulation of lysine methyltransferase (su(var)-3-9, enhancer-of-zeste, trithorax) domain-containing protein 7/9 (SET7/9) has been identified in a variety of cancers, the potential role of SET7/9 and the molecular events in which it is involved in breast cancer remain obscure. **Methods** Using the online Human Protein Atlas and GEO databases, the expression of SET7/9 was analysed. Furthermore, we investigated the underlying mechanisms using chromatin immunoprecipitation-based deep sequencing (ChIP-seq) and quantitative ChIP assays. To explore the physiological role of SET7/9, functional analyses such as CCK-8, colony formation, and Transwell assays were performed and a xenograft tumour model was generated with the human breast cancer cell lines MCF-7 and MDA-MB-231. Mass spectrometry, coimmunoprecipitation, GST pull-down and ubiquitination assays were used to explore the mechanisms of SET7/9 function in breast cancer. **Results** We evaluated the expression of SET7/9 in different breast cancer cohorts and found that higher expression indicated worse survival times in these public databases. We demonstrated positive effects of SET7/9 on cell proliferation, migration and invasion via the activation of runt-related transcription factor 2 (RUNX2). We demonstrate that tripartite motif-containing protein 21 (TRIM21) physically associates with SET7/9 and functions as a major negative regulator upstream of SET7/9 through a proteasome-dependent mechanism and increased ubiquitination. **Conclusion** Taken together, our data suggest that SET7/9 plays a promoting role via the regulation of RUNX2, while TRIM21-mediated SET7/9 degradation acts as an anti-braking system in the progression of breast cancer.

40. Transcription factor GATA3 could be used as a potential breast cancer prognosis biomarker

Wenzhe Si,YIng Kuo

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Transcription factor GATA3 is required to specify and maintain the luminal cell fate in the mammary gland, and its expression is progressively lost during luminal breast cancer progression. However, how the loss-of-function of GATA3 contributes to the development of breast cancer is still poorly understood. Here, we report that GATA3 targets more transcriptionally repressed genes than transcriptionally active ones in mammary luminal epithelial cells. We found that GATA3 nucleates a chromatin modifying machinery composed of G9A and MTA3-, but not MTA1- or MTA2-, associated NuRD complex. Genome-wide analysis of the GATA3/G9A/NuRD(MTA3) targets identified a cohort of genes including ZEB2 and CDH2 that are critically involved in cell proliferation, migration, and

epithelial-to-mesenchymal transition (EMT). We demonstrated that the GATA3/G9A/NuRD(MTA3) complex inhibits the invasive potential of breast cancer cells in vitro and suppresses breast cancer metastasis in vivo. Strikingly, we found that the expression of G9A and MTA3 is concurrently down-regulated with GATA3 during breast cancer progression as a result of the repressed expression of ZEB2, a transcription activator for G9A and MTA3, by the GATA3/G9A/NuRD(MTA3) complex. Apparently a reciprocal feedback loop exists between the GATA3/G9A/NuRD(MTA3) complex and ZEB2, which is dysfunctioned due to the loss of GATA3 during breast cancer progression. Our study uncovered a mechanistic link of the loss-of-function of GATA3 to breast cancer progression, providing potential targets for therapeutic intervention of breast cancer.

41. SNORD63 and SNORD96A as the non-invasive diagnostic biomarkers for Clear Cell Renal Cell Carcinoma

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Background: Increasing evidence has demonstrated that snoRNAs play crucial roles in tumorigenesis of various cancer types. However, research on snoRNAs in ccRCC was very little. This study mainly aimed to validate the differential expression and the potential diagnostic value of SNORD63 and SNORD96A in ccRCC.

Methods: SnoRNAs expression was downloaded from the SNORic and TCGA database including 516 patients with ccRCC and 71 control cases. SNORD63 and SNORD96A expression were further detected in 54 tumor and adjacent FFPE ccRCC tissues, 55 plasma and 75 urinary sediment of ccRCC patients. Then, differential expression and diagnostic value of SNORD63 and SNORD96A were further calculated.

Results: SNORD63 and SNORD96A expression were significantly increased in ccRCC tissues compared with normal tissues from the TCGA database (both, $P < 0.0001$). In addition, we found that SNORD63 and SNORD96A localized in plasma and US stably after treating with RNase A. Meanwhile, SNORD63 and SNORD96A in FFPE and US were elevated in ccRCC patients (all, $P<0.0001$). However, plasma SNORD63 expression had no significance while SNORD96A significantly increased in plasma of ccRCC patients. Notably, the AUC of SNORD63 in US was 0.7055, by comparison the AUC of plasma SNORD63 was only 0.5161. However, the AUC of plasma SNORD96A was up to 0.8909, by comparison the AUC of SNORD96A in US was 0.6788. Interestingly, the AUC of plasma SNORD96A in early stage ccRCC was highly up to 0.9359.

Conclusions: Our findings revealed that SNORD63 in US and SNORD96A in plasma could act as the promising non-invasive diagnostic biomarkers for ccRCC patients

42. Computational recognition of lncRNA signature of tumor-infiltrating B lymphocytes with potential implications in prognosis and immunotherapy of bladder cancer

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Long non-coding RNAs (lncRNAs) have been associated with cancer immunity regulation and the tumor microenvironment (TME). However, functions of lncRNAs of tumor-infiltrating B lymphocytes (TIL-Bs) and their clinical significance have not yet been fully elucidated. In the present study, a machine learning-based computational framework is presented for the identification of lncRNA signature of TIL-Bs (named 'TILBlncSig') through integrative analysis of immune, lncRNA and clinical profiles. The TILBlncSig comprising eight lncRNAs (TNRC6C-AS1, WASIR2, GUSBP11, OGFRP1, AC090515.2, PART1, MAFG-DT, and LINC01184) was identified from the list of 141 B-cell-specific lncRNAs. The TILBlncSig was capable of distinguishing worse compared with improved survival outcomes across different independent patient datasets and was also independent of other clinical covariates. Functional characterization of TILBlncSig revealed it to be an indicator of infiltration of mononuclear immune cells (i.e., natural killer cells, B-cells and mast cells), and it was associated with hallmarks of cancer, as well as immunosuppressive phenotype. Furthermore, the TILBlncSig revealed predictive value for the survival outcome and immunotherapy response of patients with anti-programmed death-1 (PD-1) therapy and added significant predictive power to current immune checkpoint gene markers. The present study has highlighted the value of the TILBlncSig as an indicator of immune cell infiltration in the TME from a non-coding RNA perspective and strengthened the potential application of lncRNAs as predictive biomarkers of immunotherapy response, which warrants further investigation.

43. LncRNA-CYTOR works as an oncogene through the CYTOR/miR-3679-5p/MACC1 axis in colorectal cancer

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A number of evidences has shown that cytoskeleton regulator RNA (CYTOR), a long non-coding RNA (lncRNA), played a pivotal role in development and progression of a variety of cancers. On the other hand, further research is needed to study the clinical significance and the detailed mechanism of

action of lncRNA-CYTOR in colorectal cancer (CRC). The current study aimed to investigate the clinical significance of CYTOR in CRC prognosis and identify the relevant potential signaling pathways and underlying mechanism of competing endogenous RNA (ceRNA). Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) indicated that the expression of CYTOR was significantly elevated in CRC tumor tissues and cell lines. Aberrant expression of CYTOR was significantly related to TNM stage, T stage, N stage, perineural and venous invasion. Survival analysis indicated that high-CYTOR expression was associated with poor overall survival (OS) in CRC patients ($p = 0.0057$), and multivariate analysis showed that high-CYTOR expression was an independent prognostic factor which led to poor overall survival. In addition, bioinformatics analysis revealed that there were 18 microRNAs (miRNAs) interacted with CYTOR, and one of them, miR-3679-5p might collaborate with metastasis-associated in colon cancer-1 (MACC1), which was selected for further analysis. Pearson correlation analysis showed a significant positive correlation between the expression levels of CYTOR and MACC1. In conclusion, the present study suggested that lncRNA-CYTOR played an important role in tumorigenesis and development through the CYTOR/miR-3679-5p/MACC1 axis.

44. A self-enforcing HOXA11/Stat3 feedback loop promotes stemness properties and peritoneal metastasis in gastric cancer cells

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Rationale: Peritoneal metastasis is one of the most common and life-threatening metastases in gastric cancer patients. The disseminated gastric cancer cells forming peritoneal metastasis exhibit a heterogeneity that contrast with those of adjacent epithelial cell of gastric mucosa and even primary gastric cancer cells. Understanding this heterogeneity and its biological meaning requires a theoretical framework and experimental support. It is supposed that the gene expression profiles of peritoneal foci could reveal the identities of genes that might function as metastatic activator. The identitied genes might be the therapeutical targets for the precision treatment of peritoneal metastasis of gastric cancer and do favor to discovery brand-new therapy strategy. **Methods:** In this study, RNA-Seq technology was used to examine transcriptional alterations between peritoneal foci, primary tumor tissues and adjacent chronic gastritis tissues. Homoebox A11, the expression of which was relatively high in both sites of primary tumor and peritoneal foci, was selected and validated the protein expression in primary gastric cancer tissues and paired peritumor ones in 190 gastric cancer patients. The gastric cancer cell models which expression of HOXA11 were variant were constructed and applied for the wound healing assay, adhesion assay, migration and invasion assay, tumor sphere formation assay,

apoptosis assay and anoikis-resistant assay in order to mimic the function of gastric cancer cells in abdominal cavity. To perform proof-of-principle in vivo study, the gastric cancer cells were injected into the abdomen of BALB/c mice to examine the peritoneal metastatic promotion of HOXA11. **Results:** The gastric cancer tissue array shown that the protein level of HOXA11 is higher in gastric cancer tissues rather than that in adjacent ones (training cohort: gastric cancer tissues 0.277±0.011 and adjacent ones 0.119±0.007, P<0.0001; validation cohort: gastric cancer tissues 0.268±0.014 and adjacent ones 0.125±0.008, P<0.0001), and the patients who belong to the HOXA11 high expressed group have rather poorer overall survival time (training cohort: HOXA11 high expressed group 17.33±2.162 month and lower ones 63.84±3.204 month, P<0.0001; validation cohort: HOXA11 high expressed group 20.5±2.885 month and lower ones 64.34±3.984 month). In vitro assay found that HOXA11 enhance cancer stemness, migration and invasion, adhesion to human peritoneal mesothelial cells, anti-apoptosis and anoikis-resistance of gastric cancer. Moreover, the Stat3 could positively regulate the transcription level of HOXA11. Finally, in vivo assay confirmed that BBI608, the inhibitor of cancer stemness which is targeting Stat3, reduce the tumor burdens of HOXA11 high-expressed gastric cancer cells in abdomen cavity of mice. **Conclusions:** this study selected and validated the function of HOXA11, which is high-expressed in both primary site and peritoneal foci of gastric cancer. HOXA11 might be a novel peritoneal metastatic activator and whether it could be the therapeutic target or not desired further study. **Key words:** peritoneal metastasis; gastric cancer; HOXA11; Stat3; BBI608

45. Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and antiferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer

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Objectives: Cancer cells are characterized by metabolic alterations. Thereinto, Stearoyl-CoA Desaturase 1 (SCD1), an enzymatic node located in the conversion of saturated fatty acids into monounsaturated fatty acids (MUFAs), has been reported to accelerate the tumorigenesis of multiple cancers. However, its role in the metabolicprocess of gastric cancer remains largely unexplored.

Materials and Methods: In this study, the expression of SCD1 and its specific target gene were detected in human gastric cancer specimens and cell lines by RNA-Sequencing and western blotting. The effects of SCD1 on gastric cancer cell proliferation were evaluated using Cell Counting Kit 8 assays and colony formation assays, the transwell assays were performed to assess the migration ability of SCD1 high-expressed gastric cancer cells. In vivo effects were investigated by a mouse tumorigenicity model. The prognostic value of SCD1 was studies in silico.

Results: SCD1 promoted tumor growth, migration and anti-ferroptotic cell death of gastric cancer. Its mechanism of action might involve alteration of cancer stemness and modulate cell cycle related proteins. Besides, SCD1 high expression might predict poor prognosis in gastric cancer patients.

Conclusions: we found SCD1 could play pro-tumorigenic role in gastric cancer cells.

Keyword: SCD1, gastric cancer, ferroptosis, lipid metabolism, proliferation;

46. 结直肠癌的分子生物标志物

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结直肠癌是世界性的公共卫生问题。尽管在早期阶段有可能治愈，但仍有相当数量的患者不可避免地会出现或最终发展为转移性疾病，而转移性疾病通常是无法治愈的。尽管在引入新的药物治疗方面取得了进展，但手术切除后的结直肠癌患者的复发率仍然较高。因此，探索分子标志物对患者分层的选择治疗方案成为可能，这对预测预后也是至关重要的。本综述将讨论预测结直肠癌预测预后和治疗的分子生物标志物，并提供最新进展。

47. Interstitial Cells of Cajal Expression Impact on the Risk of Gastrointestinal Stromal Tumor

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Background Most of GISTs were activated mutations in c-kit and its platelet-derived growth factor receptor alpha (PDGFRA), which had a significant effect on early events in GIST transformation and progression. Immunophenotypically, they express specific markers CD117/ c-kit, CD34, studies have also suggested that ICCs have also have an effect on GISTs [8]. However, the relationship between GIST and ICCs is still unknow.

Aim This study explored the effect of ICCs expression level on the risk of GISTs.

Methods 122 patients were be diagnosed as GISTs and undergo surgery. Demographic and clinical information, including gender, age, tumor site, tumor size and paraffin-embedded GISTs specimens of all patients were collected. Assessed the risk of GISTs according to the modified NIH risk classification for primary GIST. Hematoxylin-eosin staining and immunohistochemistry were detected for ICCs expression level.

Results In 122 cases of GISTs, according to the modified NIH criteria, most of GISTs cases (44 cases, 36.07%) were in very low risk, most of GISTs were located in stomach (87 cases, 71.73%), the size of tumors varied from 0.5-20 cm. CD117/ c-kit and CD34 were specific immuno-markers for ICCs and

GISTs. there were 115 cases (94.26%) in CD117/ c-kit positive, 111 cases (90.98%) were in CD34 positive, 109 cases (89.34%) in both CD117/ c-kit and CD34 positive, the CD117/-ckit positive rate in small intestine was lower than colon and rectum and stomach (P<0.05). CD34 positive was also lower than the CD117/ c-kit positive. Most High risk GISTs cases (16 cases, 48.48%) were in ICCs and CD117/c-kit (+++), near half of very low risk and low risk GISTs cases were in ICCs and CD117/ c-kit (+) (P<0.05). Most High risk GISTs cases (12cases, 36.36%) were in ICCs and CD34 (+++) (P<0.05). Near half of very low risk and low risk GISTs cases were in ICCs and CD34 (+).

Conclusion CD117 and CD34 positive grade would have an effect on GISTs risk. ICCs expression would have an impact on GISTs risk.

48. 高级别胶质瘤 IDH1 基因突变与临床病理特征和 P53、ki-67 蛋白表达的关系及其预后价值

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目的 探讨高级别胶质瘤中异柠檬酸脱氢酶 1、2（IDH1、IDH2）基因突变特征，分析其与临床病理特征和 P53、ki-67 蛋白表达的关系及其预后价值。**方法** 收集高级别胶质瘤的患者 150 例(WHO III级 72 例，IV级 78 例)。采用 Sanger 测序法检测 IDH1 和 IDH2 基因突变，IHC 检测 P53 和 ki-67 蛋白表达。比较患者生存期的差异，分析基因突变与患者预后的关系。**结果** IDH1 基因 R132H 突变率为 30.7%（46/150），IDH1 基因突变与患者较低年龄组、肿瘤部位以及 WHO 组织学分级具有显著相关性（P＜0.05），而与性别、肿瘤位置无显著相关性（P＞0.05）；IDH2 基因 R172K 突变率为 2.0%（3/150）。IHC 结果显示：高级别胶质瘤 WHO 分级与 P53 和 Ki-67 蛋白表达不显著相关（P＞0.05）。WHO IV级胶质瘤 IDH1 基因突变与 Ki-67 蛋白表达相关（P=0.042）。生存分析结果显示：在高级别胶质瘤中 WHO III级预后好于 WHO IV级（P＝0.05），IDH1 突变组预后好于 IDH1 野生组（P＜0.05）。进一步分层分析显示，WHO III级胶质瘤 IDH1 突变组预后好于野生组（P＜0.05），而在 WHO IV级胶质瘤中二者无明显差异(P＞0.05)。**结论** WHO III级胶质瘤中 IDH1 突变率高于 WHO IV级胶质瘤，IDH1 突变组有较好的临床预后。IDH1、P53 和 Ki-67 联合检测有利于胶质瘤的诊断和预后评估。

49. A novel IFNα-induced long noncoding RNA negatively regulates immunosuppression by interrupting H3K27 acetylation in head and neck squamous cell carcinoma

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Background: Interferon alpha (IFNα) is a well-established regulator of immunosuppression in head and neck squamous cell carcinoma (HNSCC), while the role of long noncoding RNAs (lncRNAs) in immunosuppression remains largely unknown.

Methods: Differentially expressed lncRNAs were screened under IFNα stimulation using lncRNA sequencing. The role and mechanism of lncRNA in immunosuppression were investigated in HNSCC in vitro and in vivo.

Results: We identified a novel IFNα-induced upregulated lncRNA, lncMX1–215, in HNSCC. LncMX1–215 was primarily located in the cell nucleus. Ectopic expression of lncMX1–215 markedly inhibited expression of the IFNα-induced, immunosuppression-related molecules programmed cell death 1 ligand 1 (PD-L1) and galectin-9, and vice versa. Subsequently, histone deacetylase (HDAC) inhibitors promoted the expression of PD-L1 and galectin-9. Binding sites for H3K27 acetylation were found on PD-L1 and galectin-9 promoters. Mechanistically, we found that lncMX1–215 directly interacted with GCN5, a known H3K27 acetylase, to interrupt its binding to H3K27 acetylation. Clinically, negative correlations between lncMX1–215 and PD-L1 and galectin-9 expression were observed. Finally, overexpression of lncMX1–215 suppressed HNSCC proliferation and metastasis capacity in vitro and in vivo.

Conclusions: Our results suggest that lncMX1–215 negatively regulates immunosuppression by interrupting GCN5/ H3K27ac binding in HNSCC, thus providing novel insights into immune checkpoint blockade treatment

50. 尿液来源的外泌体在膀胱癌无创检测中诊断价值的 meta 分析

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摘要：目的 系统评价尿液来源的外泌体在膀胱癌检测中的诊断价值。**方法** 通过在数据库中国知网 CNKI、PubMed、EMbase、Cochrane、Web of Science 检索尿液来源外泌体对膀胱癌诊断的相关文献，检索时限从建库到 2020 年 4 月。利用 QUADAS-2 评价工具对纳入的文献质量进行评估，采用统计学软件 Review Manager5.2，Stata15.1，Meta-DiSc1.4 对纳入文献中的原始数

据进行荟萃分析，诊断性能评估：计算合并的敏感性（sensitivity）、特异性(specificity)、阳性似然比（poold positive likelihood ratio，PLR），阴性似然比（negative likelihood ratio，NLR），诊断优势比（diagnostic odds ratio，DOR）、受试工作者曲线下面积（the area under curve of summarized receiver operating characteristic curve）。采用 DEEK'S 漏斗图对纳入的文献发表偏移进行评估，通过 Spearman 相关系数计算，以评估纳入文献是否存在阈值效应，使用 I^2 检验进行异质性评价。**结果** 数据库检索总共获得相关文献 281 篇，依据系统评价与荟萃分析指南（the Preferred Reporting Items for Systematic Reviews and Meta-Analyses，PRISMA），剔除不符合要求的文献，最终纳入文献 7 篇，膀胱癌患者 546 例，健康或良性对照组 204 例。Spearman 相关系数分析结果 P=0.58，P 大于 0.05，提示不存在阈值效应，故采用随机效应模型分析。计算合并分析敏感性、特异性、阳性似然比、阴性似然比、诊断优势比分别为 0.72[95% CI 0.68-0.76]， 0.79[95% CI 0.73-0.85]，3.26[95% CI 2.26-4.72]，0.29[95% CI 0.17-0.49]，13.29 [95% CI 5.36-32.94]，合并 SROC 曲线下面积为 0.8635。根据 Deeks 漏斗图不对称试验结果我们未发现发表偏移（P=0.86）。**结论** 尿液来源的外泌体在膀胱癌检测中具有较好的诊断价值。

51. Tumor-Repopulating Cells Induce PD-1 Expression in CD8+ T Cells by Transferring Kynurenine and AhR Activation

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Despite the clinical successes fostered by immune checkpoint inhibitors, mechanisms underlying PD-1 upregulation in tumor-infiltrating T cells remain an enigma. Here, we show that tumor-repopulating cells (TRCs) drive PD-1 upregulation in CD8+ T cells through a transcellular kynurenine (Kyn)-aryl hydrocarbon receptor (AhR) pathway. Interferon-g produced by CD8+ T cells stimulates release of high levels of Kyn produced by TRCs, which is transferred into adjacent CD8+ T cells via the transporters SLC7A8 and PAT4. Kyn induces and activates AhR and thereby upregulates PD-1 expression. This Kyn-AhR pathway is confirmed in both tumor-bearing mice and cancer patients and its blockade enhances antitumor adoptive T cell therapy efficacy. Thus, we uncovered a mechanism of PD-1 upregulation with potential tumor immunotherapeutic applications.

52. NF1 may serve as a novel genetic biomarker of response to treatment and prognosis in glioblastoma (GBM)

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Background: The intrinsic capacity of glioblastoma (GBM) tumor cells to infiltrate normal brain predictably results in high rates of early recurrence. Little has changed over the last decade in the treatment available for GBM with survival remaining poor and a novel genetic biomarker is necessary found to predict response to treatment and prognosis in GBM. **Methods:** Biomarker discovery was performed by a genome-wide screen using DNA extracted from tissue and blood samples of GBM patients treated with standard of care.The biomarker was then evaluated for its predictability in OS and DFS and revealed the relationship with short-term relapse after radiation therapy. **Results:** 22 kinds of mutations were detected in 51/58 GBM patients (87.9%). NF1 was the fouth frequently mutated gene and NF1-deleted/mutated GBM patients have the worst prognosis with 2-month median relapse time after radiation therapy. Median OS for NF1-deleted/mutated GBM patients (n=11) treated with surgery and Chemoradiotherapy was 9.1 mon vs 17.2 mon for NF1 wildtype ones(n=47), HR (95% CI) 1.83 (0.8753,3.817), p = 0.1. In addition, median DFS for NF1-deleted/mutated GBM patients (n=11) was 2.9 mon vs 13.2 mon for NF1 wildtype ones(n=47), p = 0.03. NF1-deleted/mutated GBMs showed reduced tumor purity and more infiltration of tumor-associated macrophages through pathological stainings. We measured the distance between 58 GBM patients tumor cells through an immunohistochemistrybased pathology imaging system and found that NF1-deleted/mutated cells have a lot more distances than NF1 wildtype ones. **Conclusions:** These data suggest that NF1-deleted/mutated GBM patients have a poor prognosis and a short-term relapse after radiation therapy. NF1 may play a role in organizing the tumor microenvironment. NF1 in GBM will be further evaluated in a planned randomized ph 2b study in newly diagnosed GBM patients.

53. Circulating exosome-derived bona fide long non-coding RNAs predicting the occurrence and metastasis of hepatocellular carcinoma

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Although the diagnosis and therapy approach developed, techniques for the early diagnosis of HCC remain insufficient which results in poor prognosis of patients. The traditional biomarker AFP, however, has been proved with low specificity. Circulating exosomal ncRNAs revealed different

profiles reflecting the characteristics of tumour. In this study, we mainly focused on circulating exosomal ncRNAs which might be the fingerprint for HCC, especially for the diagnosis or metastasis prediction. A high throughput lncRNA microarray in exosomes extracted from cell-free plasma was applied. The risk score analysis was employed to screen the potential exosome-derived lncRNAs in two independent sets based on different clinical parameters in 200 paired HCC patients. After a multi-stage validation, we finally revealed three lncRNAs, ENSG00000248932.1, ENST00000440688.1 and ENST00000457302.2, increased in HCC comparing with the both chronic hepatitis (CH) patients and cancer-free con- trols. ROC curve revealed a higher sensitivity and specificity in predicting the occur- rence of HCC from cancer-free controls and CH patients with the area under curve (AUC) of 0.905 and 0.879 by combining AFP. The three lncRNA panel combined with AFP also indicted a fingerprint function in predicting the metastasis of HCC with the AUC of 0.870. In conclusion, ENSG00000248932.1, ENST00000440688.1 and ENST00000457302.2 might be the potential biomarker for the tumorigenesis pre- diction from CH patients or healthy controls and may also be applied for dynamic monitoring the metastasis of HCC.

54. Nanotrap-enabled quantification of KRAS-induced peptide hydroxylation in blood for cancer early detection

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Circulating peptide is a potential source of biomarkers for cancer detection. However, the existence of large molecular weight proteins in plasma have a disastrous effect on circulating peptides isolating and detecting. Herein, nanotrap fractionation following by mass spectrometry have been applied to quantify the levels of bradykinin (BK) and hydroxylated bradykinin (Hyp-BK) as a relative measure of KRAS-regulated Prolyl-4-hydroxylase alpha-1 (P4HA1) which may serve as early diagnosis marker for pancreatic ductal adenocarcinoma (PDAC). We found that P4HA1 can be upregulated by $KRAS^{G12V}$, which is a PDAC driver mutation, using HPNE/KRAS and HPNE cells. And we revealed

that P4HA1 is overexpressed in PDAC tumors, compared to normal and inflamed pancreatic tissues. RNA interference revealed that P4HA1 activity was primarily responsible for Hyp-BK production. Mass spectrometry analysis revealed that plasma Hyp-BK/BK ratio was higher in PDAC than pancreatitis patients and healthy controls, while the area under the receiver operating characteristic (ROC) curve (AUC) is 0.8209 (95%CI, 0.7269–0.9149). The Hyp-BK/BK association with PDAC was reproduced in another cohort, where this ratio was found to increase with advancing tumor stage. These novel findings paved the way for wider applications of Nanotrap coupled mass spectrometry as a powerful tool for revealing biosignatures from pla(https://link.springer.com/article/10.1007/s12274-019-2405-9）

55. Novel predictive epigenetic signature for temozolomide in non-G-CIMP glioblastomas

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Objective: To identify novel epigenetic signatures that could provide predictive information that is complementary to promoter methylation status of the O-6-methylguanine-DNA methyltransferase (MGMT) gene for predicting temozolomide (TMZ) response, among glioblastomas (GBMs) without glioma-CpGs island methylator phenotype (G-CIMP).

Methods: Different cohorts of primary non-G-CIMP GBMs with genome-wide DNA methylation microarray data were included for discovery and validation of a multimarker signature, combined using a RISK score model. Different statistical analyses and functional experiments were performed for clinical and biological validation.

Results: By employing discovery cohorts with radiotherapy (RT) and TMZ versus RT alone and a strict multistep selection strategy, we identified seven CpGs, each of which was significantly correlated with overall survival (OS) of non-G-CIMP GBMs with RT/TMZ, independent of age, MGMT promoter methylation status, and other identified CpGs. A RISK score signature of the 7 CpGs was developed and validated to distinguish non-G-CIMP GBMs with differential survival outcomes to RT/TMZ, but not to RT alone. The interaction analyses also showed differential outcomes to RT/TMZ versus RT alone within the RISK score-based subgroups. The signature could also improve the risk classification by age and MGMT promoter methylation status. Functional experiments showed that HSBP2 appeared to be epigenetically regulated by one identified CpG and was associated with TMZ resistance, but it was not associated with cell proliferation or apoptosis in GBM cell lines. The predictive value of the single CpG methylation of HSBP2 by pyrosequencing was observed in a local cohort of isocitrate dehydrogenase 1 (IDH1) R132H wild-type GBMs.

Conclusions: This novel epigenetic signature might be a promising predictive (but not a general

prognostic) biomarker and be helpful for refining the MGMT-based guiding approach to TMZ usage in non-G-CIMP.

56. Upregulation of miR-802 suppresses the proliferation of HCC via inhibiting the expression of CASC3

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MicroRNAs (miRNAs) have been well-documented to involve in Hepatocellular carcinoma (HCC) occurrence and progression. However, the expression and function of miR-802 in this cancer is still unknown. In this study, we find that miR-802 which was down-regulated in highly differentiated HCC tissues and HepG2 cell lines using RT-qPCR and immune florescence, and further identified as a key regulator for the proliferation of HCC. Additionally, we found that cancer susceptibility candidate 3 (CASC3) is a direct target of miR-802 by previous studies. Rescue experiments also demonstrated that miR-802 can regulate the balance between CDK8/Cyclin D1 and BCL-2/Caspase-3 by targeting CASC3. In summary, our study has identified miR802 played the role of tumor suppressor in HCC progression and clarified a new mechanism of the miR-802/CASC3 axis in the regulation of proliferation in HCC, which provide potential new targets to protect the body against HCC.

57. A novel lncRNA NONHSAT053785 acts as an independent risk factor for intrahepatic metastasis of hepatocellular carcinoma

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Purpose: Long non-coding RNAs (lncRNAs) in body fluids have been considered as promising novel biomarkers for tumor-related diseases. The present study aimed to investigate the expression level of lncRNA NONHSAT053785 in serum and its correlation with clinical characteristics of hepatocellular carcinoma (HCC) patients.

Methods: The droplet digital PCR (ddPCR) was used to measure the serum levels of NONHSAT053785 in 112 HCC patients, 96 chronic hepatitis B (CHB) patients, and 99 healthy controls (HC). The correlation between NONHSAT053785 and clinical characteristics were analyzed by chi-square test and Spearman’s correlation test. The risk factors of intrahepatic metastasis (IM) were detected by univariate and multivariate analysis. Furthermore, the diagnostic value of

NONHSAT053785 in HCC and its predictive ability in IM was evaluated by the receiver operating characteristic (ROC) curves.

Results: The level of NONHSAT053785 was significantly increased in the serum of HCC patients and was higher in HCC patients with IM as compared to those without. Additionally, the expression level of NONHSAT053785 was significantly related to IM, Child-Pugh classification, and peripheral blood indicators such as liver metabolic enzymes and positively correlated to IM, Barcelona Clinic Liver Cancer (BCLC) staging, and some peripheral blood indicators. Furthermore, the serum NONHSAT053785 was indicated as an independent predictor for IM in the elderly, non-smoking, drinking, and tumor size ⩾5 cm subjects. The area under the ROC curve (AUC) was 0.801 (P <0.0001) for diagnosis of HCC and 0.678 (P =0.0015) for predicting IM.

Conclusion: The increase in serum NONHSAT053785 levels was related to an increased risk of IM, and hence, may serve as a novel biomarker for the diagnosis of HCC and the prediction of IM.

Keywords: long noncoding RNA, hepatocellular carcinoma, intrahepatic metastasis, risk factor.

58. MSIsensor-pro: fast, accurate and matched normal-sample-free detection of microsatellite instability

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Background. Microsatellite instability (MSI), is a key biomarker in cancer therapy and prognosis. Traditional experimental assays are as laborious and time consuming. Due to the requirement of matched normal samples, NextGeneration Sequencing (NGS)-based computational methods would not work on Leukemia samples, paraffin stored samples as well as patient derived xenografts/organoids. Here, we introduce MSIsensor-pro, an ultrafast, accurate and versatile MSI detecting NGS-based computational method to directly handle tumor samples of various target sequencing regions, sequencing depths and tumor purities.

Methods. MSIsensor-pro introduces a multinomial distribution (MND) model to quantify polymerase slippages of microsatellite for each tumor sample and a discriminative site (DMS) selection method to enable MSI detection without matched normal samples. The magnitudes of deletion slippages (hysteresis synthesis, denoted as p) and insertion slippages (presynthesis, denoted as q) in the MND model are estimated with sequencing data in a given sample. Then, the p and q values are used to evaluate the stability of microsatellites sites in the tumor sample. Finally, the proportion of the unstable sites is used to score MSI status.

Results. We noticed that even without matched normal samples, based on benchmark result on 1,532 TCGA samples, MSIsensor-pro’s AUC (0.994) value was much higher than mSINGS (0.594), which

also not requires matched normal. It is slightly higher than those of MSIsensor (0.989) and mantis (0.986), requiring both normal and tumor samples. For samples with low sequencing depth (20x) and low tumor purity (20%), the AUCs of MSIsensor-pro (0.998 and 0.966), MSIsensor (0.968 and 0.960) and mantis (0.959 and 0.935) were much higher than those of mSINGS (0.658,0.517). Additionally, MSIsensor-pro requires much less computational resources and runs more efficiently than all the other methods. Finally, MSIsensor-pro achieves more than 0.98 AUC with just 50 random DMS sites, indicating its potential application of MSIsensor-pro in target sequencing.

Discussion. By eliminating the requirement of matched normal samples, MSIsensor-pro enables MSI detections in paraffin stored samples, Leukemia samples and patient derived xenografts/organoids. MSIsensor-pro is able to score MSI with as few as 50 microsatellite sites, indicating its potential applications on target sequencing panels, stool DNA and liquid biopsy samples such as circulating tumor DNA (ctDNA).

59. 吉非替尼联合恩度一线治疗 EGFR 突变阳性晚期肺腺癌的临床观察

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目的：探讨吉非替尼与重组人血管内皮抑素（恩度）联合一线治疗 EGFR 突变阳性晚期肺腺癌的临床效果及药物不良反应。

方法：以成都中医药大学附属第五人民医院 2018 年 1 月—2020 年 3 月收治的 60 例 EGFR 18-21 号外显子突变、不能手术或术后复发转移的肺腺癌患者为研究对象，随机分为对照组和研究组，每组 30 例，对照组患者使用单药吉非替尼口服治疗，研究组在此基础上联合恩度微泵治疗，21 天为 1 个周期，共进行 4 个周期。比较两组患者的近期疗效、疼痛缓解情况、药物不良反应、肿瘤标志物变化、功能状态的情况。

结果：研究组患者客观缓解率（ORR）较对照组有明显提高，分别为 83.33%、56.67%，存在显著性差异（P＜0.05）。研究组患者治疗后的疼痛缓解情况优于对照组，两组比较存在显著性差异（P＜0.05）。研究组及对照组患者药物不良反应的发生情况比较，无显著性差异。治疗后两组患者的肿瘤标志物水平均显著降低，研究组下降程度优于对照组，差异有统计学意义(P＜0.05)。研究组患者治疗后的功能状态评分显著高于对照组，且差异有统计学意义(P＜0.05) 。

结论：吉非替尼与恩度联合一线治疗 EGFR 突变阳性晚期肺腺癌，可有效提高临床疗效，降低相关肿瘤标志物水平，同时不会增加药物不良反应率，安全性较高，值得在晚期非小细胞肺癌的一线治疗中推广。

60. Metabolomic Markers of Colorectal Tumor With Different Clinicopathological Features

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Background: Colorectal cancer (CRC) is the result of complex interactions between the tumor's molecular profile and metabolites produced by its microenvironment. Despite recent studies identifying CRC molecular subtypes, a metabolite classification system is still lacking. We aimed to explore the distinct phenotypes and subtypes of CRC at the metabolite level. **Methods:** We conducted an untargeted metabolomics analysis of 51 paired tumor tissues and adjacent mucosa using ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry. Multivariate analysis including principal component analysis, orthogonal partial least squares discriminant analysis and heat maps, univariate analysis, and pathway analysis were used to identify potential metabolite phenotypes of CRC. Unsupervised consensus clustering was used to identify robust metabolite subtypes, and evaluated their clinical relevance. **Results:** A total of 173 metabolites (including nucleotides, carbohydrates, free fatty acids, and choline) were identified between CRC tumor tissue and adjacent mucosa. We found that lipid metabolism was closely related to the occurrence and progression of CRC. In particular, CRC tissues could be divided into three subtypes, and statistically significant correlations between different subtypes and clinical prognosis were observed. **Conclusions:** CRC tumor tissue exhibits distinct metabolite phenotypes. Metabolite differences between subtypes may provide a basis and direction for further clinical individualized treatment planning.

61. CXCL13 及其受体 CXCR5 在乳腺癌中的作用

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趋化因子是一类与功能相关的小分子分泌蛋白, 因其具有白细胞趋化性和细胞因子活性而被命名。根据半胱氨酸的数量和间距, 趋化因子被分为四种亚型: CC, CXC, C 和 CX3C 亚型。趋化因子通过与相应的 G 蛋白相连的跨膜受体相互作用而发挥对中性粒细胞、嗜酸性粒细胞、嗜碱性粒细胞、单核细胞、肥大细胞、树突状细胞(DC) 、自然杀伤(NK) 细胞和 T 淋巴细胞的强大趋化作用。CXCL13 为 CXC 亚家族的一员，是微环境中的一种炎症因子，在炎症性疾病和肿瘤的进展中起着至关重要的作用。 CXCR5 是 CXCL13 的受体，在胚胎发育、干细胞的迁移和各种免疫反应中发挥重要作用, 是许多生理和病理过程中指导细胞运动的中心因素。最近

发现肿瘤细胞的转移机制和白细胞的迁移相类似, 趋化因子 CXCL13 及其受体与肿瘤的生长、侵袭、转移和分泌密切相关, 实验表明 CXCR5 可能成为抑制肿瘤生长、转移的重要靶目标。乳腺癌是世界女性中最普遍的疾病。尽管在诊断、预防和治疗方面取得了重大进展，但由于分子异质性和复杂的生物学行为表现，预期的结果仍未实现。研究表明 CXCL13 与 CXCR5 的高表达与乳腺癌的预后不良密切相关。本文将对趋化因子 CXCL13 及其受体 CXCR5 在乳腺癌转移、进展中的作用以及与此相关的信号转导、调节因子进行综述。以期揭示其在乳腺癌发生、发展中的重要作用。

关键词：趋化因子、乳腺癌、CXCL13、CXCR5

62. A novel NGS-based approach for concurrent detection of mitochondrial DNA copy number and mutation

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Numerous studies have identified essential contributions of altered mitochondrial DNA (mtDNA) copy number and mutation in many common disorders including cancer. To date, capture-based next-generation sequencing (NGS) has been widely applied to detect mtDNA mutation, whereas lacks ability in assessing mtDNA copy number. Current strategy for quantifying mtDNA copy number mainly relies on quantitative PCR (qPCR), which is limited in degraded samples. Here, we developed a novel capture-based NGS approach using both mtDNA and nuclear DNA (nDNA) probes to capture target fragments, enabling simultaneous detection of mtDNA mutation and copy number in different sample types. We first evaluated the impacts of selecting reference genes on mtDNA copy number calculation, and finally selected 3 nuclear DNA fragment of 4000bp as internal reference for detection. Then, we verified the effective application of this approach in DNA samples of formalin-fixed, paraffin embedded (FFPE) specimens and body fluids, indicating the widespread applicability. Importantly, our approach exhibited more accurate and stable results in detecting mtDNA copy number compared with qPCR in degraded DNA samples. Moreover, our data indicated this approach had good reproducibility in detecting both mtDNA copy number and mutation among three sample types. Altogether, we have developed a versatile and cost-effective capture-based NGS approach for concurrent detection of mtDNA copy number and mutation, which can find numerous applications in research and diagnosis.

63. miR-29 家族在宫颈癌中的研究进展

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微小 RNA（miRNA/miR）是具有约 22 个核苷酸的小非编码 RNA 序列，主要通过靶向 mRNA 的 3'-非翻译区（3'-UTR）来调节转录或翻译的效率及稳定性，从而在多种肿瘤的发生和发展过程中发挥重要作用。近年来，多项研究报道 miR-29 家族在宫颈癌中可能发挥着类似抑癌基因的作用，抑制癌细胞的增殖、凋亡、侵袭及迁移等过程。本文就 miR-29 家族的生物学功能及其在宫颈癌发生、发展中的作用机制做一综述。

64. miR-194-5p 在肿瘤中研究的新进展

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微小 RNA（miRNA/miR）是具有约 22 个核苷酸的非编码小 RNA 序列，主要通过靶向 mRNA 的 3'-非翻译区（3'-UTR）来调控转录或翻译的效率及稳定性，从而在肿瘤的发生、发展过程中发挥重要作用。大量研究发现 miR-194-5p 在多种恶性肿瘤组织或血液中呈低表达，发挥着类似抑癌基因的作用，能改变癌细胞增殖、侵袭、迁移及化学抗性等生物学行为。本文就 miR-194-5p 在不同肿瘤中的作用及其作用机制加以阐述。

65. MiRNA-144 在宫颈癌中的研究进展

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全球范围内,宫颈癌的发病率和死亡率在女性恶性肿瘤中均居于第四位，严重威胁女性的健康，因此早期诊断治疗非常重要。微小 RNA（MicroRNA，miRNA）是一类长度约 21-25 个核苷酸的非编码内源性小分子 RNA，其主要通过调控靶基因的转录与翻译发挥其生物学功能。目前已有多项研究发现 miRNA-144 在宫颈癌中表达下调，促进宫颈癌的发生发展，有望成为宫颈癌早期诊断的生物标志物；也有研究证实其同时参与宫颈癌对放化疗敏感性的调控，有望成为宫颈癌潜在的治疗靶点。本文就 miRNA-144 的生物学功能及其在宫颈癌作用和分子机制做一综述。

66. 敲低锌指增强子结合蛋白 1（ZEB1）抑制胃癌细胞的增殖、侵袭和迁移

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[摘 要]目的 通过 RNA 靶向干扰降低人胃癌 BCG823 细胞中锌指增强子结合蛋白 1（ZEB1）基因表达, 观察 ZEB1 低表达对胃癌 BCG823 细胞的侵袭、迁移及增殖能力的影响，及相关基因 lncRNA HOTAIR、E-cadherin 表达情况。**方法** 用载体构建针对人 ZEB1 基因表达的干扰质粒 shZEB1，脂质体转染胃癌 BCG823 细胞后，经 G418 及有限稀释法筛选稳定转染细胞株。通过实时定量 PCR 和 Western blot 法检测 BCG823 细胞 ZEB1 mRNA 和蛋白水平，MTT 法检测其增殖能力，Transwell^{TM} 小室侵袭试验检测转染细胞侵袭能力、划痕试验检测细胞迁移能力，实时定量 PCR 检测 lncRNA HOTAIR、上皮钙黏素（E-cadherin）mRNA 水平。**结果** 成功构建干扰质粒 shZEB1，敲低 BCG823 细胞 ZEB1 水平后，BCG823 细胞的增殖、侵袭和迁移能力降低、lncRNA HOTAIR 水平降低、而 E-cadherin 表达增高。**结论** 用 RNA 干扰技术可靶向降低 BCG823 胃癌细胞 ZEB1 的水平，引起 lncRNA HOTAIR 水平及细胞增殖、侵袭、迁移力下降。

67. Circular RNA hsa_circ_0068871 regulates FGFR3 expression and activates STAT3 by targeting miR-181a-5p to promote bladder cancer progression

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Background: FGFR3 plays an important role in the development of bladder cancer (BCa). Hsa_circ_0068871 is a circRNA generated from several exons of FGFR3. However, the potential functional role of hsa_circ_0068871 in BCa remains largely unknown. Here we aim to evaluate the role of hsa_circ_0068871 in BCa.

Methods: We selected miR-181a-5p as the potential target miRNA of hsa_circ_0068871. The expression levels of hsa_circ_0068871 and miR-181a-5p were examined in BCa tissues and paired adjacent normal tissues by quantitative real-time PCR. To characterize the function of hsa_circ_0068871, BCa cell lines were stably infected with lentivirus targeting hsa_circ_0068871, followed by examinations of cell proliferation, migration and apoptosis. In addition, xenografts experiment in nude mice were performed to evaluate the effect of hsa_circ_0068871 in BCa. Biotinylated RNA probe pull-down assay, fluorescence in situ hybridization and luciferase reporter

assay were conducted to confirm the relationship between hsa_circ_0068871, miR-181a-5p and FGFR3.

Results: Hsa_circ_0068871 is over-expressed in BCa tissues and cell lines, whereas miR-181a-5p expression is repressed. Depletion of has_circ_0068871 or upregulation of miR-181a-5p inhibited the proliferation and migration of BCa cells in vitro and in vivo. Mechanistically, hsa_circ_0068871 upregulated FGFR3 expression and activated STAT3 by targeting miR-181a-5p to promote BCa progression.

Conclusions: Hsa_circ_0068871 regulates the miR-181a-5p/FGFR3 axis and activates STAT3 to promote BCa progression, and it may serve as a potential biomarker.

68. Exploration of the molecular characteristics of the tumor-immune interaction and the development of an individualized immune prognostic signature for neuroblastoma

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Neuroblastoma (NBL) exists in a complex tumor–immune microenvironment. Immune cell infiltration and tumor–immune molecules play a critical role in tumor development and significantly impact the prognosis of patients. However, the molecular characteristics describing the NBL–immune interaction and their prognostic potential have yet to be investigated systematically. We first employed multiple machine learning algorithms, such as Gene Sets Enrichment Analysis and cell type identification by estimating relative subsets of RNA transcripts, to identify immunophenotypes and immunological characteristics in NBL patient data from public databases and then investigated the prognostic potential and regulatory networks of identified immune-related genes involved in the NBL–immune interaction. The immunity signature combining nine immunity genes was confirmed as more effective for individual risk stratification and survival outcome prediction in NBL patients than common clinical characteristics (area under the curve [AUC] = 0.819, C-index = 0.718, $p < .001$). A mechanistic exploration revealed the regulatory network of molecules involved in the NBL–immune interaction. These immune molecules were also discovered to possess a significant correlation with plasma cell infiltration, MYCN status, and the level of chemokines and macrophage-related molecules ($p < .001$). A nomogram was constructed based on the immune signature and clinical characteristics, which showed high potential for prognosis prediction (AUC = 0.856, C-index = 0.755, $p < .001$). We systematically elucidated the complex regulatory mechanisms and characteristics of the molecules involved in the NBL–immune interaction and their prognostic potential, which may have important

implications for further understanding the molecular mechanism of the NBL–immune interaction and identifying high-risk NBL patients to guide clinical treatment.

69. GPAA1 promotes gastric cancer progression via upregulation of GPI-anchored protein and enhancement of ERBB signalling pathway

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Background: Gastric cancer is one of the most malignant tumors with wide prevalence in China, which is regulated by aberrantly overexpressed oncogenes. However, the existed therapies are too limited to meet the unmet needs of patients, so it is urgent to identify more therapeutic targets and explore the underlying mechanism. GPAA1 has been found to upregulated in some cancers, but its function and mechanism remains largely unknown.

Methods: Data mining was conducted to figure out the reason of overexpression and expression pattern in tumor and adjacent tissues of GPAA1. In vitro and in vivo experiments evaluating proliferation and metastasis were performed using cells stably deletion or overexpression of GPAA1. Tissue microarray established by Ren Ji hospital was utilized to analyze expression profile of GPAA1 and its correlation with prognosis. Western blot, In Situ Proximity Ligation Assay, and Co-immunoprecipitation (Co-IP) were conducted to uncover the mechanism referring to GPAA1 in gastric cancer.

Findings: GPAA1 was a remarkably upregulated oncogene in gastric cancer due to its amplification. The overexpression of GPAA1 was confirmed by specimens of Ren Ji cohort and associated with expression of ERBB2, predicting unsatisfying outcomes of patients. Aberrantly upregulated GPAA1 dramatically contributed to growth and metastasis of cancer in vitro and in vivo studies. Mechanistically, GPAA1 enhanced the amount of metastasis-associated GPI-anchored proteins to strengthen tumor metastasis, meanwhile, it also intensified lipid raft which consequently promotes interaction between EGFR and ERBB2, as well as the downstream proliferation-promotive signaling. Interpretation: GPAA1 facilitates expression of cancer-related GPI-anchored proteins and provides a more powerful platform, lipid raft, to promote EGFR-ERBB2 dimerization, which contributes to tumor growth and metastasis, further, cancer progression. GPAA1 could be a promising diagnostic biomarker and therapeutic target for gastric cancer.

70. Sarcopenia as a prognostic indicator for Chinese renal cell carcinoma patients undergoing nephrectomy

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Background We conducted a multicenter clinical study to investigate the effect of sarcopenia on survival of the Chinese population after nephrectomy for renal cell carcinoma (RCC).

Patients and methods We collected clinical information of 443 patients who underwent nephrectomy between 2014 and 2019. Lumbar skeletal muscle index (SMI) and total psoas index (TPI) measured by preoperative computed tomography were used to assess sarcopenia. Kaplan-Meier survival curves were used to assess overall survival (OS) and cancer-specific survival (CSS) of the patients. Cox regression risk models were used to evaluate the relationship of sarcopenia with OS and CSS.

Results 97 (21.9%) patients were assessed as sarcopenia based on TPI and 157 (35.4%) patients were assessed as sarcopenia based on SMI. Patients with sarcopenia were older, lower body mass index (BMI), and shorter survival times compared with their counterparts. Patients with sarcopenia had lower 3- and 5-year OS and CSS than patients without sarcopenia. There were positive correlations between TPI, SMI and BMI (All $P < .001$). Multivariate Cox regression analysis showed that when TPI or SMI was used to assess sarcopenia, patients with sarcopenia had a higher risk of OS (TPI: HR = 2.755; 95% CI 1.593–4.764; $P < .001$; SMI: HR = 2.885; 95% CI 1.658–5.018; $P < .001$) and CSS (TPI: HR = 2.198; 95% CI 1.082–4.463; $P = .029$; SMI: HR = 2.584; 95% CI 1.294–5.157; $P = .007$). In addition, there were no statistical differences between the TPI and SMI measures in assessing sarcopenia for predicting OS ($P = .406$) and CSS ($P = .475$).

Conclusion In this large multicenter study of patients undergoing nephrectomy in the Chinese RCC population, sarcopenia was an independent predictor of OS and CSS.

71. Sarcopenia predicts prognosis of bladder cancer patients after radical cystectomy: a study based on the Chinese population

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This study aimed to determine the potential utility of sarcopenia estimated by the psoas cross-sectional area as a prognostic factor in patients with bladder cancer (BCa) after radical cystectomy in the Chinese population. Patients with BCa who underwent radical cystectomy from 2009 to 2018 were analyzed retrospectively. Sarcopenia was evaluated using the total psoas index, which was calculated by measuring the cross-sectional area of the psoas muscle of the third lumbar vertebra, and normalized to the patient's height. The Kaplan-Meier survival curves were used to calculate the overall survival

(OS) and disease-free survival (DFS). The prognostic value of sarcopenia was analyzed by using Cox regression model, and a nomogram of BCa based on sarcopenia was generated by R software. Of the 200 patients, 67 (33.5%) were identified as sarcopenic. Sarcopenia was associated with an increased hospital time (32.88 days vs 29.19 days; p = 0.011), 3-year mortality (41.8% vs 24.8%; p = 0.044), and 5-year mortality (44.8% vs 30.8%; p = 0.001). Sarcopenia was related to the poor prognosis of patients with BCa. Univariate and multivariate cox regression analysis showed that sarcopenia was an independent predictor of OS and DFS, and the nomogram based on sarcopenia had better accuracy and discrimination (area under the curve (AUC): OS = 0.756, CSS = 0.784). Sarcopenia can be used as an independent predictor of OS and DFS for radical cystectomy BCa patients, and the nomogram was a reliable model for predicting the prognosis after radical cystectomy.

72. Knockdown of Lumican inhibits proliferation and migration of bladder cancer

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Lumican (LUM) is differentially expressed between normal and cancer tissues. The purpose of this study was to investigate the role of LUM in the proliferation and migration of bladder cancer (BCa) cells. Our study included 97 cases of BCa diagnosis from our hospital between June 2013 and June 2016. The expression of LUM was analyzed by immunohistochemistry and Western blot. To characterize the function of LUM, BCa cells were stably infected with a lentivirus against LUM, and cell proliferation, migration and cell cycle were investigated. In addition, xenograft experiments were performed in nude mice to evaluate the role of LUM in BCa. Our results showed that LUM was overexpressed in BCa tissues and cell lines in comparison to normal tissues. LUM expression was related to pathological type, T stage and N stage ($p < 0.05$). In addition, depletion of LUM inhibited the proliferation and migration of BCa cells by inactivating MAPK signaling. In conclusion, LUM promotes the proliferation and migration of BCa cells and may serve as a potential therapeutic target for BCa.

73. Diagnostic and Prognostic Values of Serum EpCAM, TGM2, and HE4 Levels in Endometrial Cancer

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Objectives: This study aims to investigate the diagnostic and prognostic values of EpCAM, TGM2,

and HE4 in endometrial cancer (EC).

Methods: In this study, 42 patients diagnosed with EC (EC group), 41patients diagnosed with myoma (benign group), and 43 healthy women (healthy group), who applied to Affiliated Hospital of Xuzhou Medical University between March 2018 - September 2019 were recruited. Serum EpCAM, TGM2, and IL-33 levels were measured by ELISA, while serum HE4 and CA-125 levels were measured by ECLIA. The serum markers listed above were also measured in12 paired pre- and post- operative EC patients. The diagnostic and prognostic values of serum markers were analyzed.

Results: The serum EpCAM, TGM2, HE4, CA-125, and IL-33 levels were significantly higher in the EC group. The sensitivity and specificity of combined detection of EpCAM and HE4 was 92.86 and 69.05%, which were significantly higher than using a single marker o rother combinations.Among these markers,serum HE4 levels were significantly higher in patients with myometrial invasion, metastasis, and lymphovascular invasion($p = 0.006$, $p = 0.0004$, $p = 0.0004$, respectively). And serum TGM2 levels were significantly decreased in post-operative than that of pre-operative EC patients ($p < 0.001$).

Conclusions: The combination of EpCAM and HE4 showed the highest specificity and sensitivity in the diagnosis of EC. HE4 was successful in the detection of high-risk individuals preoperatively. Additionally, TGM2 might be a prognostic factor for EC.

74. 基于代谢基因组特征预测喉癌患者的预后

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目的:尽管喉癌治疗(包括外科治疗和放化疗)取得了进展，但喉癌的生存率仍然很低。代谢基因在不同肿瘤的诊断和预后提供了新的视野，但是目前缺乏代谢基因评估喉癌的研究。

方法:通过生物信息学分析从癌症基因组图谱（TCGA）和基因表达综合数据库(GEO)的原始数据中提取差异表达的代谢基因。共有 111 例喉癌患者和 12 对正常样本，以及临床病理数据(年龄、性别和 AJCC 分期)作为训练组。对于 GEO，无进展生存作为终点事件，总共选择了 109 个样本(包括 75 个非复发性和 34 个复发性喉癌)作为验证队列；进行单因素 Cox 回归和 LASSO 分析，以确定与总生存率显著相关的代谢基因。使用 ROC 曲线评估候选基因的预测喉癌预后效能。进行基因集富集分析(GSEA)以探索高风险组和低风险组的重要信号通路和潜在影响预后的机制。

结果:与临床变量相比，13 个代谢基因特征（PSP、SMS、EPHX2、SHMT1、POLD1、ACOX3、FTH1、ASNS、CA9、MTHFD2、PLCG1、GPT 和 DNMT)）评分显示出更好的预测

喉癌预后的诊断效能，并且高危组的患者预后明显差于低危组。ROC 显示 5 年和 3 年生存期预后的诊断价值分别为 0.929 和 0.899，优于用临床病理模型。在 GEO 验证队列中获得的一致结果。表明该基因特征可以区分有无复发的喉癌患者。用 TCGA 数据对 AJCC 分期的风险评分进行分析，风险评分与临床 T 分期(P=0.035)和 N 分期(P=0.042)显著相关。但在 M 期无显著差异(p = 0.915)。GSEA 显示在高危患者中，五种信号通路显著上调，包括淀粉、蔗糖、脂肪酸、β 丙氨酸、n-聚糖生物合成、氨基糖和核苷酸糖代谢途径。

结论: 本研究首次报道这 13 个代谢基因可作为喉癌的独立预后生物标志物，为喉癌的个体化治疗提供重要的预后信息和预测。

75. The Prognostic value of 4.1 mRNA Expression in Non-Small-Cell Lung Cancer

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ABSTRACT

Background: The mechanism of 4.1 family in human cancer has not been elucidated. In this study we investigate the value as a prognostic factor of mRNA expression of 4.1 family in NSCLC

Methods: A survival analysis was carried out through the Kaplan–Meier plotter (KM plotter) database. KM's method was used to estimate the prognostic value of 4.1 mRNA Expression in Non-Small-Cell Lung Cancer.

Results: Expression of four members are linked to overall survival (OS) in NSCLC patients, among which 4.1G, 4.1B, 4.1R are concerned with first progression (FP), and 4.1G, 4.1R are correlated with post progression survival (PPS) besides. Only 4.1B expression is associated with OS in squamous cell carcinoma, as four members with OS in adenocarcinoma. What's more, 4.1G, 4.1N high mRNA are linked to better FP in adenocarcinoma, and 4.1R overexpression is linked to better PPS. The expression of 4.1G is associated with the prognosis in female, whereas 4.1R in male. Furthermore, 4.1G and 4.1B play as protective roles in non-smoking populations, while 4.1N overexpression is related to poorer PPS. All the four family members are associated with early stage in NSCLC. 4.1G, 4.1B and 4.1R are closely related to surgical resection, yet 4.1N has no prognostic significance in patients receiving treatments. However, the results need to be verified in clinical trials further.

Conclusion: Our results offer new opinion about the prognostic value of 4.1 protein family in NSCLC, which may contribute to the development of new therapy for NSCLC.

76. Analyses of expressions and prognostic values of Polo-like kinases in non-small cell lung cancer

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Background Despite great advances in its early diagnosis and treatment, lung cancer is still an intractable disease and the second leading cause of cancer-related deaths and morbidity in the world. The family of Polo-like kinases (PLKs) consists of five serine/threonine kinases, which have been reported to participate in various human diseases. However, the expression and prognostic value of each PLK in human lung cancer have not been fully understood. This study analyzed mRNA expression and prognostic value of different PLKs in human non-small cell lung cancer (NSCLC).

Methods First, mRNA expression of PLKs in patients with NSCLC from the Oncomine and the Gene Expression Profiling Interactive Analysis (GEPIA) database was investigated. Then, a Kaplan–Meier plotter was employed for survival analysis. The sequence alteration for PLKs was analyzed using The Cancer Genome Atlas (TCGA) and the cBioPortal database. Additionally, we analyzed the association among different PLKs using the LinkedOmics database. Finally, the enrichment analysis of PLKs was achieved using the DAVID database.

Results The mRNA expression levels of PLK1 and PLK4 were significantly overexpressed, while mRNA expression level of PLK3 was underexpressed in patients with NSCLC. mRNA expressions of PLK1 and PLK4 were significantly and positively related to the tumor stage of NSCLC. Increased expressions of PLK1, PLK4, and PLK5 and decreased expression of PLK2 were attributed to limited overall survival time in NSCLC. PLK1 was positively correlated with PLK4 via the LinkedOmics database.

Conclusions PLKs are relevant targets for NSCLC treatment, especially PLK1 and PLK4.

Keywords Lung cancer, Polo-like kinases, Prognosis, Oncomine, Kaplan–Meier plotter

77. Signaling pathways and clinical application of RASSF1A and SHOX2 in lung cancer

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Background: An increasing number of studies have focused on the early diagnostic value of the methylation of RASSF1A and SHOX2 in lung cancer. However, the intricate cellular events related to RASSF1A and SHOX2 in lung cancer are still a mystery. For researchers and clinicians aiming to

more profoundly understand the diagnostic value of methylated RASSF1A and SHOX2 in lung cancer, this review will provide deeper insights into the molecular events of RASSF1A and SHOX2 in lung cancer. **Methodology:** We searched for relevant publications in the PubMed and Google Scholar databases using the keywords "RASSF1A", "SHOX2" and "lung cancer" etc. First, we reviewed the RASSF1A and SHOX2 genes, from their family structures to the functions of their basic structural domains. Then we mainly focused on the roles of RASSF1A and SHOX2 in lung cancer, especially on their molecular events in recent decades. Finally, we compared the value of measuring RASSF1A and SHOX2 gene methylation with that of the common methods for the diagnosis of lung cancer patients. **Results:** The RASSF1A and SHOX2 genes were confirmed to be regulators or effectors of multiple cancer signaling pathways, driving tumorigenesis and lung cancer progression. The detection of RASSF1A and SHOX2 gene methylation has higher sensitivity and specificity than other commonly used methods for diagnosing lung cancer, especially in the early stage. **Conclusions:** The RASSF1A and SHOX2 genes are critical for the processes of tumorigenesis, development, metastasis, drug resistance, and recurrence in lung cancer. The combined detection of RASSF1A and SHOX2 gene methylation was identified as an excellent method for the screening and surveillance of lung cancer that exhibits high sensitivity and specificity. **Keywords:** Clinical application; Lung cancer; RASSF1A; SHOX2; Signaling pathways.

78. miR-23c prevents hepatocellular carcinoma progression through targeting METTL3 to inhibit m6A-mediated stabilization of FSTL5

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METTL3-mediated m6A modification has been reported to regulate various cancer development, However, the study focused on miRNA’s regulatory effect of m6A modification on hepatocellular carcinoma (HCC) progression is still limited. Prognosis of indicated patients’ cohort were analyzed by using TCGA datasets. Lentivirus was used to overexpress or knockdown METTL3 in cells. Clone formation assay, and transwell assay were used to investigate the change of the cancer cell proliferation, invasion, and migration. Luciferase reporter assay was used to verify the potential binding between miRNA and mRNA. Immunochemical (IHC) staining was used to detect the histopathological changes of tumor tissues. Methylated RNA immunoprecipitation was used to identify the RNA m^6A level. We further established the tumor transplantation model in mice to investigate the change of tumor progression. We found that downregulated miR-23c indicates poor prognosis in HCC. Clone formation and transwell assay revealed that inhibition of miR-23c promotes HCC cancer cell proliferation, migration, and invasion. Luciferase reporter assay showed that miR-

23c targets to METTL3 directly. In vitro and in vivo studies showed that miR-23c inhibits HCC cancer cell proliferation, migration, and invasion through downregulating METTL3. YTHDF2 promoted the FSTL5 mRNA degradation through and m6A-dependent manner. We identified the downregulated miR-23c in HCC, and reported the crosstalk of miRNA with the m6A-mediated protein expression. We herein identify the m6A-promoted FSTL5 stability mediated by YTHDF2. The miR-23c/METTL3/YTHDF2/FSTL5 axis might provide novel insight for HCC-targeted therapy.

79. 基于生物信息学分析 RANBP17 在胶质母细胞瘤中的表达及功能

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目的 分析 RAN 结合蛋白 17（RANBP17）在胶质母细胞瘤（GBM）中的表达及其与临床特征和预后的相关性，进一步探讨 RANBP17 的生物学作用及功能。**方法** 通过 Oncomine、GEPIA、UALCAN 等 3 个数据库分析和验证 GBM 组织中的 RANBP17 mRNA 的表达情况。利用 LinkedOmics、PrognoScan、PROGgeneV2 等数据库分析 RANBP17 的表达与 GBM 患者预后之间的关系。利用 LinkedOmics 数据库筛选出 RANBP17 表达相关基因，并利用 DAVID 数据库和 R 语言对 RANBP17 表达相关基因进行 GO 和 KEGG 功能富集分析。利用 String 数据库和 Cytoscape 软件对 RANBP17 表达相关基因进行 PPI 网络构建和 hub 基因筛选，并利用 Uniprot 数据库进行功能分析。**结果** GBM 中 RANBP17 表达水平明显低于正常脑组织（P<0.05）,RANBP17 高表达患者总生存期明显高于低表达患者（P<0.05），LinkedOmics 数据库筛选出 RANBP17 表达相关基因，GO 分析显示 RANBP17 表达相关基因主要参与信号转导、炎症反应、凋亡过程负调控、细胞增殖正调控等生物过程，主要参与了细胞质、细胞外的外泌体、细胞膜、细胞质基质等细胞组成；主要具有蛋白结合、蛋白同源二聚化活性、钙离子结合等分子功能。KEGG 通路主要富集在 MAPK、核糖体、癌症的转录失调、病灶的粘附等信号通路。PPI 网络分析显示 C3、GNB2、LPAR3 等基因与 RANBP17 有潜在的相互作用（P< 0.05）。**结论** 数据挖掘有效地揭示了 GBM 中 RANBP17 表达及其与临床特征和预后的相关性，同时揭示了其潜在功能的信息，RANBP17 可能作用于 C3，GNB2，LPAR3 等基因，影响 GBM 生物学功能，发挥抑癌基因的作用，为进一步研究 RANBP17 在 GBM 发生发展中的作用机制奠定基础。 **关键词：**RAN 结合蛋白 17；胶质母细胞瘤；生物信息学；作用；调控机制。

80. Circulating long non-coding RNA HULC and ZNFX1-AS1 are potential biomarkers for patients with gastric cancer

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Background LncRNA ZNFX1-AS1 (ZFAS1) is a newly discovered long non-coding RNA (LncRNA), but its value in the diagnosis of gastric cancer is unclear. The aim of this study was to investigate the potential role of ZFAS1 in gastric cancer and to evaluate the clinical significance of ZFAS1 as a biomarker for gastric cancer screening.

Methods Quantitative real-time polymerase chain reaction (qRT-PCR) was used to screen for gastric cancer-associated LncRNAs in gastric cancer patients, gastric stromal tumor patients, gastritis or gastric ulcer patients, and healthy controls. The correlation between ZFAS1 expression and clinicopathological features was analyzed. The biological effects of ZFAS1 on proliferation, migration and invasion of gastric cancer cells were studied by MTT assay, colony formation assay and transwell migration assay. The potential mechanism of ZFAS1 was demonstrated using ELISA and qRT-PCR. The relationship between ZFAS1 and tumorigenesis was demonstrated using in vivo tumor formation assays.

Results The expression of LncRNA ZFAS1 in plasma of preoperative patients with gastric cancer was significantly higher than that of the other 4 groups. Increased expression of ZFAS1 was significantly associated with lymph node metastasis, TNM staging, and poor prognosis. ZFAS1 knockdown inhibited the proliferation, migration and invasion of gastric cancer cells. In contrast, ZFAS1 overexpression promoted proliferation, migration and invasion of gastric cancer cells. LIN28 and CAPRIN1 are key downstream mediators of ZFAS1 in gastric cancer cells. ZFAS1 overexpression promoted the growth of gastric cancer cells in vivo. Meanwhile, ZFAS1 knockdown expression inhibited the growth of gastric cancer cells in vivo.

Conclusion LncRNA ZFAS1 promoted invasion and proliferation of gastric cancer cells by modulating LIN28 and CAPRIN1, suggesting that ZFAS1 can be used as a potential biomarker for the diagnosis and prognosis of gastric cancer.

81. Long non-coding RNA FOXD1-AS1 promotes the progression and glycolysis of nasopharyngeal carcinoma by sustaining FOXD1 expression

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Long non-coding RNAs (lncRNAs) play a vital role in the progression of several cancers, including nasopharyngeal carcinoma (NPC). However, the mechanism of lncRNA involvement in the progression of NPC remains to be elucidated. Hence, we conducted in vivo and in vitro experiments to determine the molecular mechanism of FOXD1-AS1. We found that FOXD1-AS1 was over-expressed in NPC cells and tissues, and was significantly associated with poor survival rate in patients with NPC. We also found that FOXD1-AS1 promotes cellular proliferation, migration, invasion, and glycolysis, and inhibits apoptosis by upregulating the expression of FOXD1. Furthermore, FOXD1 could transcriptionally up-regulate the expression of key glycolytic genes to promote the glycolysis levels of NPC. The identified FOXD1-AS1 may serve as a potential prognostic biomarker and therapeutic target for patients with NPC.

82. Long noncoding RNA AFAP1-AS1 is a critical regulator of nasopharyngeal carcinoma tumorigenicity

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Background: The long noncoding RNA Actin filament associated protein 1 antisense RNA1 (AFAP1-AS1) is a critical player in various cancers. However, the clinical value and functional mechanisms of AFAP1-AS1 during the tumorigenicity of nasopharyngeal carcinoma (NPC) remain unclear. Here, we investigated the clinical application and potential molecular mechanisms of AFAP1-AS1 in NPC tumorigenesis and progression.

Methods: The expression level of AFAP1-AS1 was determined by qRT-PCR in 10 paired fresh human NPC tissues and adjacent normal tissues. RNAscope was performed on 100 paired paraffin-embedded NPC and adjacent nontumor specimens. The biological functions of AFAP1-AS1 were assessed by in vitro and in vivo functional experiments. RNA-protein pull-down assays were performed to detect and identify the AFAP1-AS1-interacting protein KAT2B. Protein-RNA immunoprecipitation (RIP) assays were conducted to examine the interaction of AFAP1-AS1 and KAT2B. Chromatin immunoprecipitation (ChIP) and luciferase analyses were utilized to identify the binding site of transcription intermediary factor 1 alpha (TIF1α) and H3K14ac on the RBM3 promoter.

Results: AFAP1-AS1 is upregulated in NPC and is a poor prognostic indicator for survival in NPC patients. AFAP1-AS1 was required for NPC proliferation in vitro and tumorigenicity in vivo. Mechanistic investigations suggested that AFAP1-AS1 binds to KAT2B and promotes acetyltransferase activation at two residues (E570/D610). KAT2B further promotes H3K14 acetylation and protein binding to the bromo domainof TIF1α. Consequently, TIF1α acts as a nuclear transcriptional coactivator of RBM3 transcription, leading to YAP mRNA stabilization and enhanced NPC tumorigenicity.

Conclusions: Our findings suggest that AFAP1-AS1 functions as an oncogenic biomarker and promotes NPC tumorigenicity through enhanced KAT2B acetyltransferase activation and YAP mRNA stabilization.

83. The methyltransferase METTL18 is a critical regulator of breast cancer metastasis

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Background: Histone methyltransferases are critical chromatin regulators. Emerging evidence suggests that lysine methylation can act as a key modifier in cancer. However, the mechanism and biological significance are unclear. Here, we identified methyltransferase like 18 (METTL18) as a critical regulator of breast cancer, where it is highly expressed.

Methods: The expression level of METTL18 was determined by The Cancer Genome Atlas (TCGA) dataset and the METABRIC microarray dataset. Immunohistochemical staining was performed on matched metastatic lymph node and the primary tumor of 100 breast cancer patients, respectively. The biological functions of METTL18 were assessed by in vitro and in vivo functional experiments. Immunoprecipitation assays were performed to detect and identify the METTL18-interacting protein SNIP1. Chromatin immunoprecipitation (ChIP) and luciferase analyses were utilized to identify the binding site of transcription c-MYC on the YAP promoter.

Resluts: METTL18 upregulation was associated with reduced survival in breast cancer patients. RNA sequencing analysis revealed that METTL18 knockdown was accompanied by inhibition of the YAP signaling pathway. In breast cancer cell lines, METTL18 depletion inhibited metastasis both in vitro and in vivo. Mass spectrometry analysis identified a METTL18-binding protein: smad nuclear interacting protein 1 (SNIP1). Mechanistic investigations demonstrated that SNIP1 is associated with and methylated by METTL18 at a lysine residue (K301). Furthermore, we observed that METTL18-dependent methylation of SNIP1 recruits its coactivator, lysine acetyltransferase 2A (KAT2A), to promote c-MYC binding to the promoters of its target genes. This binding led to activated YAP transcription and subsequently triggered YAP downstream signaling, thereby enhancing breast cancer

cell metastasis. Reexpression of wild type (WT) SNIP1 combined with METTL18, but not SNIP1 with a mutation at amino acid (aa) 301, Lys-to-Arg (K301R), could rescue the METTL18 depletion-mediated impairment of c-MYC-chromatin interaction by recruiting KAT2A, thereby resulting in restored YAP transcription and breast cancer metastasis. Finally, METTL18 depletion renders metastatic tumors hypersensitive to the drug that targets YAP signaling.

Conclusions: Our results define a critical role for METTL18 in breast cancer metastasis and establish METTL18 as a novel target in breast cancer.

84. The long non-coding RNA TMPO-AS1 promotes bladder cancer growth and progression via OTUB1-induced E2F1 deubiquitination

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Objectives

Increasing evidence indicates long non-coding RNAs (lncRNAs) play crucial roles in cancer tumorigenesis and progression. TMPO antisense RNA 1 (TMPO-AS1) has been found to be involved in several cancers by acting as an competing endogenous RNA. However, the potential roles of TMPO-AS1 interacting with proteins in bladder cancer (BC) remain poorly understood.

Materials and Methods The lncRNA TMPO-AS1 expression was evaluated by online databases and was validated by qRT-PCR. Loss- and gain-of- function assays were performed to determine the biological functions of TMPO-AS1 in BC carcinogenesis. Bioinformatic analysis and mechanism experiments (luciferase reporter, chromatin immunoprecipitation, western blotting, RNA pull-down, and RNA immunoprecipitation assays) were conducted to explore the upstream and downstream molecular mechanisms of TMPO-AS1.

Results TMPO-AS1 is upregulated in BC and is associated with poor prognosis of BC patients. Functional experiments demonstrated that TMPO-AS1 promotes bladder cancer cell proliferation, migration, invasion, and inhibits cell apoptosis in vivo and in vitro. Mechanically, E2F1 is responsible for the TMPO-AS1 upregulation. Overexpression of TMPO-AS1 facilitates the interaction of E2F1 with OTUB1, leads to E2F1 deubiquitination and stabilization, and finally promotes BC malignant phenotypes, which indicates that TMPO-AS1/E2F1 forms a positive feedback loop in BC.

Conclusions TMPO-AS1/E2F1 positive feedback loop is of importance for the promotion of BC malignant phenotypes and should be considered in the quest for new BC therapeutic options.

85. Construction of a novel pretreatment biopsies-based immune signature for prediction of pathological response and outcomes in esophageal squamous cell carcinoma with neoadjuvant chemoradiotherapy: a multicenter retrospective study

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Background: Current strategies are insufficient to predict pathologically complete response (pCR) for esophageal squamous cell carcinomas (ESCCs) before treatment. Here, we aim to develop a novel long non-coding RNA (lncRNA) signature for pCR and outcome prediction of ESCCs through a multicenter analysis for a Chinese population.

Methods: Differentially expressed lncRNAs (DELs) between pCRs and less than pCR (<pCR) in the pretreated cancer biopsies were identified from 28 cases in Guangzhou cohort and verified from 30 cases in Beijing discovery cohort. Then a prediction model was built through Fisher's linear discriminant analysis (FLDA) of 67 cases in Beijing training cohort. Then an internal cohort and an integrated external cohort (Zhengzhou and Anyang cohorts) were used to validate the predictive accuracy. The prognostic value of this signature was also evaluated.

Results: Twelve DELs were identified from Guangzhou cohort and six lncRNAs were verified. Then, a classifier of three lncRNAs (SCAT1, PRKAG2-AS1, and FLG-AS1) was established and achieved a high accuracy with an area under the receiver operating characteristic curve (AUC) of 0.952 in the training cohort, which was well validated in the internal validation cohort and external cohort with the AUCs of 0.856 and 0.817, respectively. Furthermore, the predictive score was identified as the only independent predictor for pCR. Patients with high discriminant score showed a significantly longer overall and relapse-free survival ($P < 0.05$).

Conclusions: We developed the first and applicable three-lncRNA signature of pCR and outcome prediction, which is robust and reproducible in multicenter cohorts for ESCCs with nCRT.

Keywords: esophageal squamous cell carcinoma; lncRNAs; neoadjuvant chemoradiotherapy; pathologically complete response; individualized medicine.

86. The high expression of MTH1 and NUDT5 promotes tumor metastasis and indicates a poor prognosis in patients with non-small-cell lung cancer

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MutT Homolog 1 (MTH1) is a mammalian 8-oxodGTPase for sanitizing oxidative damage to the nucleotide pool. Nudix type 5 (NUDT5) also sanitizes 8-oxodGDP in the nucleotide pool. The role of MTH1 and NUDT5 in non-small-cell lung cancer (NSCLC) progression and metastasis remains unclear. In the present study, we reported that MTH1 and NUDT5 were upregulated in NSCLC cell lines and tissues, and higher levels of MTH1 or NUDT5 were associated with tumor metastasis and a poor prognosis in patients with NSCLC. Their suppression also restrained tumor growth and lung metastasis in vivo and significantly inhibited NSCLC cell migration, invasion, cell proliferation and cell cycle progression while promoting apoptosis in vitro. The opposite effects were observed in vitro following MTH1 or NUDT5 rescue. In addition, the upregulation of MTH1 or NUDT5 enhanced the MAPK pathway and PI3K/AKT activity. Furthermore, MTH1 and NUDT5 induce epithelial–mesenchymal transition both in vitro and in vivo. These results highlight the essential role of MTH1 and NUDT5 in NSCLC tumor tumorigenesis and metastasis as well as their functions as valuable markers of the NSCLC prognosis and potential therapeutic targets.

87. Correlation Analysis of Clinical Parameters of Luminal A/B Subtype in Invasive Breast Cancer and Prognostic significance of p53 expression in triple negative breast cancer

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Objective： To explore the correlation between age distribution and clinical parameters of four different molecular subtypes of breast cancer. Furthermore, we aimed to evaluate the association of p53 and Ki67 overexpression in triple negative breast cancer with various prognostic parameters.

Methods: The expressions of ER, PR, Her-2, tumor cell proliferation-associated nuclear antigen and p53 were detected by immunohistochemistry. The tumor size, regional lymph node and distant

metastasis and pathological TNM staging were analyzed statistically in all patients.

Results： There were statistically significant differences in vascular cancer embolus and histological grade between the breast cancer patients with different molecular subtypes (P<0.01). Among the 3 age groups of the molecular subtypes of breast cancer, the incidence was most common between 40 and 60 years old (67.05%). In addition, the positive rate of p53 and Ki67 in triple negative breast cancer group is higher than those in non-triple negative breast cancer, and the difference is statistically significant（P<0.05）.

Conclusion： The age distribution in breast cancer Luminal A, Luminal B (HER-2+) and the triple negative breast cancer is 40-60 years old. In triple negative breast cancer, the positive rates of P53 and Ki67 are higher which has statistical significance with various clinical reference values. Moreover, there are statistical significance in tumor thrombus, histological grade and tumor diameter in vessels, which can provide the theoretical basis for the clinical diagnosis.

88. Targeting SKA3 suppresses the proliferation and chemoresistance of laryngeal squamous cell carcinoma via impairing PLK1–AKT axis-mediated glycolysis

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Spindle and kinetochore-associated complex subunit 3 (SKA3) is a well-known regulator of chromosome separation and cell division, which plays an important role in cell proliferation. However, the mechanism of SKA3 regulating tumor proliferation via reprogramming metabolism is unknown. Here, SKA3 is identified as an oncogene in laryngeal squamous cell carcinoma (LSCC), and high levels of SKA3 are closely associated with malignant progression and poor prognosis. In vitro and in

vivo experiments demonstrate that SKA3 promotes LSCC cell proliferation and chemoresistance through a novel role of reprogramming glycolytic metabolism. Further studies reveal the downstream mechanisms of SKA3, which can bind and stabilize polo-like kinase 1 (PLK1) protein via suppressing ubiquitin-mediated degradation. The accumulation of PLK1 activates AKT and thus upregulates glycolytic enzymes HK2, PFKFB3, and PDK1, resulting in enhancement of glycolysis. Furthermore, our data reveal that phosphorylation at Thr360 of SKA3 is critical for its binding to PLK1 and the increase in glycolysis. Collectively, the novel oncogenic signal axis "SKA3-PLK1-AKT" plays a critical role in the glycolysis of LSCC. SKA3 may serve as a prognostic biomarker and therapeutic target, providing a potential strategy for proliferation inhibition and chemosensitization in tumors, especially for LSCC patients with PLK1 inhibitor resistance.

89. 荧光定量 PCR 法检测 EGFR 突变的缺陷：一例 EGFR 罕见突变（L747P）病例报道及文献复习

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研究背景：EGFR 基因突变是非小细胞肺癌选择个体化治疗方案的必检分子靶标之一，其中 EGFR 基因 19 外显子缺失突变阳性是对一代酪氨酸激酶抑制剂（TKI）敏感的经典标志物。对于非小细胞肺癌的初诊患者，目前在临床上应用最广泛的 EGFR 突变检测方法是基于荧光定量 PCR 的方法。

研究方法及结果：本文报道一例分别用两种基于荧光定量 PCR 法的试剂盒（ARMS 法及 Rotor-Gene 法）检测均显示 EGFR 19 外显子缺失突变阳性的病例，经一代 TKI（凯美纳）治疗 2 个月后发生淋巴结转移，再次用高通量测序法（NGS）检测原发灶和转移灶，显示 EGFR 的实际突变方式为 L747P (2239-2240 TT>CC)。这个突变位点和方式不包括在上述两个荧光定量 PCR 法试剂盒的检测位点中，但检测结果却均显示为阳性，分析原因可能是 L747P 与试剂盒的某个检测位点序列类似，导致引物错配产生假阳性结果。该突变位点在有限的文献个案报道中显示对一代 TKI 原发耐药，而对二代 TKI 敏感。本文报道的病例改用二代 TKI（阿法替尼）治疗后，目前已获得 16 个月的无进展生存期并在持续治疗中。

研究结论：L747P (2239-2240 TT>CC)是一个罕见的 EGFR 基因 19 外显子突变位点，且为一代 TKI 原发耐药位点，现有的荧光定量 PCR 检测试剂盒会将该突变误检为 EGFR 基因 19 外显子缺失阳性，误导临床治疗方案的选择。随着 NGS 技术在临床的广泛应用，会有更多的罕见突变位点被发现，必然也会出现对靶向药物不同的敏感性，需要引起足够的重视。对于使用靶向药物后快速发生进展的患者，要特别关注分子病理诊断结果是否有失误的可能，并及时选择其他的检测方法进行验证。

90. 基于质谱筛选的人源性 m/z 6449 Da 蛋白肽对胃腺癌细胞的生物活性作用

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胃腺癌在我国高发，缺乏生物活性强、毒副作用弱且靶点专一的多肽类抗肿瘤药物。组织中高频低表达的 6449Da 活性肽是胃腺癌血清特异性非炎症性生物标志物。本研究拟探索胃腺癌新 m/z 6449 Da 生物活性肽对胃腺癌细胞的生物学行为影响及其作用机制，为新型抗胃腺癌活性肽药物的临床转化及问世提供理论基础。使用生物信息学方法对 6449 Da 活性肽进行性能预测及分析，固相合成法合成该活性肽，同时从 C-端逐个敲除氨基酸以寻找其最短功能片段，通过体外细胞实验及荷瘤鼠体内实验方法检测该活性肽的最短功能片段及其对胃腺癌细胞增殖、凋亡、迁移、跨膜侵袭、细胞周期、细胞定位和瘤体组织生长的作用及其分子机制。6449 Da 活性肽 C 端前 20 个氨基酸为信号肽，活性位点主要集中在信号肽以外的 40 个氨基酸组成的 WSGC 肽；WSGC 肽对胃腺癌细胞的毒性作用要比对正常胃粘膜上皮细胞作用强，对胃腺癌细胞细胞毒性作用有相对特异性；IC50 和 IC80 浓度的 WSGC 肽能抑制胃腺癌细胞增殖，诱导细胞分裂 S 期的阻滞，提高肿瘤细胞凋亡比例，降低或抑制细胞迁移及跨膜侵袭；WSGC-FITC 主要分布于胃腺癌细胞膜表面，很少进入胞质或胞核；经过 IC50 及 IC80 剂量的 WSGC 肽干预胃腺癌细胞 48h 后，IC50 及 IC80 组胃腺癌细胞中 Bax 和 Caspase-3 的 mRNA 及蛋白表达水平均高于对照组，而 IC50、IC80 组胃腺癌细胞中 Bcl-2，Ki67, PCNA，NOTCH1，Jagged 1，MAML3，CSL 及 HES1 的 mRNA 及蛋白表达水平均明显低于对照组。通过梯度 WSGC 肽浓度干预胃腺癌荷瘤免疫缺陷小鼠模型，发现经过 40 nmol/g、80 nmol/g 剂量 WSGC 治疗后，胃腺癌瘤体重量及体积均低于对照组；随着 WSGC 肽用药剂量的增加，胃腺癌荷瘤小鼠模型瘤体组织中细胞凋亡率均呈递增趋势；与对照组相比，胃腺癌荷瘤小鼠模型瘤体组织中 Bax 和 Caspase-3 蛋白的表达随着 WSGC 肽剂量的增加而增高，而 Bcl-2，Ki67 及 PCNA 蛋白的表达随着 WSGC 肽剂量的增加而递减。 Notch 信号通路及其下游调控网络介导定位于细胞膜表面的 6449 肽功能片段 WSGC 肽对胃腺癌细胞有相对特异性的促凋亡、抑制增殖作用，诱导细胞 S 期的阻滞，降低或抑制细胞迁移及跨膜侵袭，抑制瘤体组织生长，对催生一种新型抗胃腺癌多肽药物的问世及促进胃腺癌的防治工作提供理论基础。

91. Assessment of promoter methylation and expression of SIX2 as a diagnostic and prognostic biomarker in Wilms' tumor

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This study was designed to evaluate the utility of expression and DNA methylation patterns of the sine oculis homeobox homolog 2 (SIX2) gene in early diagnosis and prognosis of Wilms' tumor (WT). Methylation-specific poly-merase chain reaction (MSP), real-time quantitative polymer-ase chain reaction (qRT-PCR), receiver operating characteris-tic (ROC), and survival curve analyses were utilized to mea-sure the expression and DNA methylation patterns of SIX2 in a cohort of WT tissues, with a view to assessing their diag-nostic and prognostic value. Relative expression of SIX2 mRNA was higher, while the promoter methylation level was lower in the WT than control group ($P<0.05$) and closely associated with poor survival prognosis of WT children ($P<0.05$). Increased expression and decreased methylation of SIX2 were correlated with increasing tumor size, clinical stage, vascular invasion, and unfavorable histological differentiation ($P<0.05$). ROC curve analysis showed areas under the curve (AUCs) of 0.579 for methylation and 0.917 for expression in WT venous blood, indicating higher diag-nostic yield of preoperative SIX2 expression. The preoperative venous blood SIX2 expression level serves as an underlying biomarker for early diagnosis of WT. SIX2 overexpression and concomitantly decreased promoter methylation are signifi-cantly associated with poor survival of WT children.

92. Reticulocalbin 2 correlates with recurrence and prognosis in colorectal cancer Running Title: Reticulocalbin 2 predicts poor prognosis in CRC

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Reticulocalbin (RCN) family members could play oncogenic roles in human malignancies and facilitate tumor cell proliferation and metastasis. However, the expression pattern and potential function of Reticulocalbin2 (RCN2) in colorectal cancer has not been addressed yet. In the present study, we investigated the protein expression of RCN2 by immunohistochemistry assay, analyzed its association with tumor progression, recurrence and prognosis in 326 cases of patients. Results suggested that the expression of RCN2 was up-regulated in colorectal cancer compared with normal specimens. RCN2 expression was closely related to tumor size and the depth of invasion. Kaplan-

Meier analysis proved that RCN2 was associated with both disease-free survival and overall survival of patients with colorectal cancer. Moreover, cox's proportional hazards analysis showed that high RCN2 expression was an independent prognostic marker of poor outcome. Consistently,overexpressing RCN2 promotedCRC cell proliferation both in vitro and in vivo and knockdown RCN2 showed the opposite results. These results provided the first evidence that RCN2 level was increased in colorectal cancer and significantly correlated with tumor growth and proliferation. It also indicated that RCN2 might serve as a potential marker of tumor recurrence and prognosis of colorectal cancer.

93. Identification of second primary tumors from lung metastases in patients with esophageal squamous cell carcinoma using whole-exome sequencing

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Backgroud: Esophageal squamous cell carcinoma (ESCC) patients with a synchronous or metachronous lung tumor can be diagnosed with lung metastasis (LM) or a second primary tumor (SPT), but the accurate discrimination between LM and SPT remains a clinical dilemma. This study aimed to investigate the feasibility of using the whole-exome sequencing (WES) technique to distinguish SPT from LM.

Methods: We performed WES on 40 tumors from 14 patients, including 12 patients with double squamous cell carcinomas (SCCs) of the esophagus and lung (lymph node metastases were sequenced as internal controls) diagnosed as LM according to pathological information and 2 patients with paired primary ESCC and non-lung metastases examined as external controls.

Results: Shared genomic profiles between esophageal (T) and lung (D) tumors were observed in 7 patients, suggesting their clonal relatedness, thus indicating that the lung tumors of these patients should be LM. However, distinct genomic profiles between T and D tumors were observed in the other 5 patients, suggesting the possibility of SPTs that were likely formed through independent multifocal oncogenesis.

Conclusions: Our data demonstrate the limitations and insufficiency of clinicopathological criteria and that WES could be useful in understanding the clonal relationships of multiple SCCs.

94. Potential unreliability of uncommon ALK/ROS1/RET genomic breakpoints in predicting the efficacy of targeted therapy in NSCLC

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Introduction: Variable genomic breakpoints have been identified through the application of target-capture next-generation DNA sequencing (DNA NGS) for ALK/ROS1/RET fusion detection in non-small cell lung cancer (NSCLC). We investigated whether ALK/ROS1/RET genomic breakpoint location can predict matched targeted therapy efficacy.

Methods: NSCLCs were analyzed by DNA NGS, target-specific next-generation RNA sequencing (RNA NGS), whole-transcriptome sequencing (WTS) and immunohistochemistry (IHC).

Results: In total, 3787 NSCLC samples were analyzed. DNA NGS detected ALK, ROS1 and RET fusions in 241, 59 and 76 cases, respectively. These fusions were divided into canonical (single EML4-ALK, CD74/EZR/TPM3/SDC4-ROS1 and KIF5B/CCDC6-RET fusions), non-canonical (single non-EML4-ALK, non-CD74/EZR/TPM3/SDC4-ROS1 and non-KIF5B/CCDC6-RET fusions) and primary/reciprocal (both primary and reciprocal rearrangements were detected) subtypes based on genomic breakpoint position, and non-canonical and primary/reciprocal subtypes were defined as uncommon fusions. Further RNA sequencing/IHC showed that 6 of 47 (12.8%) uncommon fusions actually were non-productive rearrangements that generated no aberrant transcripts/proteins. Moreover, genomic breakpoints of canonical ALK/RET, but not ROS1, fusions always predicted breakpoints at the transcript level, whereas 85.4% (35/41) of uncommon fusions actually produced canonical fusion transcripts. Patients with uncommon ALK fusion (n=31) who received first-line crizotinib exhibited shorter median progression-free survival (PFS) than patients with canonical ALK fusion (n=53, 8.4 months versus 12.0 months; P=0.004). However, no difference in PFS was observed when only ALK RNA/protein-positive cases were analyzed (P=0.185).

Conclusions: Uncommon ALK/ROS1/RET genomic breakpoint is an unreliable predictor of matched targeted therapy efficacy. Functional validation by RNA or protein assay may add value for accurate detection and interpretation of rare fusions.

95. p62/SQSTM1 analysis identifies prognostic markers in uveal melanoma

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Uveal melanoma is one of the most commonly occurring adult intraocular malignant tumors, with a relatively low initial detection rate, higher liver metastasis rate, and lower survival rate. No specific biomarkers have been found for diagnosis and treatment. p62/SQSTM1 has now been identified as a new target for the detection and treatment of cancer. This study analyzes gene expressions of p62/SQSTM1 and survival curves on GEPIA and UALCAN. Mutation analysis of p62/SQSTM1 was performed on c-BioPortal. Correlations between Methylation and gene expression and survival time were analyzed on MethSurv and SMART. Associations between expression and methylation of p62 / SQSTM1 and immune features were performed on TISIDB. We found that expression of p62/SQSTM1 is positively correlated with malignancy of uveal melanoma. 5'UTR and gene body methylation sites have a more important prognostic value. Promoter methylation was positively correlated with immune inhibitor CD274. p62/SQSTM1 in general or its methylation sites, in particular, may be used as a potential marker for uveal melanoma prognosis, diagnosis, and metastasis.

96. Identifcation of prognostic alternative splicing signatures in hepatitis B or/ and C viruses related hepatocellular carcinoma

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Background: Alternative splicing (AS) takes a crucial part in regulating cell and organism homeostasis, involving in oncogenesis and tumor progression. Considering that alteration of host cell splicing is a common feature of viral infections, and Hepatitis B virus (HBV) or/and Hepatitis C virus (HCV) infection are the key determinants contributed to HCC, we aim to analyze AS in HBV or/and HCV related hepatocellular carcinoma (HCC).

Methods: RNA-seq data with corresponding clinical features were acquired from Liver Hepatocellular Carcinoma (LIHC) of the Cancer Genome Atlas (TCGA). TCGASpliceSeq provided mRNA AS patterns of TCGA-LIHC tumors, including seven types of AS events: alternate acceptor site (AA), alternate donor site (AD), alternate promoter (AP), alternate terminator (AT), exon skip (ES), mutually exclusive exons (ME) and retained intron (RI) Univariate and multivariate Cox regression analyses were conducted to screen survival-associated AS events. The receiver operating

characteristic curve (ROC) used to evaluate the predictive accuracy. Splicing network was built to investigate the relationship between splicing factors and AS events.

Results: A total of 11086 AS events of 4382 genes (567 AAs in 460 genes, 466 ADs in 341genes, 963 APs in 383 genes, 6278 ATs in 2,739 genes, 1,986 ESs in 1,267 genes, 29 MEs in 29 genes and 797 RIs in 623 genes) were detected in 153 HCC patients with HBV or/and HCV infection. Differentially expressed AS (DEAS) events were identified in HBV-LIHC, HCV-LIHC, (HBV+HCV)-LIHC groups. These DEAS-related genes were performed Gene Ontology enrichment analysis. These associated gene enrichment pathways involved in DEAS events were significantly different. In HBV-LIHC subgroup, the top enriched terms were transition metal ion transport and transport vesicle in biological process (BP) and cellular component (CC), while in HCV-LIHC subgroup, RNA catabolic process, ribosome and structural constituent of ribosome were mainly revealed in BP, CC and molecular function (MF). Also, DNA damage response, detection of DNA damage, ribosomal subunit and structural constituent of ribosome were significant in three Go categories of (HBV+HCV)-LIHC subgroup. In addition, ninety-six survival-associated AS events were obtained by univariate Cox regression. The related independent prognostic AS events in each AS types were: 5 in AA, 9 in AD, 4 in AP, 5 in AT, 7 in ES, 3 in RI. According to the median value of the risk score as the cut-off, the total HBV or/and HCV related LIHC patients were divided into high-risk and low-risk groups. The predictive values of six prognosis models were significantly ($P < 0.001$), especial in ES type ($P = 7.13e-07$). Final prognostic model could significantly distinguish the prognosis. ROC curve analysis determined good predictive accuracy with AUC values of 0.873 for five-year survival. We identified RBFOX2 as the hub gene in splicing network based on differentially expressed splicing factors, and obtained MAP3K13_AT as the key AS event in survival-related splicing network.

Conclusion: In summary, our results highlight the AS signatures in HCC patients with HBV or/and HCV infection. Meanwhile, AS events and splicing factors in different virus-infected HCC subgroups can provide novel perspectives as biomarkers and individualized therapeutic targets.

97. Prevalence of Elevated Anti-p53 in Chinese Patients with Upper GI or Colorectal Cancer

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Background: Tumor markers, including anti-p53, have been used in cancer management.

Objectives: we aimed to describe the prevalence of elevated anti-p53 and other tumor markers in newly diagnosed or recurrent patients with upper gastrointestinal (GI) cancer or colorectal carcinoma (CRC) in Chinese population and to evaluate whether the addition of anti-p53 would detect more

cancer cases that were negative for the established tumor markers.

Methods: 187 healthy individuals, 169 patients with upper GI cancer and 217 patients with CRC were recruited. All subjects were required to provide up to 10 ml blood. The following biomarkers were measured for each included subject: anti-p53, CEA, CA19-9, CA125, CA15-3, CA72-4, CYFRA 21-1, HE4, ProGRP and SCC.

Results: at the cutoff of 0.02 μg/ml the sensitivity of anti-p53 in upper GI cancer and CRC in the Chinese population is low (9.47% and 25.93%). The specificity of anti-p53 in the healthy cohort at this cutoff is very high 98.4%. By adding anti-p53 to other tumor markers, the sensitivities are increased by 18-26% for detecting CRC, and by 8-10% for detecting upper GI cancer, and the specificities are decrease slightly by 1-2%.

Discussion The current study indicates that the prevalence of anti-p53 in upper GI and colorectal is low but specificity in healthy controls is very high (98.4%, 95%CI, 95.38-99.67). Addition of anti-p53 to the Elecsys tumor markers can improve the sensitivity to detect cancer with a minimal loss of specificity based on the healthy controls. The best improvement in sensitivity was seen in patients with colorectal cancer, while the benefit of adding anti-p53 to tumor markers in upper GI cancer was small.

In conclusion, multi marker analysis using anti-p53 may improve the diagnostic value for colorectal cancer patients. However, it is necessary to conduct further studies to validate anti-p53 autoantibodies for clinical use in China. These studies should evaluate anti-p53 and colorectal cancer markers in a multi-center setting with appropriate benign disease controls.

98. 围手术期输血影响晚期卵巢癌预后的临床研究

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【摘要】目的 通过回顾性病例对照研究探讨输血对 III-IV 期卵巢癌患者预后的影响。方法 回顾 2009 年 1 月-2019 年 1 月成都市第五人民医院收治并手术的 III-IV 期卵巢癌患者 206 例，根据手术后是否存在肉眼残留病灶，分为 R0 组和 R1 组，比较输血组与对照组总生存（overall survival ,OS）、无进展生存（progression-free survival,PFS）是否存在差异；通过 COX 回归，探讨输血是否为 III-IV 期卵巢癌患者预后的独立因素。**结果** 输血组与对照组比较表明，输血组的总生存期（OS）（HR=1.87,95%CI:37.51～44.60,p=0.000）和无进展生存期（PFS）（HR=1.97,95%CI:32.20～39.91,p=0.000）更差，差异有统计学意义（p<0.05）；输血是影响 III-IV 期卵巢癌预后的独立因素（OR=1.91,95%CI:1.08～3.40,p=0.02），除此之外，手术时间大于>3 小时（OR=0.48,95%CI:0.27～0.83）、分期（OR=2.27,95%CI:1.25～12.05）及病理类型（OR=3.40,95%CI:1.18～9.78）也是影响患者预后的因素。结论 III-IV 期卵巢癌患者围手术期

输入同种异型红细胞可使患者预后更差，围手术期输入同种异型红细胞是影响晚期卵巢癌预后的独立因素，应尽可能减少患者围手术期输入同种异型红细胞。

99. Epstein-Barr virus miR-BART3-3p promotes tumorigenesis by targeting p53/TP53BP1 pathway and its circulating levels serve as biomarker in Nasopharyngeal Carcinoma

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Purpose: To investigate the potential of circulating- Epstein-Barr Virus (EBV) coded miR BART3-3p as noninvasive biomarkers to diagnose and predict outcomes for nasopharyngeal carcinoma, and explore its role in tumorigenesis of NPC.

Experimental Design: Plasma miRNA profiling of 7 healthy donors and 7 NPC patients was performed using miRNA-seq to identify differential expression of miRNA. The diagnostic capability was conducted in 483 NPC and 243 control group. This study explores the prognostic value of pre-treatment miR-BART3-3p in 465 M0 NPC and post-treatment miR-BART3-3p in 245 NPC. Further, in vitro and in vivo studies were conducted to define the role of miR-BART3-3p in NPC tumorigenesis and the underlying molecular mechanisms.

Results: Plasma miRNA profiling showed that miR-BART 13-3p were up-regulated in plasma with NPC, while cannot be detected in healthy donors. MiR-BART13-3p was detected in 97.9% (473/483) NPC, 8.6% (21/243) control group. The AUC of miR-BART7-3p was 0.977. Kaplan-Meier survival and multivariable analysis showed that high expression of pre-treatment miR-BART3-3P was correlated with poor PFS in NPC patients (67.3% vs. 80.7%, $p<0.001$; HR = 1.57, 95%CI: 1.05–2.34, $p = 0.026$). Besides, the detectable rate of post-treatment miR-BART7-3p was 28.6%. Patients with detectable miR-BART3-3p at post-treatment had statistically significantly worse DMFS (81.5% vs. 61.4%, $p<0.001$) than patients with undetectable. Ectopic expression of miR-BART3-3p promoted NPC cell proliferation in vitro and facilitated xenograft tumor growth in vivo. Molecularly, p53, and TP53BP1 were identified to be a direct target of miR-BART3-3p in NPC cells, and p53 and TP53BP1 mRNA and protein expression was inversely correlated with miR-BART3-3p in NPC tissues, respectively. By rescued experiments, the reconstitution of TP53BP1 expression abrogated all the phenotypes upregulated by miR-BART3-3p.

Conclusions: Circulating miR-BART3-3p can serve as a diagnostic and prognostic biomarker for NPC. Our findings indicated the newly identified miR-BART3-3p/p53 signaling axis may provide further insights into a better understanding of NPC initiation and development, and targeting of this

pathway could be further studied as a therapeutic strategy for NPC patients.

100. Metformin-Induced Killing of liver Initiating Cells via inhibition on PI3-K/Akt-dependent pathway

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Abstract

Background: Liver tumor-initiating cells (T-ICs) are a subpopulation of tumor cells with the capacity of self-renew and differentiate into distinct cell types that comprise the bulk of the hepatoma. Liver T-ICs have been elucidated to render tumor recurrence and chemo-resistance and targeting T-ICs might be a novel strategy for HCC therapy. Metformin has been shown to selectively kill cancer cells, and HCC cell lines are sensitive to the effects of metformin. However, the mechanism underlying the enhanced susceptibility of HCC to metformin has not been elucidated. **Methods:** Spheroid assay and in vitro cell behavior assay were used to detect the influence of metformin on the self-renewal effect of HCC cells in vitro. Real-time PCR assay was used to detect the mRNA level of CD90, CD133 and Sox2 after SMMC-7721 cells were treated with metformin. Western blot assay was used to detect the change of p-Akt and p-mTOR protein expression after SMMC-7721 cells were treated with metformin. Animal models were conducted to explore the influence of metformin on SMMC-7721- injected NOD/SCID mice. **Results:** Metformin decreases the proportion of tumor stem cells in HCC cells. CD90, CD133 and Sox2 were significantly downregulated in HCC cells treated by metformin. The spheroid formation ability of HCC cells was attenuated obviously at the presence of metformin. What’s more, PI3-K/Akt pathway was found downregulated in metformin-treated HCC cells and the inhibition ability was diminished by blockage of PI3-K/Akt pathway. **Conclusions:** Metformin plays an important role in HCC tumor-initiating cells through PI3-K/Akt signaling and may be a promising therapeutic drug for HCC patients.

101. 尿液 DNA 甲基化在早期、微小、残留和复发膀胱癌诊断中的多中心临床研究

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目的：目前膀胱癌的诊断和监测方法主要通过侵入性的膀胱镜检查，然而无创尿液诊断技术如脱离细胞学，FISH 和 BTA 等肿瘤标记物检测，在敏感性和特异性上仍不理想。因此，开发高敏感性检测早期、微小、残留和复发膀胱癌的诊断技术，可以大幅改善膀胱癌患者的治疗疗效和生存预后。

方法：我们开发了一种基于飞行时间质谱的新方法来检测尿液肿瘤细胞 DNA 甲基化。首先通过对我院、TCGA 和 GEO 队列的甲基化大样本数据进行联合分析，找到膀胱癌显著差异和特异性的甲基化位点。接着，我们通过在 313 例单中心回顾性队列中建立和验证膀胱癌甲基化诊断模型，进一步在 175 例的多中心前瞻性队列中验证甲基化模型诊断的有效性。并将本技术与目前临床常用的尿脱离细胞学和 FISH 进行诊断效能的比较分析。

果：我们首先在联合分析中发现了 26 个显著差异的膀胱癌甲基化位点。我们建立并验证了这个基于两个甲基化位点的诊断模型，它对膀胱癌患者的诊断具有较高的准确性（86.7%）、敏感性（90.0%）和特异性（83.1%）。而且，这个基于飞行时间质谱的甲基化检测技术在敏感性上显著高于尿脱离细胞学和 FISH。在早期的 Ta 且低级别的肿瘤中，甲基化技术，细胞学和 FISH 的敏感性依次为 64.5%对 11.8%，15.8%。在微小肿瘤检测中，上述三者的敏感性为 81.0%对 14.8%，37.9%。在术后残留肿瘤检测中，上述三者的敏感性为 93.3%对 27.3%，64.3%。在肿瘤复发监测中，上述三者的敏感性为 89.5%对 31.4%，52.8%。基于这个检测，我们建立尿液诊断评分，它能反映肿瘤的恶性程度和肿瘤负荷。

结论：尿液肿瘤细胞 DNA 甲基化检测是一种快速（1-2 天）、高通量（同时检测 100 个病人）、无创、高诊断效能的方法，可减少不必要的膀胱镜检查和盲目的二次手术。

102. Enhancer-Driven lncRNA BDNF-AS Induces Endocrine Resistance and Malignant Progression of Breast Cancer through the RNH1/TRIM21/mTOR Cascade

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Epigenomic alterations can give rise to various tumor-promoting properties, including therapeutic resistance of cancer cells. Here, we identify an lncRNA, BDNF-AS, whose overexpression is specifically driven by a MEF2A-regulated enhancer in endocrine-resistant and triple-negative breast cancer (TNBC). High levels of BDNF-AS in breast cancer tissues not only feature endocrine resistance in hormone receptor (HR)-positive patients but also correlate with poor outcomes in both HR-positive and TNBC patients. Mechanistically, BDNF-AS acts as a molecular scaffold to promote RNH1 protein degradation via TRIM21-mediated ubiquiti- nation of RNH1 at K225. Subsequently, BDNF-AS abolishes RNH1-regulated and RISC-mediated mTOR mRNA decay, therefore sustaining the activation of mTOR signaling. Importantly, mTOR inhibitor, but not PI3K inhibitor, could reverse tamoxifen resistance induced by the overexpression of BDNF-AS. These results point toward a master regulatory role of an enhancer-activated cascade of BDNF-AS/RNH1/TRIM21/mTOR in endocrine resistance and malignant progression of breast cancer.

103. The Expression Profile of Serum Thrombospondin-2, a Novel Tumor Marker , in General Population and Cancer Patients in China

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Purpose.The expression profile of serum thrombospondin-2 in general population and cancer patients in China have not been reported. **Methods**.This study evaluated the expression level of serum thrombospondin-2 in general population and various cancer patients, the 95% confidence interval was used for the derivation of reference range.The comparison of the expression levels in controls for age and gender was performed. The associations between candidate biomarkers (thrombospondin-2 [THBS2] expression and tumor metastasis status were also explored. **Results**.125 healthy controls and 275 various cancer patients were enrolled. The mean ± SD in serum THBS2 levels in general population was 42.37±12.24ng/ml, there was no significant sex and age difference, the reference range is 18.37-66.36ng/ml. Various tumors show different patterns of THBS2 expression: all cases from mediastinal malignant tumor, bone, esophagea and gastric cancer show a low

expression level; more than 60% of lung, colorectal, breast and cervical cancer patients had a low serum THBS2 level and the data are quite close in all; most cases from ovarian, brain cancer ,nasopharyngeal carcinoma exhibit a decreasing expression of THBS2 but the overall data are relatively scattered; expression level of THBS2 in hepatoma and lymphoma showed the two extremes, most of them present a relatively high level and others appeared very low. There was no statistical difference of serum THBS2 level between metastasis and non-metastasis group in breast, lung, cervical, colorectal cancer, nasopharyngeal carcinoma and hepatoma (P >0.05) while a significant negative correlation was observed in ovarian cancer (P = 0.0209). **Conclusions**.The expression profile of serum THBS2 display an obvious heterogeneity among various cancers , ovarian cancer patients detected with low THBS2 expression were more prone to develop metastasis in China.

104. 血清外泌体 miRNA 在胰腺癌诊断中的标记性作用

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目的：胰腺癌是恶性程度高的恶性肿瘤之一，80%以上胰腺癌尤其胰尾癌确诊即是中晚期，因此提高早期诊断对胰腺癌患者具有重要的意义。液体活检技术是近年来肿瘤诊断领域的突破性技术，血清外泌体是其中基础性检材之一，一直是研究的热点。本研究拟建立胰腺癌血清外泌体 miRNA 表达谱，鉴定出对胰腺癌诊断意义的外泌体 miRNA 诊断标记，并初步分析这些诊断标记的生物学作用。

方法：从 24 例胰腺癌患者，12 例胰腺良性肿瘤患者和 24 例健康对照中分离出血清外泌体和外泌体 miRNA，使用高通量测序（NGS）进行外泌体 miRNA 分析并鉴定出上述三组中显著差异表达的 miRNA，利用生物信息学分析其在胰腺癌发生发展中的潜在作用。

结果：高通量测序之后，胰腺癌组、胰腺良性肿瘤组和健康对照组两两相比取显著差异表达 miRNA（选取标准 Fold change >= 2,Qvalue < 0.05），最终取上述三组差异表达 miRNA 的交集，差异表达 miRNA 共 3 个，分别是 miR-1-3p，miR-885-5p 和 miR-145-5p。其中 miR-1-3p 在胰腺癌患者外泌体中表达较健康人和胰腺良性肿瘤患者低，miR-885-5p 和 miR-145-5p 在胰腺癌患者外泌体中表达较健康人和胰腺良性肿瘤患者高，差异均有统计学意义（Qvalue <= 0.05）。进一步对 3 个差异 miRNA 采用生物信息学分析，KEGG 分析表明 miR-1-3p，miR-885-5p 和 miR-145-5p 的靶基因均可分类在一些与胰腺癌发展相关的通路发挥调节作用，且其靶基因在 p53 信号通路，TGF-β 信号通路、PI3K-Akt 及 Ras 等信号通路上显著富集（Qvalue <= 0.05）。GO 分析表明 miRNAs 可以调节重要的生物学过程，如细胞增值调控、信号传导等等。应用 miranda、rnahybrid 和 targetscan 生物信息学软件预测 miRNA 的靶基因，取三者交集 miR-145-5p 的靶基因共有 292 个，两两相结合 miR-1-3p 靶基因共 116 个，miranda 与 targetscan

预测 miR-885-5p 靶基因共 120 个。

结论：我们的研究鉴定出胰腺癌与良性肿瘤及健康这血清中差异表达的外泌体 miRNA，可以作为胰腺癌诊断意义的非侵入性候选生物标记，且根据生物信息学分析显示差异表达的外泌体 miRNA 参与了胰腺癌的发生发展。

105. Circular RNA circCORO1C promotes laryngeal squamous cell carcinoma progression by modulating the let-7c-5p/PBX3 axis

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Background

Laryngeal squamous cell carcinoma (LSCC) is a common malignant tumor of the head and neck. LSCC patients have seriously impaired vocal, respiratory, and swallowing functions with poor prognosis. Circular RNA (circRNA) has attracted great attention in cancer research. However, the expression patterns and roles of circRNAs in LSCC remain largely unknown.

Methods:

RNA sequencing was performed on 57 pairs of LSCC and matched adjacent normal mucosa tissues to construct circRNA, miRNA, and mRNA expression profiles. RT-PCR, qPCR, Sanger sequencing, and FISH were undertaken to study the expression, localization, and clinical significance of circCORO1C in LSCC tissues and cells. The functions of circCORO1C in LSCC were investigated by RNAi-mediated knockdown, proliferation analysis, EdU staining, colony formation assay, Transwell assay, and apoptosis analysis. The regulatory mechanisms among circCORO1C, let-7c-5p, and PBX3 were investigated by luciferase assay, RNA immunoprecipitation, western blotting, and immunohistochemistry.

Results:

circCORO1C was highly expressed in LSCC tissues and cells, and this high expression was closely associated with the malignant progression and poor prognosis of LSCC. Knockdown of circCORO1C inhibited the proliferation, migration, invasion, and in vivo tumorigenesis of LSCC cells. Mechanistic studies revealed that circCORO1C competitively bound to let-7c-5p and prevented it from decreasing the level of PBX3, which promoted the epithelial–mesenchymal transition and finally facilitated the malignant progression of LSCC.

Conclusions:

circCORO1C has an oncogenic role in LSCC progression and may serve as a novel target for LSCC therapy. circCORO1C expression has the potential to serve as a novel diagnostic and prognostic biomarker for LSCC detection.

106. B7-H6：T 淋巴母细胞淋巴瘤潜在的肿瘤标志物和治疗靶点

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研究背景: B7-H6 是一种新型免疫共刺激分子，正常细胞（除部分激活的单核细胞和树突状细胞）基本不表达，多种肿瘤细胞表面表达，提示预后不良。T 淋巴母细胞淋巴瘤（T-LBL）缺乏可靠的治疗靶点，研究 T-LBL 是否表达 B7-H6 以及相关临床意义仍有待研究。

研究方法: 本研究使用免疫组化技术分析 65 例 T-LBL 经福尔马林固定的石蜡包埋组织切片的 B7-H6 表达水平，结合相关临床指标和生存分析进行回顾性分析。构建 B7-H6 敲减的 Jurkat 细胞株，检测细胞增殖和迁移、侵袭能力。应用转录组测序技术分析相关差异表达基因。

研究结果: 结果显示 65 例组织中 61.5% (40/65)表达 B7-H6，其中 38.5% (25/65)表达在细胞膜/胞浆。尽管生存分析未提示 B7-H6 表达具有生存预后意义，但临床资料分析显示 B7-H6 阳性组中，B 组症状（发热、盗汗和消瘦）（P=0.01），ECOG 体力评分(3–4 分)（P=0.02）和乳酸

脱氢酶增高（P=0.04）的比例明显高于 B7-H6 阴性组。同时，阳性组中期疗效评估完全缓解率显著低于阴性组（P=0.02）。敲减 B7-H6 表达可明显削弱 Jurkat 细胞的增殖，迁移和侵袭能力。RNA 测序分析提示 B7-H6 和 RAG-1 表达正相关。

研究结论: B7-H6 蛋白可以作为 T 淋巴母细胞淋巴瘤潜在的肿瘤标志物和治疗靶点。

107. An individualized transcriptional signature to predict the epithelial-mesenchymal transition based on relative expression ordering

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The epithelial-mesenchymal transition (EMT) plays a critical role in cancer cell metastasis and immune system activation. Identification of gene expression signatures predicting the EMT status of cancer cells is essential for development of novel therapeutic strategies. However, quantitative identification of EMT markers is limited by batch effects, the platform used, or normalization methods. Here, using transcriptome data of ovarian cancer (OvCa) cohorts from publically available databases, we developed a qualitative 16-gene pair signature (16-GPS) to distinguish the mesenchymal phenotype from the epithelial phenotype, based on the hypothesis that a set of EMT-related relative expression orderings (REOs) that were highly stable in epithelial samples but reversed in mesenchymal samples. Our method was superior to previous quantitative methods in terms of classification accuracy and applicability in individualized patients without data normalization. Patients with mesenchymal-like OvCa showed poorer overall survival than patients with epithelial-like OvCa. Additionally, EMT score was positively correlated with the expression of immune checkpoint genes and the metastasis. Overall, we established a robust EMT 16-GPS independent of detection platform, batch effects, and individual variations. The 16-GPS represented a novel qualitative signature for investigating the EMT and provided insights into immunotherapy in patients with OvCa.

108. Exosomes-mediated Mortalinprotein promotes malignant transformation of cervical epithelial through p53-Gadd45A signaling

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Background: Malignant transformation can impede programmed cell death or apoptosis, thus allowing the cells to grow uncontrolled and resulting in cancer. For cervical cancer (CC), it is crucial

for normal cervical epithelium to acquire malignant traits, yet it remians unclear about how precancerous lesions develop into CC. Tumor-derived exosomes are emerging mediators to tumorigenesis. In this research, we explored the mechanisms about the key factor Mortalin from CC-derived exosomes in progression of malignant transformation.

Methods: Mortalin was screened out to be one of differential expression proteins in Exosomal proteomics profiling in plasma of CC by using Label free-quantitative LC/MS technology. The relative expression of Mortalin was detected by Western blot and qPCR. MeRIP-qPCR technology which combined MeRIP-seq with RNA-seq following was used to explore the m6A modification of Mortalin transcription. And ChIP assay were employed to validate H3K27 acetylation. Over-expression and shRNA-mediated knockdown were also applied to validate malignant transformation of exosomal Mortalin in CC. The effect of downstream target p53-Gadd45A were predicted via transcriptomics and erified by flow cytometry.

Results： Mortalin was screened out to be significantly riched n plasma exosomes from CC patients than n cervical eoplasia (CIN) patients and healthy individuals. In upstream regulation, P300-mediated H3K27 acetylation and METTL3 mediated m6A modification in SiHa cells was both confirmed as up-regulated mechanisms to Mortalin ranscription. oreover, a series gain or loss functional assays were done to prove the precise role of exosomal Mortalin enhanced cervical epithelial ells with the ability of proliferation, migration and reduced the level of apoptosis in vitro and in vivo. Mechanically,CC-derived exosomal Mortalin could prevent p53-Gadd45A interaction from performing the function of stable cell cycle and DNA repair by rresting p53 from returning to the nucleus, contributing to the state of dysfunction and instability of cervical epithelial cells and then leading to malignant phenotypes.

Conclusions: Our data demonstrated that enhanced expression of Mortalin in CC could be attributed to upstream pathways of P300-mediated H3K27 acetylation and METTL3 mediated m6A modification. Tumor cell packaged mortalin into exosomes and transferred to cervical epithelial cells in order to induce malignant transformation through mortalin-p53-Gadd45Apathway causing inactivation of p53-mediated apoptosis, which signify a brilliant mechanism of exosomal proteins accelerating carcinogenesis process, providing a new ideas for effective diagnosis biomarkers and anti-tumor therapies.

Keywords: Cervical cancer, Mortalin, Exosomes, Malignant transformation

109. Preoperative fibrinogen-albumin ratio, potential prognostic factors for bladder cancer patients undergoing radical cystectomy: a multicenter study

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Background: This study aimed to determine the potential utility of preoperative fibrinogen-albumin ratio (PAR) as a prognostic factor in patients with bladder cancer (BCa) after radical cystectomy (RC).

Methods: A retrospective analysis of BCa patients who underwent RC at two hospitals was performed, with 140 patients as training set and another 127 patients as validation set. Kaplan-Meier survival curves were used to calculate the overall survival (OS) and disease-free survival (DFS) factors. The prognostic value of PAR was analyzed by using Cox regression model, and a nomogram of BCa based on PAR was generated by R software.

Results: In the training set, the optimal cut-off value of PAR was 0.08. High level of PAR was related to the poor prognosis of patients with BCa, and PAR has a more accurate prognostic ability than platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR). Multivariate cox regression analysis showed that PAR was an independent predictor of OS (>0.08 vs ≤0.08 HR, 2.031, 95% CI = 1.071-3.851; p = 0.030) and DFS (>0.08 vs ≤0.08 HR, 2.330, 95% CI = 1.160-4.680; p = 0.017), and the nomogram based on PAR had better accuracy and discrimination (area under the curve (AUC): OS = 0.760, DFS = 0.762).

Conclusions: PAR can be used as an independent predictor of OS and DFS for RC patients, and the nomogram based on PAR was a reliable model for predicting the prognosis after RC.

110. The Role of ARL4C in Erlotinib Resistance: Activation of the Jak2/Stat 5/

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Cancer patients who initially benefit from Erlotinib, a drug targeting EGFR path, eventually develop resistance to the drug. The underlyingmechanismis largely unknown. This study investigated the role of ARL4C in Erlotinib resistance development of NSCLC. qRT-PCR and Western blotting were performed to analyze the expression of mRNA and protein of ARL4C in two NSCLC cell lines (HCC827 and PC-9). Several assays (MTS, colony formation, transwell migration, luciferase reporter, and chromatin-immunoprecipitation) were used to explore the role of ARL4C in biofunctional

changes of Erlotinib-resistant cells and their associations with Jak2/Stat 5/β-catenin signaling. Results demonstrated that (1) long-termuse of Erlotinib resulted in downregulation of ARL4C ; (2) overexpression of ARL4C could regain the sensitivity to Erlotinib in the drug-resistant HCC827/ER cells, while downregulation of ARL4C increased HCC827, and PC-9 cells' resistance to the drug; (3) Erlotinib-induced downregulation of ARL4C resulted in phosphorylation of Jak2/Stat5 and upregulation of β-catenin and their related molecules Axin2 , CD44 , Ccnd1 , Lgr-5 , and MMP7 , which promoted the malignant behaviors of Erlotinib-resistant cells; (4) chromatin immunoprecipitation and luciferase reporter assay revealed that Stat5 could bind to β-catenin promoter to upregulate molecules to maintain the malignant behaviors, which might count for how Erlotinib-resistant cell survived while EGFR path was blocked; (5) the expression of ARL4C was not associated with known EGFR gene mutations in both Erlotinib-resistant cells and NSCLC tissues. Our data suggest that Erlotinib resistance of NSCLCs is associated with downregulation of ARL4C via affecting Jak/Stat/β-catenin signaling. ARL4C could serve as a biomarker to predict the effectiveness of TKI targeting therapy and a potential therapeutic target for overcoming Erlotinib resistance in NSCLC.

111. Direct Targeting of CREB1 with Imperatorin Inhibits TGFβ2-ERK Signaling to Suppress Esophageal Cancer Metastasis

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Metastasis accounts for 90% of cancer death worldwide, and effective therapeutic strategies are lacking. We aim to identify the key drivers in tumor metastasis and screen therapeutics for treatment of esophageal squamous cell carcinoma (ESCC). Gene Ontology analysis of TCGA gene expression datasets of ESCC patients with or without lympy metastasis identified that TGFβ2 was highly enriched in the pathways essential for tumor metastasis, and upregulated in the metastatic ESCC tumors. High TGFβ2 expression in ESCC correlated with metastasis and patient survival, and functionally contributed to tumor metastasis via activating ERK signaling. By screening of a library consisting of 429 bioactive compounds, imperatorin was verified as a novel TGFβ2 inhibitor, with robustly suppressive effect on tumor metastasis in multiple mice models. Mechanistically, direct binding of imperatorin and CREB1 inhibit phosphorylation, nuclear translocation of CREB1 and its interaction with TGFβ2 promoter, represses TGFβ2 expression and fibroblasts-secreted CCL2, and then inactivates ERK signaling to block cancer invasion and abrogates the paracrine effects of fibroblasts on tumor angiogenesis and metastasis. Overall, our findings suggest the use of TGFβ2 as a diagnostic and prognostic biomarker and therapeutic target in ESCC, and support the potential of

imperatorin as a novel therapeutic strategy for cancer metastasis.

112. Exosomal transfer of p-STAT3 promotes acquired 5-FU resistance in colorectal cancer cells

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Abstract：

Background: Acquired resistance remains a limitation of the clinical use of 5-fluorouracil (5-FU). Because exosomes, are important vesicles participating in intercellular communication, their contribution to the development of acquired 5-FU resistance needs to be elucidated. In this study, we aimed to examine the underlying mechanisms of exosomes from 5-FU resistant cells (RKO/R) in sustaining acquired 5-FU resistance in sensitive cells (RKO/P).

Methods: Exosomes from a 5-FU-resistant cell line (RKO/R) and its parental cell line RKO/P were isolated and co-cultured with 5-FU-sensitive cells. Real-time cellular analysis (RTCA) and FACS analysis were used to examine cell viability and apoptosis. Exosomal protein profiling was performed using shotgun proteomics. Inhibitors and siRNAs were applied to study the involvement of selected proteins in 5-FU resistance. The effect of exosomal p-STAT3 (Tyr705) on the caspase cascade was examined by western blotting (WB) and high content analysis. Xenograft models were established to determine whether exosomal p-STAT3 can induce 5-FU resistance in vivo.

Results: Our results indicated that exosomes from RKO/R cells significantly promoted cell survival during 5-FU treatment. Proteomics and WB analysis results indicated that GSTP1 and p-STAT3 (Tyr705) were enriched in exosomes from RKO/R cells. Inhibition of p-STAT3 re-sensitized RKO/P cells to 5-FU via caspase cascade. Furthermore, p-STAT3 packaged by exosomes from RKO/R cells increased resistance of tumor cells to 5-FU in vivo.

Conclusions: Our results reveal a novel mechanism by which p-STAT3-containing exosomes contribute to acquired 5-FU resistance in CRC. This study suggests a new option for potentiating the 5-FU response and finding biomarkers for chemotherapy resistance.

Keywords: P-STAT3, Exosomes, 5-FU resistance, Colorectal cancer

113. 结肠癌组织中差异表达 circRNA 的筛选与验证

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目的 筛选结肠癌组织中差异表达的环状 RNA（circRNA），并分析其可能在结肠癌发生发展中的作用。**方法** 收集 3 例结肠癌患者的肿瘤组织标本及癌旁正常组织标本，用 Arraystar Human circRNA Arrays V2 芯片检测、筛选差异表达的 circRNA；进行聚类分析筛选显著差异表达 circRNA，并用 real-time PCR 方法进行初步验证。筛选到的 circRNA 利用 GO 数据库和 KEGG 数据库分别进行基因功能注释分析及信号通路富集分析。**结果** 结肠癌组织与癌旁组织比较，按照 P<0.05 和 FC >1.5 筛选标准，筛选出 114 个差异表达 circRNAs，其中 62 个 circRNAs 上调表达，52 个 circRNAs 下调表达，经过聚类分析筛选出在结肠癌癌中显著下调的 8 个 circRNA：hsa_circRNA_404686 、hsa_circRNA_102293 、hsa_circRNA_000367 、hsa_circRNA_10427 、hsa_circRNA_001729 、hsa_circRNA_100790 、hsa_circRNA_105039 、hsa_circRNA_102049。Real-time PCR 结果显示这 8 个 circRNAs 在结肠癌组织中表达水平降低。GO 和 KEGG 富集分析结果显示，被富集的基因主要参与转录调节、RNA 结合、蛋白质结合、细胞周期和 p53 信号通路等。**结论** 在结肠癌组织筛选到 8 个显著下调的 circRNA，经基因功能注释分析其参与肿瘤的发生发展，可能会成为结肠癌诊断及预后评估的生物标志物。

114. 动态心电图监测含氟尿嘧啶方案治疗头颈部恶性肿瘤所致的心脏毒性

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摘要 目的 研究 24 小时动态心电图（24h-DCG）在监测含氟尿嘧啶方案治疗头颈部恶性肿瘤（HNC）相关心脏毒性中的作用。**方法** 将 7 个肿瘤中心 2015 年 07 月至 2018 年 06 月接诊的、同意使用含氟尿嘧啶方案化疗的 HNC 患者共 89 例，采用非随机前瞻性的方法，根据病人的意愿分为观察组（48 例）及对照组（41 例）。在每周期化疗前后，观察组用 24h-DCG 监测其心电图情况，对照组用 12 导联心电图（ECG）监测病人心电图情况，对比这两种方法在检测含氟尿嘧啶方案的心脏毒性的发生率、严重程度等方面的作用。**结果** 两组可评价病人共 78 例，

其中观察组 42 例，对照组 36 例。观察组总的心电图异常改变及I级心脏毒性的发生率明显高于对照组（P<0.05）；而两组II-IV级心脏毒性的发生率则无明显差异（P>0.05），但观察组有更轻的趋势。**结论** 24h-DCG 比 12 导联 ECG 检测氟尿嘧啶类药物治疗 HNC 所致的心脏毒性更加灵敏，能更易、更早发现心脏毒性。

115. Activation of SREBP-1c alters lipogenesis and promotes tumor growth and metastasis in gastric cancer

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Purpose: Aggressively growing tumors are characterized by significant variations in metabolites, including lipids, and can involve the elevated synthesis of de novo fatty acids.

Methods: Ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS)-based metabolomics and lipidomics were performed to compare human gastric cancer tissues and adjacent normal tissues from clinical patients. A series of cellular and molecular biological methods were applied to validate the lipidomics results.

Results: Palmitic acid (PA) was found to be significantly downregulated in gastric cancer tissues, and it was found that a high concentration of PA specifically inhibited cell proliferation and impaired cell invasiveness and migration in vitro in AGS, SGC-7901, and MGC-803 gastric cancer cell lines. Moreover, sterol regulatory element-binding protein 1 (SREBP-1c) was activated in human gastric cancer tissues, and it promoted the expression of a series of genes associated with the synthesis of fatty acids, such as SCD1 and FASN. SREBP-1c knockdown rescued the migration and invasion defects in AGS and SGC-7901 gastric cancer cells.

Conclusion: Taken together, our findings confirmed the variation in fatty acid synthesis in gastric cancer and identified SREBP-1c as a promising target for gastric cancer treatment.

116. Could CTSK and COL4A2 be specific biomarkers of poor prognosis for patients with gastric cancer in Asia?—a microarray analysis based on regional population

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Background: In the purpose of identifying reliable biomarkers for evaluating prognosis, monitoring recurrence and exploring new therapeutic targets, it is quite necessary to screen for the genetic changes and potential molecular mechanisms of the occurrence and development of gastric cancer

(GC) from the aspects of race and region. **Methods:** Target datasets were retrieved from Gene Expression Omnibus (GEO) database with “gastric cancer” as the key word, and corresponding data was downloaded. The differentially expressed genes (DEGs) were obtained by using limma R package, and the Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway for DEGs were analyzed in Enirchr database. Protein-protein interaction (PPI) network and molecular module were also constructed through STRING database and Cytoscape software. Survival analyses were completed for DEGs in GEO and Kaplan-Meier plotter database via cross validation. Finally, the correlation between gene expression and the infiltration cell levels in tumor microenvironment (TME) was explored based on the tumor immune estimation resource (TIMER) database. **Results:** Five GC-related microarray datasets were selected and used for differential analysis, and 222 DEGs were identified. GO analyses of DEGs were mainly involved in cell metabolism and the formation of extracellular matrix (ECM). The top enriched pathways of DEGs were protein digestion and absorption, ECM-receptor interaction, focal adhesion (FA), PI3K-Akt signaling pathway. Survival analyses of DEGs revealed that the expression levels of CTSK and COL4A2 were significantly associated with poor prognosis of GC patients in Asian. Specifically, the high expression of CTSK had a closely related to the infiltration level of inflammatory cell in TME. **Conclusions:** CTSK and COL4A2 could play a critical role in the pathogenesis of GC and act as the promising prognostic biomarkers. CTSK could induce the formation of immunosuppressive TME and promote the immune escape of GC cells

117. MicroRNA-4721, induced by EBV-miR-BART22, targets GSK3β to enhance the tumorigenic capacity of nasopharyngeal carcinoma through WNT/β-catenin pathway

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Nasopharyngeal carcinoma (NPC) is prevalent in east and southeast Asia. In the previous study, EBV-miR-BART22 induced tumor metastasis and stemness and was significantly involved in NPC progression. Here, we observed that miR-4721 was induced by EBV-miR-BART22 through PI3K/AKT/C-JUN/Sp1 signaling to promote its transcription. In a subsequent study, we observed that miR-4721 served as a potential oncogenic factor promoting NPC cell cycle progression and cell

proliferation in vitro and in vivo. Mechanism analysis indicated that miR-4721 directly targeted GSK3β and reduced its expression, which therefore elevated β-catenin intra-nuclear aggregation and activated its downstream cell cycle factors including CCND1 and C-MYC. In clinical samples, miR-4721 and GSK3β were respectively observed to be upregulated and downregulated in NPC progression. Elevated expression of miR-4721 was positively associated with clinical progression and poor prognosis. Our study firstly demonstrated that miR-4721 as an oncogene was induced by EBV-miR-BART22 via modulating PI3K/AKT/C-JUN/Sp1 signaling to target GSK3β, which thus activates WNT/β-catenin-stimulated cell cycle signal and enhance the tumorigenic capacity in NPC. miR-4721 may be a potential biomarker or therapeutic target in NPC treatment in the future.

118. Apatinib exhibits synergistic effect with pyrotinib and reverses acquired pyrotinib resistance in HER2-positive gastric cancer via stem cell factor/c-kit signaling and its downstream pathways

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Background: Recently, progress has been made in the development of targeted therapies for human epidermal growth factor receptor 2 (HER2)-positive gastric cancer (GC). However, drug resistance has severely limited the efficacy of anti-HER2 therapies. Pyrotinib is a novel pan-HER inhibitor. Although it is effective in HER2-positive GC treatment, its efficacy in combination with apatinib and associated resistance mechanisms in HER2-positive GC remains unclear.

Methods: In this study, the combination effects of pyrotinib and apatinib were examined in two pyrotinib-sensitive GC cells and xenografts. The RNA sequencing was used to determine the underlying mechanisms of acquired pyrotinib resistance. The role of imatinib and apatinib in reversing pyrotinib resistance was tested in pyrotinib-resistant cells and xenografts.

Results: Here, we reported that a combination of pyrotinib and apatinib exhibits synergistic effect in HER2-positive NCI-N87 xenografts, and showed enhance antitumor efficacy in HER2-positive GC, both in vitro and in vivo. Moreover, uupregulation of the stem cell factor (SCF) levels, and the PI3K/AKT and MAPK pathways was associated with acquired pyrotinib resistance in HER2-positive GC. Mechanistically, we demonstrated that the activation of the SCF/c-kit signaling and its downstream PI3K/AKT and MAPK pathwaysmediated pyrotinib resistance by promoting cell survival and proliferation. Imatinib and apatinib augmented the sensitivity of pyrotinib-resistant cells and xenografts to pyrotinib, by blocking SCF/c-kit signaling.

Conclusions: These results highlight the effectiveness of pyrotinib combined with apatinib in HER2-

positive GC and acquired pyrotinib resistance, thus providing a theoretical basis for new treatment methods.

119. A gene-expression predictor for efficacy of induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma

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Background: Induction chemotherapy (IC) followed by concurrent chemoradiotherapy is the mainstay treatment for patients with locoregionally advanced nasopharyngeal carcinoma. However, some patients obtain little benefit and experience unnecessary toxicities from IC. We intended to develop a gene-expression signature that can identify beneficiaries of IC.

Methods: We screened chemosensitivity-related genes by comparing gene expression profiles of patients with short-term tumor response or nonresponse to IC (n=95) using microarray analysis. Chemosensitivity-related genes were quantified by digital expression profiling in a training cohort (n=342) to obtain a gene signature. We then validated this gene signature in the clinical trial cohort (n=187) and an external independent cohort (n=240). Tests of statistical significance are 2-sided.

Results: We identified 43 chemosensitivity-related genes associated with the short-term tumor response to IC. In the training cohort, a 6-gene signature was developed that was highly accurate at predicting the short-term tumor response to IC (area under the curve [AUC]=0.87, sensitivity=87.5%, specificity=75.6%). We further found that IC conferred failure-free survival benefits only in patients in the benefit group (hazard ratio [HR]=0.54, 95% confidence interval [CI]=0.34 to 0.87; P=.01) and not on those in the no-benefit group (HR=1.25, 95%CI=0.62 to 2.51; P=.53). In the clinical trial cohort, the 6-gene signature was also highly accurate at predicting the tumor response (AUC=0.82, sensitivity=87.5%; specificity=71.8%) and indicated failure-free survival benefits. In the external independent cohort, similar results were observed.

Conclusions: The 6-gene signature can help select beneficiaries of IC and lay a foundation for a more individualized therapeutic strategy for locoregionally advanced nasopharyngeal carcinoma patients.

120. Plasma Epstein–Barr virus microRNA BART8-3p as a diagnostic and prognostic biomarker in nasopharyngeal carcinoma

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Background. Nasopharyngeal carcinoma (NPC) is an Epstein–Barr Virus (EBV) associated tumor that highly common in Southern China. Our previous sequencing data demonstrated that EBV encoded microRNA BART8-3p, was highest up-regulated in NPC and was closely associated with metastasis of NPC in vitro. However, the values of plasma BART8-3p in NPC patients have not yet been well characterized. **Material and methods.** Here, we quantified the plasma BART8-3p by quantitative Real-Time PCR in 205 newly diagnosed, non-metastatic NPC patients that treated with intensity-modulated radiotherapy (IMRT), and investigated its expression and impact on NPC patients' survival through Kaplan-Meier analyses and Multivariate analyses. **Results.** Plasma BART8-3p was highly expressed in NPC patients than in healthy controls, and yielded a 92% predictive values for detecting NPC. Importantly, levels of pretreatment BART8-3p greatly dropped after therapy. High pretreatment or posttreatment BART8-3p expression was an independently unfavorable prognostic maker for NPC. For locally advanced NPC with high levels of pretreatment BART8-3p, receiving no less than 6 cycles of chemotherapy was associated with better outcome. **Conclusion.** Plasma BART8-3p is a promising biomarker for detection and prognosis of NPC.

121. Early Assessment of Metastatic Risk for Colorectal Cancer

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Metastasis is the main fetal cause of the colorectal cancer (CRC). It is often started by local invasion of tumor cells to the nearby lymphatic cells. Therefore, early assessment of local invasion risk can assist prioritizing therapeutic rigimen and thus substantially increase the survival rate of CRC patients. In this study, a small CRC cohort of eight inpatients was recruited, half of which had local lymphatic metastasis. We collected the cancer, paracancer, and normal tissues from the cohort members and determined the exome-wide mutation profiles by deep sequencing. Upon the mutation profiles, we designed a novel modified Bayesian model to quantitatively evaluate the local invasion risk. Via connecting the accumalated local invation risk to the patient survival rate, we identified eleven potential metastasis driver mutations in eight genes. These driver gene mutations exhibited a determinant roles in the model for early CRC metastasis assessment. For user convinience, we also deployed an online server (http://bioinf.xmu.edu.cn/AmetaRisk) for rapid CRC metastasis assessment. In summary, this study systematically assessed the metastatic risk of local lymphatic invasion in basis

of germline mutations for the first time. It proposed a early warning mechanism for potential metastasis. It also provided valuable clues for mechanistic investigation of early metatasis.

122.伊立替康通过 ROS 介导的 JAK2-STAT1-CXCL1 通路促进结直肠癌细胞的转移

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拓扑异构酶抑制剂伊立替康可以通过阻止 DNA 的复制来阻止 DNA 损伤修复和诱导细胞周期阻滞，进而抑制细胞增殖。虽然拓扑异构酶抑制剂类的化疗药物已广泛应用于临床，但其对癌细胞转移的影响尚不清楚。在这里，我们发现拓扑异构酶抑制剂依托泊苷、阿霉素和伊立替康可以促进结直肠癌细胞亚群的迁移和侵袭。其中伊立替康是结直肠癌临床治疗中常用化疗药物，因此我们进一步着重研究伊立替康对结直肠癌细胞运动能力的影响。在体内实验中，我们将伊立替康处理后的结直肠癌 LoVo 细胞通过尾静脉注射进入 NOD/SCID 免疫缺陷小鼠体内，发现伊立替康处理后的结直肠癌 LoVo 细胞在小鼠体内的转移能力较对照组显著增强。我们研究发现伊立替康等上述拓扑异构酶抑制剂处理结直肠癌 LoVo 细胞和 SW480 细胞的条件培养基也具有这种能力。此外实验发现伊立替康等拓扑异构酶抑制剂也可以促进小细胞肺癌 H446 细胞运动能力增强。结直肠癌 LoVo 细胞和 SW480 细胞蛋白质谱筛选显示拓扑异构酶抑制剂上调了趋化因子 CXCL1 的表达和分泌。我们将蛋白质谱分析结果在结直肠癌 LoVo 细胞、SW480 细胞和小细胞肺癌 H446 细胞中均进行了验证。重要的是，基因敲除 CXCL1 或使用抗体中和 CXCL1 可以拮抗伊立替康等拓扑异构酶抑制剂促进结直肠癌细胞的迁移和侵袭。进一步的研究发现，伊立替康等拓扑异构酶抑制剂增强了 JAK2 和 STAT1 的磷酸化。基因敲除或使用小分子化合物抑制 JAK2 或 STAT1 激活拮抗了伊立替康等拓扑异构酶抑制剂诱导的 CXCL1 表达上调、JAK2 磷酸化激活上调、STAT1 磷酸化激活上调和细胞运动能力增强的细胞表型。此外，伊立替康等拓扑异构酶抑制剂增加了细胞活性氧水平，促进了 PTP1B 的氧化，而还原性谷胱甘肽则逆转了伊立替康等拓扑异构酶抑制剂诱导的 JAK2-STAT1 激活、CXCL1 表达上调和细胞运动能力增强的细胞表型。我们的研究表明伊立替康等拓扑异构酶抑制剂可以通过激活活性氧和 JAK2-STAT1 信号通路促进 CXCL1 的表达和分泌，从而促进结直肠癌细胞的迁移和侵袭。我们的结果支持了 ROS 干预作为另一种预防伊立替康等拓扑异构酶抑制剂类化疗药物诱导肿瘤转移的方法的前景。

123. 胃癌细胞中 Cullin1 基因表达与肿瘤细胞上皮间充质转化的关系

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目的 检测 Cullin1 基因在胃癌组织和细胞株中的表达情况，并对其参与肿瘤上皮间充质转化（EMT）的机制进行探讨。**方法** 应用实时荧光定量 RT-PCR（qRT-PCR）和蛋白印迹（Western blotting）技术分别检测 12 例胃癌与配对癌旁组织中 Cullin1 mRNA 和蛋白的表达情况；合成抑制内源性 Cullin1 表达的小干扰 RNA（siRNA）并转染 SGC7901 细胞；MTT 实验检测肿瘤细胞的增殖活性；应用划痕实验（Wound healing test）及 Transwell 小室侵袭实验检测细胞的侵袭迁移能力；通过 qRT-PCR 及 Western blotting 检测转染前后细胞中 EMT 相关基因 E-cadherin、N-cadherin、Vimentin、Snail、MMP-9 的表达情况。**结果** 与癌旁正常组织相比，胃癌组织中 Cullin1 mRNA 和蛋白的表达水平均明显升高（P<0.05）。Cullin1-siRNA 有效抑制了 SGC7901 细胞中内源性 Cullin1 表达；MTT 结果显示转染 48h 后 Cullin1-siRNA 转染组细胞活性明显低于非特异性 siRNA 转染组（NS-siRNA）和空白对照组（Blank control）（P<0.05）。Cullin1-siRNA 转染后 SGC7901 细胞的迁移及侵袭能力与 NS-siRNA 组、Blank control 组比较均明显降低（P<0.05）。Cullin1-siRNA 转染后 SGC7901 细胞 N-cadherin、Snail、MMP-9 表达明显降低，E-cadherin 表达升高（P<0.05），而 Vimentin 在转染前后无明显变化（P>0.05）。**结论** Cullin1 基因可能通过调节部分 EMT 基因而促进了胃癌侵袭转移，有可能成为胃癌治疗的靶基因。

124. LIF as a novel biomarker predicts lymph node and distant metastasis for pancreatic cancer

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Patients with pancreatic cancer have a very low survival rate and most of them were diagnosed with lymph node metastasis and distant metastasis, which is grim for clinicians in spite of many efforts to improve OS and RFS over the last 20 years. So searching a new biomarker for predicting lymph node and distant metastasis for pancreatic cancer is crucial. Leukaemia inhibitory factor (LIF) has been reported to be overexpressed in many types of cancer and is known to be involved in the development of various cancers including pancreatic cancer. However, the role of LIF as a biomarker in pancreatic cancer remains unclear. In our study, univariate and multivariate Cox regression analyses showed LIF in the pancreatic tumor tissues was an independent risk factor related with worse OS and RFS, we found that high LIF expression was related to poorer clinicopathological features such as lymph node

metastasis and pTNM stage. We also found LIF expression obviously increases in pancreatic cancer serum compared with healthy controls. Moreover，based on the area under the receiver operating characteristic (ROC) curve, we found serum LIF is a better biomarker than other biomarkers (CA199 and CEA) in predicting LN and distant metastasis.

Keywords: Pancreatic cancer; biomarkers; diagnosis; prediction; metastasis

125. Metallophosphoesterase 1, a novel candidate gene in hepatocellular carcinoma malignancy and recurrence

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Abstract

Background: There is an unmet need to identify novel mechanism-based prognostic genes associated with hepatocellular carcinoma (HCC) recurrence that can predict patient outcomes and provide therapeutic targets. This study aims to identify potential novel driver genes and mutations in HCC.

Methods: Single nucleotide variations (SNVs) contributing to HCC recurrence were identified using whole exome sequencing of 5 DNA samples extracted from a single HCC patient with HBV-induced cirrhosis. SNVs were verified in primary HCC (n=87), recurrent HCC (n=34), and benign liver disease with cirrhosis tissues (n=43). A candidate gene was identified, and its association and function in HCC development and recurrence were examined.

Results: 177 SNVs were identified and 70 SNVs were verified. A MPPE1 missense mutation on chr18_11897016 was the most frequent mutation (16.5%) in primary and recurrent HCC tissues, occurring with a higher frequency in recurrent HCC than primary HCC or benign liver tumor tissues. The MPPE1 mutation was significantly associated with HCC recurrence (P=0.003), TNM stage (P=0.002), and Child-Pugh classification (P =0.039), and was an independent risk factor for HCC recurrence (HR=1.969; 95%CI=1.043–3.714, P=0.037).. The knockdown of MPPE1 in HCC cell lines significantly inhibited cell proliferation, migration and invasion, induced cell cycle arrest and apoptosis in vitro, and inhibited xenograft tumor growth in nude mice in vivo (P<0.05). Conclusions: MPPE1 is a novel gene associated with HCC malignancy and recurrence.

126. microRNA-10a 抑制结肠癌肝转移肿瘤相关成纤维细胞活性的研究

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【摘要】 目的 探讨 microRNA-10a（miR-10a）对肝脏微环境中肿瘤相关成纤维细胞（TAFs）的增殖、迁移以及促性因子白细胞介素 6（IL-6）、白细胞介素 8（IL-8）、白细胞介素 1β（IL-1β）mRNA 表达水平的影响。**方法** 收集同一结肠癌患者癌旁正常肝组织和转移至肝脏的病灶组织，采用组织块法建立原代人肝正常成纤维细胞（NFs）和原代 TAFs。通过形态学观察和细胞免疫荧光染色对 NFs 和 TAFs 进行鉴定，并通过流式细胞术鉴定二者的纯度。用实时荧光定量聚合酶链反应（RT-qPCR）检测 NFs 和 TAFs 中 miR-10a 的表达水平，并在低表达 miR-10a 的细胞中过表达 miR-10a。随后采用 CCK-8 实验、划痕实验和 RT-qPCR 分别检测 miR-10a 对该细胞增殖、迁移能力以及 IL-6、IL-8、IL-1β mRNA 表达水平的影响。**结果** 细胞免疫荧光染色显示人细胞角蛋白 18（CK-18）在 NFs 和 TAFs 中均不表达；成纤维细胞特异性蛋白-1（FSP-1）在两细胞中均表达；α-平滑肌肌动蛋白（α-SMA）在 NFs 中弱表达，在 TAFs 中强表达。流式细胞术显示 NFs 与 TAFs 中 α-SMA 阳性率为 95%和 95.3%。miR-10a 在 TAFs 的表达水平为 NFs 的 0.65 倍（P<0.01）。过表达 miR-10a 后 TAFs 在第 3、4、5 天增殖能力显著低于同时期的 NC 组细胞（P<0.05，P<0.05，P<0.01）；TAFs 的迁移能力在 24 h 和 48 h 分别较 NC 组降低 25%和 15%（P<0.01，P<0.05），TAFs 中 IL-6、IL-8、IL-1β 的表达水平分别较 NC 组降低 54%、27%和 42%（P<0.01，P<0.01，P<0.05）。**结论** miR-10a 在 TAFs 中呈低表达，miR-10a 过表达抑制了 TAFs 的增殖和迁移，并降低炎性因子 IL-6、IL-8、IL-1β mRNA 的表达，这可能是 TAFs 抑制肝脏形成转移灶的重要因素。

127. SLFN11 inhibits hepatocellular carcinoma tumorigenesis and metastasis by targeting RPS4X via mTOR pathway

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Background: Hepatocellular carcinoma (HCC) remains one of the most refractory malignancies worldwide. It is well known that Hepatitis B and C viral infections are the major risk factors that drive HCC. It was reported that the proteins of Schlafen (SLFN) family play a vital role in the regulation of mammalian biological functions, such as the inhibition of viral replication and induction of immune response. Schlafen family member 11 (SLFN11) has been reported to play an important role in inhibiting the production of human immunodeficiency virus 1 (HIV-1). However, whether SLFN11 also inhibits hepatitis B virus (HBV), and affects HBV-induced HCC remain to be systematically investigated.

Methods: Tissue samples were collected from 182 patients with HCC who underwent radical hepatectomy in the Department of Liver Surgery, Zhongshan Hospital, Fudan University from January 1, 2009 to January 1, 2010. In addition, another independent cohort which contains 110 paired HCC samples from patients in 2012 were enrolled as validation cohort. Quantitative reverse transcription polymerase chain reaction, western blot and IHC staining were conducted to investigate the potential role and prognostic value of SLFN11 in HCC. Then SLFN11 was stably overexpressed or knocked down in HCC cell lines. To further explore the potential biological function of SLFN11 in HCC, cell counting kit-8 (CCK-8) assays, colony formation assays, wound healing assays and transwell cell migration and invasion assays were performed in vitro. Meanwhile, HCC subcutaneous xenograft tumor models were established for in vivo assays. Subsequently, immunoprecipitation (IP) and liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analyses were applied to understand the molecular mechanisms of SLFN11 in HCC. Co-IP, immunofluorescence and IHC staining were used to analyze the relationship between ribosomal protein S4 X-linked (RPS4X) and SLFN11. Finally, the therapeutic potential of SLFN11 with mTOR pathway inhibitor INK128 on inhibiting HCC growth and metastasis was evaluated in vitro and in vivo orthotopic xenograft mouse models.

Results: We demonstrate that SLFN11 expression is decreased in HCC, which is associated with

shorter overall survival and higher recurrence rates in patients. In addition, we show that low SLFN11 expression is associated with aggressive clinicopathologic characteristics. In the two independent cohorts, univariate and multivariate Cox regression analysis demonstrated that low expression of SLFN11 was an independent risk factor affecting the overall and recurrence-free survival rate for HCC patients after curative resection. Moreover, overexpression of SLFN11 inhibits HCC cell proliferation, migration, and invasion, facilitates apoptosis in vitro, and impedes HCC growth and metastasis in vivo, all of which are attenuated by SLFN11 knockdown. Mechanistically, SLFN11 physically associates with RPS4X and blocks the mTOR signaling pathway. In orthotopic mouse models, overexpression of SLFN11 or inhibition of mTOR pathway inhibitor by INK128 reverses HCC progression and metastasis.

Conclusions: SLFN11 may serve as a powerful prognostic biomarker and putative tumor suppressor by suppressing the mTOR signaling pathway via RPS4X in HCC. Our study may therefore offer a novel therapeutic strategy for treating HCC patients with the mTOR pathway inhibitor INK128. These encouraging preclinical results warrant validation in future clinical trials for HCC.

128. YTHDF1 在前列腺癌中的机制研究

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前列腺癌是常见的泌尿系统恶性肿瘤之一，根据美国 2020 年最新的癌症统计结果显示，前列腺癌的发病率在男性肿瘤中居于首位，而前列腺癌的死亡率在男性肿瘤中也居于第二位。另外，根据中国的癌症统计结果，从 2000 年到 2011 年，随着我国生活水平的改善，环境污染问题以及膳食结构的逐步西化，前列腺癌的发病率和死亡率也出现了明显上升的趋势。迄今为止，该疾病的发病机制尚不完全清楚。课题组研究发现，YTHDF1 在许多实体瘤中高频扩增，而在前列腺癌肿瘤组织和细胞系中的表达尤其高。在前列腺癌肿瘤细胞系中敲低 YTHDF1 表达后，显著抑制了肿瘤细胞的增殖和迁移能力，并可使细胞周期阻滞在 G2/M 期。与此同时发现，SKP1-cullin 1 E3 泛素连接酶组分之一的 RNF7 的蛋白表达水平，在 YTHDF1 敲低表达后显著下调表达，而 SKP1/cullin 1/RNF7 的下游底物蛋白：细胞周期调控蛋白 p27 和 AKT 去磷酸化酶 PHLPP1，由于 RNF7-E3 泛素连接酶的缺失而表达上调。课题组的前期研究已经明确 YTHDF1 可进而通过识别 mRNA 上的 m6A 修饰位点，进一步提高蛋白翻译的效率。本研究通过体外生化实验，类器官体外培养等实验方法，进一步研究发现 YTHDF1 可以通过提高 m6A 修饰的 RNF7 的 mRNA 蛋白翻译效率，促进 p27 和 PHLPP1 的蛋白降解，激活 PI3K/AKT 信号通路，进而促进前列腺癌细胞的恶性增殖和肿瘤进程。该研究为未来前列腺癌的临床诊断和治疗提供了新靶点。

129. New Insight into Practice in Clinical Testing of mRNA Splicing Variant Associated with Exonic Skipping Mutations

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Background

Sanger sequencing is economically recommended for individuals from a family with a specific BRCA1/2 pathogenic or likely pathogenic variant. In clinical practice, however, identification of germline splicing variants remains challenging in family members, leading to a proportion of patients or individuals with risk of suspected BRCA-associated hereditary cancers omitted.

Design

Here we focused on a family involved by multiple cancers. The proband was a 48- year-old woman diagnosed of ovarian cancer and breast cancer carrying a heterozygous variant of BRCA1 c.4987-5T>C (p.?). Although this variant has conflicting interpretations of pathogenicity (likely pathologic or variant of uncertain significance) at the present, the proband's affected sister along with the asymptomatic daughter, niece and nephew underwent gene testing for BRCA1 c.4987-5T>C. Genomic DNA was extracted from blood samples, and amplified by primer pair 1 covering c.4987-105 to c.5074+69 and primer pair 2 covering c.4987-299 to c.5074+69, respectively. Considering the variant of BRCA1 c.4987-5T>A was previously proposed to induce strong splicing defects and exon 17 skipping, analyses of RNA from examinees' peripheral blood were subsequently performed, using a two-step reverse transcriptase-PCR (RT-PCR) protocol. mRNA was amplified by primer set ranging from exon 15 to exon 17. PCR products were purified for Sanger sequencing. Next, the obtained sequences were compared with reference sequences.

Results

Intriguingly, the proband's sister and daughter shared identical BRCA1 exon 17 skipping at mRNA level, but the sister showed "wild-type" status at DNA level when using primer pair 1, and the daughter BRCA1 c.4987-5T>C. We supposed that the sister may carry certain de novo mutations in deep intronic regions, although uncommon, which interfered the binding of primer pair 1 to her DNA sequence. Primer pair 2 was thus used, and BRCA1 c.4987-5T>C was observed in both samples from the sister and daughter by DNA-based Sanger sequencing this time. Besides, the proband's sister indeed carried other concurrent mutations in BRCA1 (c.4987-68A>G and c.4987-92A>G).

Neither asymptomatic niece nor nephew tested positive for BRCA1 c.4987-5T>C at DNA and RNA level by Sanger sequencing. Despite the controversial pathogenic interpretations of BRCA1 c.4987-5T>C, further genetic counseling and close screening strategy were recommended for the proband's daughter taking into account the cancer history of her family.

Conclusion

Results from our study demonstrate the necessity of performing simultaneous genetic DNA and RNA testing in identifying splicing variants associated with exonic skipping mutations when NGS not available. We also recommend designing multiple primer pairs for DNA-based Sanger sequencing to address unexpected de novo mutations in deep intronic regions.

130. AKR1B10 confers resistance to radiotherapy via FFA/TLR4/NF-κB axis in nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is one kind of human head and neck cancers with high incidence in Southern China, Southeast Asia and North Africa. In spite of great innovations in radiation and chemotherapy treatments, the 5-year survival rate is not satisfactory. One of the main reasons is resistance to radiotherapy which leads to therapy failure and recurrence of NPC. The mechanism underlying remains to be fully elucidated. Aldo-keto reductase B10 (AKR1B10) plays a role in the formation and development of carcinomas. However, its role in resistance to radiotherapy of NPC is not clear. In this research, the relationship between AKR1B10 expression and the treatment effect of NPC patients, NPC cell survival, cell apoptosis, and DNA damage repair, as well as the effect and mechanism of AKR1B10 expression on NPC radioresistance was explored. A total 58 paraffin tissues of NPC patients received radiotherapy were collected including 30 patients with radiosensitivity and 28 patients with radioresistance. The relationship between AKR1B10 expression and the treatment effect as well as clinical characteristics was analyzed by immuno-histochemical experiments, and the roles of AKR1B10 in cell survival, apoptosis and DNA damage repair were detected using the AKR1B10 overexpressed cell models. Furthermore the mechanism of AKR1B10 in NPC radioresistance was explored. Finally, the radioresistance effect of AKR1B10 expression was evaluated by the tumor xenograft model of nude mice and the method of radiotherapy. The results show AKR1B10 expression level was correlated with radiotherapy resistance, and AKR1B10 overexpression promoted proliferation of NPC cells, reduced apoptosis and decreased cellular DNA damage after radiotherapy. The probable molecular mechanism is AKR1B10 expression activating FFA/TLR4/NF-κB axis in NPC cells. This was validated by using the TLR4 inhibitor TAK242 to treat AKR1B10 expressed NPC cell which reduced the phosphorylation of NF-κB. The data of this study suggests that AKR1B10 can induce radiotherapy resistance and promote cell survival via FFA/TLR4/NF-κB axis in NPC, which may provide a novel target to fight against radiotherapy resistance of NPC.

Keywords: Nasopharyngeal carcinoma; AKR1B10; radiotherapy resistance; FFA/TLR4/NF-κB axis

131. Single-cell Transcriptome-based Multilayer Network Biomarker for Predicting Prognosis and Therapeutic Response of Gliomas

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Occurrence and development of cancers are governed by complex networks of interacting intercellular and intracellular signals. The technology of single-cell RNA sequencing (scRNA-seq) provides an unprecedented opportunity for dissecting the interplay between the cancer cells and the associated microenvironment. Here we combined scRNA-seq data with clinical bulk gene expression data to develop a computational pipeline for identifying the prognostic and predictive signature that connects cancer cells and microenvironmental cells. The pipeline was applied to glioma scRNA-seq data and revealed a tumor-associated microglia/macrophage-mediated EGFR/ERBB2 feedback-crosstalk signaling module which was defined as a multilayer network biomarker (MNB) to predict survival outcome and therapeutic response of glioma patients. We used publicly available clinical datasets from large cohorts of glioma patients to examine the prognostic significance and predictive accuracy of the MNB which outperformed conventional gene biomarkers and other methods. Additionally, the MNB was found to be predictive of the sensitivity or resistance of glioma patients to molecularly targeted therapeutics. Moreover, the MNB was an independent and the strongest prognostic factor when adjusted for clinicopathologic risk factors and other existing gene signatures. The robustness of the MNB was further tested on additional datasets. Our study presents a promising scRNA-seq transcriptome-based multilayer network approach to elucidate the interactions between tumor cell and tumor-associated microenvironment and to identify prognostic and predictive signatures of cancer patients. The proposed MNB method may facilitate the design of more effective biomarkers for predicting prognosis and therapeutic resistance of cancer patients.

132. Targeting YAP1/LINC00152/FSCN1 Signaling Axis Prevents the Progression of Colorectal Cancer

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As a transcription coactivator, Yes-associated protein 1 (YAP1)'s role in tumorigenesis is well established. However, the mechanism of YAP1-regulating long noncoding RNAs (lncRNA) in tumors is still largely unknown. Here, a YAP1 target gene, long intergenic noncoding RNA 00152 (LINC00152), which is highly expressed in colorectal cancer (CRC), is identified. The oncogenic

functions of LINC00152 in CRC are demonstrated by a panel of in vitro and in vivo experiments. Further studies reveal the potential downstream mechanisms of LINC00152, which can act as a competing endogenous RNA sponging with miR-632 and miR-185-3p to regulate Fascin actin-bundling protein 1 (FSCN1) expression and thus promote the malignant proliferation and metastasis in CRC cells. Targeting the YAP1/LINC00152/FSCN1 axis inhibits the progression of CRC. This finding provides a new regulatory model of the "YAP1-lncRNA" in CRC, which gives rise to a new perspective, "YAP1/LINC00152/miR-632-miR-185-3p/FSCN1," to explore the cancer-promoting mechanism of YAP1 involved in CRC.

133. Immune and Stromal Scoring System Associated with Prognosis and Response to Immune Checkpoint Inhibitors: A Gene-Based Multi-Cancer Analysis

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Tumor microenvironment (TME) was associated with tumor progression and response to immunotherapy. Previous tools provided the estimation methods of TME cell infiltration. However, there is still a lack of single index to reflect immune and stromal signals associated with tumor prognosis and immune checkpoint inhibitor (ICI) therapy responses. We developed a novel immune and stromal activation scoring system named ISTMEscore via unique workflow. A total of 15 datasets were used for both training and validation of our system, containing 2965 samples of lung adenocarcinoma (LUAD), skin cutaneous melanoma (SKCM) and head and neck squamous cell carcinoma (HNSC). According to their immune and stromal scores, patients were divided into 4 subtypes. The patients with high immune and low stromal scores (HL) were associated with low ratio of T cell co-inhibitory/stimulatory molecules and low levels of angiogenesis markers, while the patients with low immune and high stromal scores (LH) had the opposite characteristics. We next built TME networks interacted by cells, receptors and ligands. The HL patients had immune-centered networks, while the patients with low immune and stromal scores (LL) had desert-like network. Moreover, the HL patients presented decreased copy numbers of alteration burden. For the clinical characteristics, our TME classification was an independent prognostic factor. In the 5 cohorts of ICI therapy, the LH patients were linked to the lowest response rate. In conclusion, our ISTMEscore system could predict the prognosis and immunotherapy response. Compared to previous TME scores, the ISTMEscore had superior prediction capabilities in prognosis and ICI response for multiple tumors.

134. NrF2/ARE and NF-κB pathway regulation may be the mechanism for lutein inhibition of human breast cancer cell

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Though lutein can inhibit cancer cell proliferation via alleviating oxidative injury, the molecular mechanisms of lutein involvement in the nuclear factor E2-related factor-2/antioxidant response element (NrF2/ARE) and NF-**κ**B pathways remain poorly understood. **Materials & methods**: MTT, flow cytometry, quantitative real-time PCR (qRT-PCR) and western blot assays were performed. **Results:** After treatment with lutein, breast cancer cell proliferation was significantly decreased in a dose-dependent manner. Lutein induced nuclear translocation and protein expression of NrF2, improved the expression of cellular antioxidant enzymes and attenuated reactive oxygen species levels. Moreover, lutein treat ment decreased NF-**κ**B signaling pathway related NF-**κ**B p65 protein expression.

Conclusion: The effect of lutein antiproliferation was mediated by activation of the NrF2/ARE pathway, and blocking of the NF-**κ**B signaling pathway

135. 叶黄素对乳腺癌细胞活力的影响

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目的: 探究叶黄素对人乳腺癌 T47D 细胞活力的影响及其可能的作用机制。方法: 将人乳腺癌 T47D 细胞随机分为对照组和叶黄素(浓度分别为 6. 25、12. 5、25 和 50 mg /L) 干预组，采用 MTT 法检测叶黄素对 T47D 细胞活力的影响; RT-qPCR 检测核因子 E2 相关因子 2(Nrf2) ，谷胱甘肽过氧化物酶 1(GPx1) 及超氧化物歧化酶 2(SOD2) 的 mRNA 水平; 荧光探针 DCFH-DA 法检测细胞内活性氧簇(ROS) 水平; Western blot 检测 Nrf2 和 p65 的蛋白表达。结果: MTT 结果显示叶黄素抑制人乳腺癌 T47D 细胞的活力，且呈时间和剂量依赖关系。RT-qPCR结果显示各浓度叶黄素干预组细胞中 Nrf2，GPx1 及 SOD2 的 mRNA 水平均较对照组升高(P ＜ 0. 05) ; 且叶黄素干预组细胞内 ROS 水平显著下降(P ＜ 0. 01) 。Western blot 结果显示，叶黄素干预 48 h 后，Nrf2 蛋白表达增加(P ＜0. 05) ，p65 蛋白表达降低(P ＜ 0. 05) ，呈剂量依赖关系。结论: 叶黄素对乳腺癌细胞活力的抑制作用可能与上调 Nrf2 的表达、诱导抗氧化酶 GPx1 及 SOD2 mRNA 表达和降低氧化应激水平，阻断 NF-κB 信号通路有关。

136. MicroＲNA-141 靶向 Keap1 调控 Nrf2 /AＲE 信号通路 对乳腺癌 T47D 细胞活力的影响

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目的: 探讨微小ＲNA-141(miＲNA-141) 靶向 Keap1 调控 Nrf2 /AＲE 信号通路对乳腺癌 T47D 细胞活力的影响。方法: 乳腺癌 T47D 细胞分别转染 miＲNA-141 模拟物(mimic) 和阴性对照序列(NC) ，作为 miＲNA-141 组和 NC 组，并设立未转染空白对照组，采用 real-time PCＲ 法检测细胞中 miＲNA-141 的含量; MTT 法与荧光探针 2’7’-二氢二氯荧光素二乙酸酯(DCFH-DA) 法分别检测细胞活力和活性氧簇(ＲOS) 水平; Western blot 法检测胞质接头蛋白 Keap1、核因子 E2 相关因子 2(Nrf2) 、超氧化物歧化酶 2(SOD2) 和谷胱甘肽过氧化酶 1(GPx1) 的表达;双萤光素酶实验检测 miＲNA-141 与 Keap1 的关系。结果: 转染 miＲNA-141 mimic 后，miＲNA-141 组的 miＲNA-141 表达量明显增高，细胞活力、ＲOS 水平和 Keap1 蛋白表达均下降，而细胞核 Nrf2 蛋白 SOD2 和 GPx1 表达升高(P ＜0. 05) ; 双萤光素酶实验结果显示 Keap1 为 miＲNA-141 的靶基因。结论: miＲNA-141 可能通过靶向负调控 Keap1 激活 Nrf2 /AＲE 信号通路，诱导抗氧化酶的表达，以降低细胞氧化应激水平，从而抑制乳腺癌细胞的活力

137. Association of Clock-like Mutational Signature with Immune Check-point Inhibitor Outcome in Patients with Melanoma and NSCLC

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Immune checkpoint inhibitor (ICI) therapy has achieved remarkable clinical benefit in melanoma and NSCLC. Tumor mutational signatures are the fingerprints of endogenous and exogenous factors that have acted throughout tumorigenesis and heterogeneity; however, its association with immune response in ICI-treated samples remain unclear. Here, we leveraged whole-exome sequencing (WES)-based mutational profile combined with clinicopathologic characteristics from melanoma and NSCLC datasets to examine whether tumor genomic features contribute to clinical benefit to ICI treatment. Besides, mutational data acquired from targeted next-generation sequencing assay (MSK-IMPACT panels) was also employed for further corroboration. A mutational signature (known as age-related clock-like-processing) characterized by enrichment of C>T mutations at NpCpG trinucleotides were identified to be associated with a worse prognosis and lower TML in both WES and targeted-NGS

immunotherapy cohorts. We also analyzed gene transcriptomic profiles and identified immune regulation-related gene pathways that were significantly altered in samples with different clock-like signature grouping. Leucocyte subsets analysis further revealed that clock-like signature was associated with the reduction of cytotoxic-cells infiltration and elevation of regulatory T-cells. Overall, our work re-annotated the age-related clock-like signature was associated with worse prognosis and lower immune activity, offering opportunities to stratify patients into optimal immunotherapy plans based on genomic subtyping.

138. Identification a novel clinical biomarker in early diagnosis of human non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) is a malignant tumor with high morbidity and mortality. The clinical biomarkers currently used for the early diagnosis of lung cancer have poor sensitivity and specificity. Therefore, it is urgent to identify sensitive biomarkers for the early detection of NSCLC to improve the patient survival of patients. In our previously study, we identified glycoprotein alpha-1-antichymotrypsin (AACT) as an early biomarker of NSCLC. In this study, serum glycopeptides were enriched using the high-GlcNAc-specific binding lectin, AANL/AAL2, for further quantitative proteomics analysis using LC- MS/MS. A total of 55 differentially expressed proteins were identified by using demethylation labelling proteomics. Serum paraoxonase/arylesterase 1 (PON1) was selected for validation by western blotting and lectin-ELISA in samples from 120 enrolled patients. Our data showed that AANL-enriched PON1 has better diagnostic performance than total PON1 in early NSCLC, since it differed between early Stage I tumor samples and tumor-free samples (healthy and benign). Combining AANL- enriched PON1 with carcinoembryonic antigen (CEA) significantly improved the diagnostic specificity of CEA. Moreover, combined AANL-enriched PON1 and AANL-enriched AACT was significantly different between early NSCLC samples and tumor-free samples with an AUC of 0.940, 94.4% sensitivity, and 90.2% specificity. Our findings suggest that combined AANL- enriched PON1 and AANL-enriched AACT is a potential clinical biomarker for the early diagnosis of NSCLC.

139. p62 通过调控线粒体自噬影响卵巢癌细胞顺铂敏感性的机制研究

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目的：探究线粒体自噬对卵巢癌顺铂敏感性的影响及其作用机制。进一步探讨 p62 作为自噬受体是否参与到线粒体自噬及其分子机制。

方法：采用 MTT 方法分别检测了 A2780 及其耐药株 A2780/DDP 细胞单加顺铂和合加线粒体自噬抑制剂（环孢菌素 A）后的 IC50 值以及合加效应($P < 0.05$ vs. control)。在这两种细胞中使用免疫荧光的方法探究顺铂刺激（5μg/ml）后 LC3II与线粒体的共定位。在 A2780/DDP 细胞中敲减 p62 后，使用免疫荧光技术分别检测了 parkin 和 LC3II在线粒体上的定位。在 A2780 细胞中转染 UBA 结构域截短突变 p62 后，分别使用了免疫共沉淀和免疫荧光技术检测了 p62 在线粒体上的定位。构建了 mt-keima-A2780 稳转细胞株检测顺铂刺激下 A2780 细胞中的线粒体自噬流。使用免疫共沉淀技术检测 parkin 和磷酸化泛素（p-Ub）的结合，分离线粒体蛋白后蛋白免疫印迹实验检测 HK2 和 pink1 在线粒体裂解液中的表达，以及使用免疫荧光技术检测了 HK2 在线粒体上的定位。随后使用蛋白免疫印迹实验检测了 p62 敲减后和 UBA 结构域缺失后 A2780 细胞中 HK2 的表达。最后，通过 MTT，实时细胞分析技术以及 Annexin-V FITC/PI 流式分析等手段检测了顺铂刺激下 p62 的 UBA 结构域敲除后 A2780 细胞的细胞活力和凋亡情况。

结果：发现当线粒体自噬被抑制时 A2780 细胞的顺铂敏感性被逆转，p62 敲减后线粒体自噬被抑制，说明 p62 参与到顺铂刺激下卵巢癌细胞中的线粒体自我清除过程。为了进一步探究其分子机制，构建了 UBA 结构域敲除型的 p62，发现该转染组细胞中 p62 与线粒体定位下降，但是线粒体自噬流量升高，说明 p62 对于线粒体自噬的调控并不依赖于其线粒体定位。此后本研究探讨了 UBA 结构域缺失后 A2780 细胞线粒体自噬流量升高的原因，发现 parkin 与磷酸化泛素（p-Ub）结合形式增加，pink1 在线粒体裂解液中表达无差异，HK2 在线粒体上定位增加，说明 HK2 在线粒体上的募集是 p62 的 UBA 结构域缺失后使 A2780 细胞中线粒体自噬水平增加的原因。最终，UBA 结构域缺失后造成的卵巢癌线粒体自噬水平增加可以降低 A2780 细胞对于顺铂的敏感性。

结论：卵巢癌细胞中 p62 的 UBA 结构域发生突变后，HK2 的表达增加了线粒体自噬的水平，从而实现了顺铂刺激的凋亡水平的平衡调节。

140. MRI-based radiomics signature for pretreatment prediction of pathological response to neoadjuvant chemotherapy in osteosarcoma: a multicenter study

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Background: Osteosarcoma (OS) is the most common primary bone malignancy in children and adolescents with an estimated incidence rate of two-three cases per million people per year [1]. With the introduction of the neoadjuvant chemotherapy (NAC), the five-year survival rate of localized OS has significantly improved from 20% to 60–70% [2; 3]. Unfortunately, as many as 20 % of patients are resistant to this treatment, which resulted in toxicities and delayed tumor removal [4]. Hence, accurate identification of poor response to NAC in patients with osteosarcoma could avoid unnecessary chemotherapy toxicities and determine the most appropriate treatment strategy to improve survival rates or to delay disease progression [5]. We aimed to develop and validate a radiomics signature based on MRI from multicenter datasets for pretreatment prediction of pathologic response to NAC in patients with osteosarcoma.

Methods: This study was approved by the ethics committee of the third affiliated hospital of southern medical university. We retrospectively enrolled 102 patients with histologically confirmed osteosarcoma from 4 hospitals (68 in the primary cohort and 34 in the external validation cohort). All patients underwent diagnostic contrast enhancement MRI before chemotherapy. After surgery, histological responses to NAC were evaluated on the postsurgical specimens. Quantitative imaging features were extracted from contrast-enhanced fat-suppressed T1-weighted images (CE FS T1WI). The radiomics workflow is presented in **Figure 1**. Four classification methods, i.e., the least absolute shrinkage and selection operator logistic regression (LASSO-LR), support vector machine (SVM), Gaussian process (GP) and Naive Bayes (NB) algorithm, were compared for feature selection and radiomics signature construction. The predictive performance of the radiomics signatures was assessed with the area under receiver operating characteristics curve (AUC), calibration curve, and decision curve analysis (DCA).

Results: Thirteen radiomics features selected based on the LASSO-LR classifier were adopted to construct the radiomics signature (**Figure 2**), which showed significant differences between the pathologic good response (pGR) (necrosis fraction ≥90%) group and the non-pGR (necrosis fraction < 90%) group in both cohorts, except for the TAH-SMU group in the validation cohort ($p < 0.05$, seen in **Figure 3**). As shown in **Figure 4**, the features of patients with non-pGR presented higher textual

pattern complexity or heterogeneity within lesions than those of pGR. The prediction model achieved the best performance between good and poor responders with the AUC of 0.882 (95%CI, 0.837−0.918) in the primary cohort (**Figure 5a**). Calibration curves showed good agreement (**Figure 6a**). Similarly, findings were validated in the external validation cohort with good performance (AUC, 0.842 [95% CI, 0.793−0.883]) (**Figure 5b**) and good calibration (**Figure 6b**). The more superior forecasting ability of the LASSO-LR signature could also be seen in multicenter datasets (**Figure 5c–d**), confirming the good applicability of the radiomics signature for datasets from different centers. DCA analysis confirmed the clinical utility of the selected radiomics signature (**Figure 6c-d**).

Conclusion: The constructed CE FS T1WI-radiomics signature with excellent performance could provide a potential tool to predict pathologic response to NAC in patients with osteosarcoma and help tailor appropriate chemotherapy and further treatment plans.

141. Osteoblast-derived PKD1 Promotes the dormancy of prostate cancer cells in the tumor Microenvironment

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Objective: Prostate cancer (Prostate cancer, PCa) is the most common tumor that threatens the health and life of middle-aged men, and more than 80% of prostate cancer cases will develop into bone metastases. Numerous studies have shown that most of tumor cells that disseminated to bone marrow are cleared by immune system or apoptosis, but still a small amount of residual disseminated tumor cells (DTCs) can colonize in bone niche and enter a dormant state. These dormant DTCs are considered to be the root of traditional chemoradiotherapy resistance due to their potentiality for tumor recurrence and metastasis. However, the mechanism of how bone marrow microenvironment regulates tumor cell dormancy remains unclear. Further understanding of the molecular mechanism of DTCs dormancy in the bone marrow microenvironment will be beneficial to clarify the molecular mechanism of prostate cancer bone metastasis, which has important clinical guiding value.

Methods: Prostate cancer cells (PC3 and DU145 cells) were co-cultured with mouse primary osteoblasts overexpressing PKD1 or silencing PKD1 by lentivirus for 7 days. Real time PCR, western blot, flow cytometry and immunofluorescence were used to evaluate the effect of PKD1 in osteoblast on the PCa dormancy.

Results: We found that osteoblast dramatically promoted the dormancy of PC-3 cells in the co-culture system. Furthermore, overexpression of PKD1 in osteoblast enhanced the dormancy signature of PCa cells in the co-culture system, which was manifested by the decrease of Ki-67 expression and

ERK/p38 ratio, while the upregulation of p21 and p27 expression in PC-3 cells. In contrast, knockdown of PKD1 in osteoblast significantly reduced the PC-3 dormancy during the co-culture, which was characterized by an increase of Ki-67 expression and ERK/p38 ratio in PC-3 cells, as well as suppression of p21 and p27 expression. In addition, up-regulation of PKD1 in primary osteoblast significantly accelerated the production and secretion of GAS6 (Growth arrest specific gene 6), while opposite effects were obtained by down-regulation of PKD1.

Conclusions: Our research indicated that PKD1 in osteoblasts promoted the dormancy of prostate cancer cells in the bone marrow microenvironment by increasing the expression and secretion of GAS6. Osteoblast-derived PKD1 may play a crucial role in resistance to chemotherapy through inducing prostate cancer cells dormancy in the bone marrow of tumor microenvironment. It provides new ideas for overcoming the drug resistance of prostate cancer and treating the recurrence of prostate cancer.

142. Plasma protein-based signature predicts distant metastasis and induction chemotherapy benefit in Nasopharyngeal Carcinoma

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Rationale: Currently, for locoregionally advanced nasopharyngeal carcinoma (LA-NPC), there is no effective blood-based method to predict distant metastasis. We aimed to detect plasma protein profiles to identify biomarkers that could distinguish patients with NPC who are at high risk of posttreatment distant metastasis. **Methods:** A high-throughput antibody array was initially applied to detect 1000 proteins in pretreatment plasma from 16 matched LA-NPC patients with or without distant metastasis after radical treatment. Differentially expressed proteins were further examined using a low-throughput array to construct a plasma protein-based signature for distant metastasis (PSDM) in a cohort of 226 patients. **Results:** Fifty circulating proteins were differentially expressed between metastatic and non-metastatic patients and 18 were proven to be strongly correlated with distant metastasis-free survival (DMFS) in NPC. A PSDM signature consisting of five proteins (SLAMF5, ESM-1, MMP-8, INSR, and Serpin A5) was established to assign patients with NPC into a high-risk group and a low-risk group. Patients in the high-risk group had shorter DMFS ($P < 0.001$), disease-free survival (DFS) ($P < 0.001$) and overall survival (OS) ($P < 0.001$). Moreover, the PSDM performed better than N stage and Epstein-Barr virus (EBV) DNA load at effectively identifying patients with NPC at high risk of metastasis. For patients in the high-risk group, induction

chemotherapy significantly improved DMFS, DFS, and OS. **Conclusions:** The PSDM could be a useful liquid biopsy tool to effectively predict distant metastasis and the benefit of induction chemotherapy in patients with LA-NPC.

143. Pan-cancer characterization of immune-related lncRNAs identifies potential oncogenic biomarkers

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Long noncoding RNAs (lncRNAs) are emerging as critical regulators of gene expression and they play fundamental roles in immune regulation. Here we introduce an integrated algorithm, ImmLnc, for identifying lncRNA regulators of immune-related pathways. We comprehensively chart the landscape of lncRNA regulation in the immunome across 33 cancer types and show that cancers with similar tissue origin are likely to share lncRNA immune regulators. Moreover, the immune-related lncRNAs are likely to show expression perturbation in cancer and are significantly correlated with immune cell infiltration. ImmLnc can help prioritize cancer-related lncRNAs and further identify three molecular subtypes (proliferative, intermediate, and immunological) of non-small cell lung cancer. These subtypes are characterized by differences in mutation burden, immune cell infiltration, expression of immunomodulatory genes, response to chemotherapy, and prognosis. In summary, the ImmLnc pipeline and the resulting data serve as a valuable resource for understanding lncRNA function and to advance identification of immunotherapy targets.

144. 低表达 RCC1 通过调控 PD-L1 表达增加免疫检查点抑制剂疗效的研究

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目的：如今高死亡率以及高复发率始终围绕着肺腺癌患者，虽然免疫治疗带来生存获益，但仅有约 20%的患者对免疫治疗有效。为寻找对 ICI 治疗耐药的基因，我们通过基因组学的方法，发现鸟苷酸交换因子 RCC1 是预后不良的标志。但其在非小细胞肺癌发生发展中的作用以及与 ICI 治疗耐药的关系还未进行过探索。因此我们探讨了相关的分子机制。

方法：首先我们利用基因组学大数据分析的方法，在公共数据库 TCGA 与 ONCOMINE 中分析了 RCC1 在肺癌与正常肺组织中的表达水平，在 TISIDB 中分析了 RCC1 对肺腺癌免疫细胞浸

润的影响，在 KM-plotter、Prognoscan、TISIDB 三个生存数据库中分析了 RCC1 对肺腺癌患者预后的影响。其次，我们敲低了 RCC1 在 A549、H1299 两种肺腺癌细胞系中表达，用 CCK8、流式细胞术检测了 RCC1 敲低后对肺腺癌细胞增殖凋亡的影响，并用 qPCR 与 western blot 检测了 RCC1 敲低后对下游分子 CDK4/PD-L1 表达水平的影响。最后，我们用慢病毒建立 RCC1 稳定敲低 Lewis 细胞株，并建立小鼠肿瘤模型，与 PD-L1 单抗联用，观察在 RCCI 敲低的条件下，加或不加 ICI 对肿瘤生长的影响。

结果：我们发现在 TCGA 与 ONCOMINE 数据库中 RCC1 在肺腺癌中表达均高于正常肺组织。并发现 RCC1 表达程度与免疫细胞浸润数量及生存时间呈反比。体外实验中，RCC1 敲低后不仅抑制了肺腺癌细胞的增殖、增加了细胞的凋亡比例；而且增加了 PD-L1 的蛋白水平，降低了 CDK4 的蛋白水平。体内实验中，我们发现 RCC1 敲低后能减慢瘤体的生长速度，以及在联用 PD-L1 单抗的情况下，能更进一步减小瘤体的体积以及重量。

结论：RCC1 在非小细胞肺癌中呈现高表达状态，具有促癌作用，并通过调控 CDK4 轴降低 PD-L1 的蛋白水平，诱导对 ICI 耐药。本研究为增加 PD-L1 单抗疗效的提供了一个新的思路。

关键词：RCC1，肺腺癌，PD-L1， CDK4，免疫治疗

145. OSlgg: An Online Prognostic Biomarker Analysis Tool for Low-Grade Glioma (published)

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Glioma is the most frequent primary brain tumor that causes high mortality and morbidity with poor prognosis. There are four grades of gliomas, I to IV, among which grade II and III are low-grade glioma (LGG). Although less aggressive, LGG almost universally progresses to high-grade glioma and eventual causes death if lacking of intervention. Current LGG treatment mainly depends on surgical resection followed by radiotherapy and chemotherapy, but the survival rates of LGG patients are low. Therefore, it is necessary to use prognostic biomarkers to classify patients into subgroups with different risks and guide clinical managements. Using gene expression profiling and long-term follow-up data, we established anOnline consensus Survival analysis tool for LGG named OSlgg. OSlgg is comprised of 720 LGG cases fromtwo independent cohorts. To evaluate the prognostic potency of genes, OSlgg employs the Kaplan-Meier plot with hazard ratio and p value to assess the prognostic significance of genes of interest. The reliability of OSlgg was verified by analyzing 86

previously published prognostic biomarkers of LGG. Using OSlgg, we discovered two novel potential prognostic biomarkers (CD302 and FABP5) of LGG, and patients with the elevated expression of either CD302 or FABP5 present the unfavorable survival outcome. These two genes may be novel risk predictors for LGG patients after further validation. OSlgg is public and free to the users at http://bioinfo.henu.edu.cn/LGG/LGGList.jsp.

146. OSlihc: An Online Prognostic Biomarker Analysis Tool for Hepatocellular Carcinoma (published)

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Liver hepatocellular carcinoma (LIHC) is one of the most common malignant tumors in the world with an increasing number of fatalities. Identification of novel prognosis biomarker for LIHC may improve treatment and therefore patient outcomes. The availability of public gene expression profiling data offers the opportunity to discover prognosis biomarkers for LIHC. We developed an online consensus survival analysis tool named OSlihc using gene expression profiling and long-term follow-up data to identify new prognosis biomarkers. OSlihc consists of 637 cases from four independent cohorts. As a risk assessment tool, OSlihc generates the Kaplan–Meier survival plot with hazard ratio (HR) and p value to evaluate the prognostic value of a gene of interest. To test the reliability of OSlihc, we analyzed 65 previous reported prognostic biomarkers in OSlihc and showed that all of which have significant prognostic values. Furthermore, we identified four novel potential prognostic biomarkers (ATG9A, WIPI1, CXCL1, and CSNK2A2) for LIHC, the elevated expression of which predict the unfavorable survival outcomes. These genes (ATG9A, WIPI1, CXCL1, and CSNK2A2) may be potentially new biomarkers to identify at-risk LIHC patients when further validated. By OSlihc, users can evaluate the prognostic abilities of genes of their interest, which provides a platform for researchers to identify prognostic biomarkers to further develop targeted therapy strategies for LIHC patients. OSlihc is public and free to the users at http://bioinfo.henu.edu.cn/LIHC/LIHCList.jsp.

147. Cancer-derived immunoglobulin G promotes tumor cell growth and proliferation through inducing production of reactive oxygen species

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Cancer cells have been found to express immunoglobulinG(IgG), but the exact functions and underlying mechanisms of cancer-derived IgG remain elusive. In this study, we first confirmed that downregulationof IgG restrained the growth and proliferation of cancer cells in vitro and in vivo. To elucidate its mechanism, we carried out a co-immunoprecipitation assay in HeLa cells and identified 27 potential IgG-interacting proteins. Among them, receptor of activated protein kinase C 1 (RACK1), ras-related nuclear protein (RAN) and peroxiredoxin 1 (PRDX1) are closely related to cell growth and oxidative stress, which prompted us to investigate the mechanism of action of IgG in the above phenomena. Upon confirmation of the interactions between IgG and the three proteins, further experiments revealed that downregulation of cancer-derived IgG lowered levels of intracellular reactive oxygen species (ROS) by enhancing cellular total antioxidant capacity. In addition, a few ROS scavengers, including catalase (CAT), dimethylsulfoxide (DMSO), n-acetylcysteine (NAC) and superoxide dismutase (SOD), further inhibited the growth of IgG-deficient cancer cells through suppressing mitogen-activated protein kinase/extracellular-regulated kinase (MAPK/ERK) signaling pathway induced by a low level of intracellular ROS, whereas exogenous hydrogen peroxide (H 2 O 2) at low concentration promoted their survival via increasing intracellular ROS levels. Similar results were obtained in an animal model and human tissues. Taken together, our results demonstrate that cancer derived IgG can enhance the growth and proliferation of cancer cells via inducing the production of ROS at low level. These findings provide new clues for understanding tumor proliferation and designing cancer therapy.

148. Targeted autophagy inhibits glycolysis up-regulated by the HDAC6-HSP90 pathway to increase the sensitivity of HCC cells to sorafenib

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Sorafenib, as a multi-target kinase inhibitor, is the first-line drug for the treatment of advanced hepatocellular carcinoma (HCC). However, drug tolerance has become the bottleneck in the treatment of sorafenib. Current studies suggest that changes in glucose metabolism induced by sorafenib are the key cause of drug tolerance in HCC cells, but the specific regulatory mechanism remains unclear,

which makes it difficult to reverse drug resistance by targeting glycolysis. As a metabolic-recycling pathway, autophagy regulates multiple pathways including glucose metabolism by recycling components in cells. By analyzing the tumors and adjacent tissues of HCC patients, we found that the expression of key autophagy proteins was closely related to the degree of malignancy of HCC patients. Based on in vitro experiments, it was found that HCC cells with higher degree of malignancy had higher levels of autophagy. Inhibition of autophagy by chloroquine can significantly increase the sensitivity of HCC cells to sorafenib and reverse the enhancement of glycolysis induced by sorafenib. We found that sorafenib induced autophagy promoted the deacetylase activity of HDAC6 by degrading p62. Activated HDAC6 enhances the activity of PKM2, a key enzyme of glycolysis, by regulating the acetylation level of the substrate protein HSP90, mediating changes in glucose metabolism, leading to decreased sensitivity of sorafenib in HCC cells. This study further elucidated the possible mechanism of mediating HCC drug tolerance, that autophagy induced by sorafenib in HCC cells regulates key glycolytic enzymes, which providing a potential target for increasing the sensitivity of sorafenib in HCC cells.

149. Identification of ferroptosis-related genes as biomarkers for overall survival prediction in esophageal adenocarcinoma

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Background Ferroptosis is a recently recognized non-apoptotic cell death that is distinct from the apoptosis, necroptosis and pyroptosis. Considerable studies have demonstrated ferroptosis is involved in the biological process of various cancers. However, the role of ferroptosis in esophageal adenocarcinoma (EAC) remains unclear. The aim of this study was to explore the ferroptosis-related genes (FRG) expression profiles and their prognostic values in EAC.

Methods The FRG data and clinical information were downloaded from The Cancer Genome Atlas (TCGA) database. Univariate and multivariate cox regressions were used to identify the prognostic FRG, and the predictive ROC model was established using the independent risk factors. GO and KEGG enrichment analyses were performed to investigate the bioinformatics functions of significantly different genes (SDG) of ferroptosis. Additionally, the correlations of ferroptosis and immune cells were assessed through the single-sample gene set enrichment analysis (ssGSEA). Finally, significantly different genes were verified in our clinical EAC specimens and normal esophageal mucosal tissues.

Results: Twenty-eight significantly different FRG were screened from 78 EAC and 9 normal tissues. GO and KEGG enrichments showed these SDG were mainly related to the iron-related pathways and

metabolisms of ferroptosis. Gene network demonstrated the TP53, G6PD, NFE2L2 and PTGS2 were the hub genes in the biology of ferroptosis. Cox regression analyses demonstrated four FRG (CARS1, GCLM, GLS2 and EMC2) had prognostic values for overall survival (OS) (all P<0.001). ROC curves showed better efficacy to predict survival using the risk score (AUC=0.744). Immune cell enrichment analysis demonstrated that the types of immune cells and their expression levels in the high-risk group were significant different with those in the low-risk group (all P<0.05). The experimental results confirmed the ALOX5, NOX1 were upregulated and the MT1G was downregulated in the EAC tissues compared with the normal esophageal mucosal tissues (all P<0.05).

Conclusions: We identified differently expressed ferroptosis-related genes that may involve in the process in EAC. These genes have significant values in predicting the patients' OS and targeting ferroptosis may be an alternative for therapy. Further studies are necessary to verify these results of our study.

150. Lutein suppresses proliferation of human gastric cancer cells through inactivation of Nrf2 via NF-κB and GSK-3β

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Lutein (LUT) has long been recognized as a chemopreventive agent, but whether lutein-induced inhibition of gastric cancer cell growth involves weakening Nrf2 induction is not yet understood. In the present study, we demonstrated that growth of human gastric cancer cell lines, MGC-803 and SGC-7901, was abrogated due to the anti-tumor effects of lutein. The MTT and TUNEL assays were used to analyze viability and apoptosis in gastric cancer cells. The level of intracellular reactive oxygen species (ROS) was examined by 2'7'-dichlorofluorescein diacetate (DCFH-DA). qRT-PCR and western blot analyses were used to detect the expressions of heme oxygenase-1 (HO-1) and NAD(P)H dehydrogenase quinone 1 (NQO-1) at mRNA and protein levels. The expression of nuclear factor-κB (NF-κB), glycogen synthase kinase (GSK)-3β/tyrosine kinase Fyn (Fyn), Keap-1, and Nrf2 was detected by western blot. Lutein was found to inhibit proliferation and induce apoptosis in MGC-803 and SGC-7901 cells. The expression of Nrf2-dependent genes was inhibited following treatment with lutein. Moreover, we confirmed that lutein down-regulated the Nrf2 pathway by inhibiting the canonical Keap-1 dependent and non-canonical NF-κB and GSK-3β dependent mechanisms. Our data implies that lutein might be a novel chemopreventive candidate in gastric cancer.

151. Peripheral blood autoantibodies against to tumor associated antigen predict clinical outcome and pneumonitis to immune checkpoint inhibitors-based treatment in advanced non-small cell lung cancer

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Background

Clinical utility for monitoring responses and toxicities of autoantibodies to ICIs-based treatment in lung cancer is less conclusive.

Methods

Baseline plasma were collected from patients with advanced NSCLC before receiving ICIs-based treatment. ELISA was used to detect concentration of autoantibodies.

Results

We have identified a panel of 5-TAAbs to predict responses of ICIs-based treatment in a training set (n=37) and confirmed its predictive value in a validation set (n=129).

In the validation set, the positivity of this 5-TAAbs panel was significantly associated with better ORR (45.2% vs. 13.4%, P<0.001) and longer PFS (7.6 vs. 3.3m, P<0.001). Furthermore, the subgroup analysis of patients treated with combination therapy from the validation set suggested that the 5-TAAbs panel remained to be a good predictive biomarker. Patients with 5-TAAbs positive have a margin significant higher risk for CIP (20.0% vs. 6.0%, P=0.07).

Conclusion

Our 5-TAAbs panel is a potential predictive biomarker for responses and toxicities to ICIs-based treatment in patients with advanced NSCLC.

152. Epidermal growth factor receptor-tyrosine kinase inhibitor arising a tumor microenvironment favors to LAG-3 inhibitors in advanced non-small cell lung cancer

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Introduction

Former clinic investigations have demonstrated that EGFR mutation patients have moderate responses to PD-1 / PD-L1 inhibitors, while some patients who fail EGFR-TKI could benefit from immune-therapy. As a result, we explore the alterations of tumor immune microenvironment before and after EGFR-TKI treatments to detect chances and proper timing of immune-therapy among patents.

Methods

We identified 16 paired samples pre and post EGFR-TKI treatments. 4 mm thick sections were utilized to evaluate CD8, PD-L1, PD-1, LAG-3, and TIM-3 expressions by multiplexed fluorescent immunohistochemical staining. 5-10 representative original multispectral images of each sample were employed to analyze.

Results

Patients with positive CD8+T cell infiltration accounted for 37.5% at baseline. Positive expression regarding PD-L1, PD1, LAG-3, and TIM-3 cells were observed in 7 (43.8%), 4 (25%), 1 (6.25%) and 5 (31.25%) of the patients, respectively. PD-1 expression and infiltration of CD8+PD-1+exhausted T cell increased significantly in patients with EGFR L858R mutation comparing to patients with EGFR 19DEL. Patients who acquired T790M after TKI treatment had less infiltration of CD8+PD-1+ T cells and CD8+TIM-3+ T cells in TIME at baseline. Positive ICP expressions including PD-1, TIM-3, and LAG-3, significantly correlated to shorter PFS. LAG-3 was significantly upregulated after TKI treatment (P=0.003), while other checkpoint proteins remained stationary.

Conclusion

LAG-3 inhibitors might be a potential therapeutic option for EGFR mutation patients post TKI resistance. Current investigations proposed novel insights for rational applications of immune checkpoint inhibitors beyond PD-1/PD-L1 in advanced NSCLC patients with EGFR mutation.

153. Tumor educated platelet small nucleus RNAs U1, U2, U5 as potential biomarkers for the diagnosis and therapeutic prediction of lung cancer

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Background: Tumor-educated platelet (TEP) with altered RNA expression profiles has the potential to diagnose lung cancer. Platelets possess a functional spliceosome contains small nuclear RNAs (snRNAs). This study aimed to explore the novel TEP RNA biomarkers for diagnosing, predicting, or monitoring in a large lung cancer cohort. **Patients and Methods:** Platelets isolated from the plasma of lung cancer patients and healthy donors by low-speed centrifugation and subjected to RNA isolation. Platelet snRNAs U1, U2, U5 were selected and validated by qPCR, and analyzed association of U1, U2, U5 expression with therapy response assessment. **Results:** The results indicated that expression of U1, U2, U5 were significantly decreased in platelets from lung cancer patients (the area under the curve (AUC) was 0.769, 0.840, 0.809, respectively) especially from early-stage patients compared with healthy controls. Platelet counts were highly correlated with snRNAs expression levels in U1, U2, U5 in platelets of lung cancer patients. Furthermore, upregulation of U1, U2, U5 in platelets was found to be significantly correlated with PD patients as compared to PR as well as SD patients. Finally, we reported that platelets were highly associated with plasma exosomes after the treatment of lung cancer, while U1, U5 may delivered into platelets through apoptosis cells-releasing exosomes. **Conclusions:** snRNAs U1, U2, U5 have predictive roles for the detection and therapeutic evaluation of lung cancer. **Keywords:** TEP, snRNA, U1, U2, U5, diagnosis, therapeutic prediction

154. Tumor-suppressor DRD2 facilitates M1 macrophages and triggers multiple processes of programmed cell death in breast cancer

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Disruption of tumor suppressor genes (TSGs) by DNA methylation is common in the progression of breast cancer (BrCa). Identifying and characterizing new TSGs is important to develop novel strategy for BrCa treatment. In present study, DRD2 was found to be remarkably downregulated in BrCa tissues compared with normal breast tissues via RNA sequencing. Furthermore, DRD2 was downregulated by promoter methylation in BrCa. Overexpression of DRD2 significantly inhibited tumor proliferation and metastasis. DRD2 also facilitated M1 phenotype macrophages (Mφ). Moreover, DRD2 expression induced apoptosis as well as necroptosis, and triggered pyroptosis during

coculturing with Mφ in BrCa. DRD2 strongly inhibited the activation of NF-κB signaling, which was counteracted by Mφ. DRD2 expression also promotes drug-sensitivity to Paclitaxel (PTX) and improved the prognosis of HER2-positive patients with BrCa. Taking together, DRD2 is a potential biomarker for breast cancer prognosis and therapeutic target.

155. Altered proteomic signatures associated with Helicobacter pylori infection and Helicobacter pylori-related progression of gastric lesions

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Objective Helicobacter pylori (H.pylori) infection is the most recognized risk factor for progression of gastric lesions and development of gastric cancer (GC). Exploration of altered molecular profiles associated with H.pylori infection and H.pylori-related gastric lesion progression may not only help clarify the etiology underlying H.pylori-induced gastric carcinogenesis, but also identify novel biomarkers for screening high-risk populations and early diagnosis of GC. We examined alterations in proteomic profiles associated with H.pylori infection and effect modifications of altered proteomic profiles on the risk of H.pylori infection-related gastric lesion progression.

Methods All subjects were enrolled based on the National Upper Gastrointestinal Cancer Early Detection Program in Linqu, Shandong province, a recognized area with high risk of GC. We included a total of 166 subjects with gastric lesions of different stages, including superficial gastritis (n=46), chronic atrophic gastritis (n=24), intestinal metaplasia (n=71), low-grade intraepithelial neoplasia (n=9) and early GC (n=16, high-grade intraepithelial neoplasia or early stage invasive GC). Among them, we prospectively followed 39 subjects with gastric lesions for 280 to 473 days (median 383 days) with endoscopic examinations conducted again at endpoint. Tissues were collected from biopsy sites which had the most severe histology of gastric mucosa for in-depth proteomic profiling using liquid chromatography-tandem mass spectrometry. H.pylori infection status was firstly determined based on IgG serology from enzyme-linked immunosorbent assay. The ^{13}C-urea breath test (CUBT) was further performed for 94 subjects. Analyses were conducted to assess individual proteins associated with H.pylori infection as well as the interactions between key proteins and H.pylori infection on the risk of gastric lesion progression.**Results** A total of 118 (71.1%, 118/166) were seropositive for H.pylori infection, with 34 further tested positive for CUBT. Distinct proteomic profiles were observed for H.pylori positive and negative subjects. We found 220 differentially expressed proteins in gastric mucosa according to H.pylori serology status even after multiple comparison adjustment

(FDR<0.05) , including 124 up-regulated and 96 down-regulated proteins in H.pylori seropositive subjects. The associations with 200 of these proteins were even stronger for subjects tested positive for both serology and CUBT. Proteins highly expressed in H.pylori positive subjects were enriched in immune-related pathways and displayed increasing trend in expression from mild to advanced gastric lesions then to early GC. Proteins highly expressed in H.pylori negative subjects were enriched in digestion and metabolic-related pathways and had decreasing trend in expression with elevated severity of gastric lesions. Among highlighted proteins, 35 proteins significantly interacts with H.pylori infection on the risk of advanced gastric lesions. Four of them, including CA9, MAL2, AKR7A3 and SERPINB9 also significantly modified the risk of gastric lesion progression.

Conclusions We mapped altered proteomic profiles of gastric mucosa in H.pylori-infected individuals . We identified individual proteins differentially expressed with H.pylori infection, including upregulated proteins involved in immune-related pathways and downregulated proteins in digestion and metabolic-related pathways. Several H.pylori-related proteins may further modify the risk of advanced gastric lesions and even the risk of gastric lesion progression, which may serve as possible markers for defining high-risk populations and early diagnosis of GC.

156. Analysis of CNOT family gene expression, clinicopathological features and prognosis value in hepatocellular carcinoma

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The carbon catabolite repressor 4-negative on TATA (CCR4-NOT) complex, abbreviated CNOT, has deadenylation and 3'-5' exonuclease activity, mediates deadenylation in the degradation of RNA, initiates the exonuclease degradation pathway, and participates in tumor gene regulation. CNOT proteins comprise a family of global transcriptional regulators that are evolutionarily conserved in eukaryotic cells. Several subunit types of the CNOT complex have been discovered; however, little is known about the role of different subunits in tumorigenesis and development. We observed over-expression of CNOT1-11 in liver cancer and correlations with clinicopathological characteristics. The expression of some CNOTs subunits was associated with histological grade, lymph node metastasis, and tumor stage in patients with hepatocellular carcinoma (HCC). Our data suggest that some CNOTs can be used as predictors of poor prognosis in HCC patients. At the same time, we conducted an analysis of CNOTs mutations in HCC patients. Moreover, we selected CNOT6, CNOT10, and CNOT11 for protein interaction network analysis and Gene Ontology (GO) enrichment analysis to investigate their related biological processes and KEGG pathways. Finally, western blot and qRT-PCR

experiments were consistent with the database findings. Results of this study suggest that CNOT6, CNOT10, and CNOT11, acting as regulators of transcription, may play an important role in the development of HCC and may serve as biological markers in the diagnosis and prognosis of HCC.

157. Identification of DNA Topoisomerase II-alpha as a Regulatory Target in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most prevalent digestive tract cancers in China. In recent years, due to the limitation of existing diagnostic and treatment methods, tumor immunotherapy as a strategy to treat advanced HCC has been receiving increasing attention because of its excellent efficacy and safety. Meanwhile, immune-related genes (IRGs) have been identified as critical drivers of the HCC initiation and progression. DNA topoisomerase II-alpha (TOP2A) has been associated with carcinogenesis, tumor incidence, and mortality as shown in previous studies, and its expression was correlated with levels of immune cell infiltration, especially dendritic cells (DCs). However, the diverse expression patterns of TOP2A and their effects on the immune system regulation in patients with HCC remain to be elucidated. This study aimed to investigate the role of differential TOP2A expression in HCC. To this end, data on TOP2A expression and localization in cancer cell lines and tissues were obtained from several databases. Our findings revealed that TOP2A was significantly overexpressed in patients with HCC. In addition, TOP2A expression was associated with TNM stage, grade, lymph node metastasis, and TP53 mutational status. Mechanistically, we suggest that overexpression of TOP2A in patients with liver cancer can trigger an antitumor immune response by modulating the effective immune response and lymphocyte infiltration. In summary, our data demonstrated that the TOP2A expression signature might be a useful biomarker of the prognosis and a therapeutic target in HCC patients. To the best of our knowledge, this was the first report showing the correlations between TOP2A expression and its potential biological functions, predictive and prognostic value, and its effect on the immune system in patients with HCC.

Keywords: Hepatocellular carcinoma (HCC),DNA Topoisomerase II Alpha (TOP2A), Progression, Regulatory target, Bioinformatics analysis

158. Multiple targeted self-emulsifying compound RGO reveals obviously antitumor potential in hepatocellular carcinoma

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Background: There is currently no effective treatment for patients with advanced liver cancer, with chemotherapy having little impact on long-term survival. Rg3, ganoderma lucidum polysaccharide, and oridonin have shown great potential in anti-tumor therapy in previous studies, but low bioavailability and poor solubility seriously hinder their clinical application. Hence, new strategy for liver cancer are urgently needed.

Methods: Cell viability, cell proliferation, cell migration, colony formation, tubule formation, sphere formation, and flow cytometry were used to assess the effect of a new drug, RGO, (comprised of ginsenoside Rg3, ganoderma lucidum polysaccharide, and Oridonin) on hepatocellular carcinoma cells. Specific RGO-SMEDDS anti-tumor mechanisms were investigated by western blot, qRT-PCR, and immunohistochemistry. Xenografts and staining with hematoxylin and eosin were used to assess the effects of RGO-SMEDDS on tumorigenesis in vivo.

Results: we made these three plant monomers self-microemulsifying drug delivery system (RGO-SMEDDS).Treatment with RGO-SMEDDS resulted in hepatocellular carcinoma cellular G2/M phase arrest and apoptosis, inhibition of migration and invasion, and suppression of cell proliferation, both in vitro and in vivo. Furthermore, RGO-SMEDDS restored immune function by inhibition of immunosuppressive cytokine production and M2-like macrophage differentiation, reduced angiogenesis by down-regulation of vascular endothelial growth factor and its receptor, and attenuated stemness of hepatocellular carcinoma by inhibiting EGFR/AKT and GSK3α/βsignaling pathways**.**

Conclusion: RGO-SMEDDS exerted its anti-tumor effects by reducing angiogenesis, remodeling immune microenvironments, and promoting apoptosis, without obvious toxic side effects. With these attributes RGO-SMEDDS is a promising therapy for the treatment of hepatocellular carcinoma patients.

Keywords: hepatocellular carcinoma, ginsenoside Rg3, ganoderma lucidum polysaccharide, Oridonin, epidermal growth factor receptor

159. Depression and stress levels increase risk of liver cancer through epigenetic downregulation of hypocretin

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Background: Recent studies suggest that Hypocretin (HCRT, Orexin) are involved in stress regulation of depression through the hypothalamic-pituitary-adrenal (HPA) axis. However, the molecular mechanism by which Hypocretin regulate neurobiological responses is unknown. Herein, the effects of chronic stress on the epigenetic modification of HCRT and its association with depression were explored with regard to a potential role in cancer progression.

Methods: In the study, Sprague Dawley(SD) rats were used to establish an animal model of cancer with depression by administrating n-nitrosodiethylamine (DEN) and chronic unpredictable mild stress (CUMS). RNA-Sequencing was used to detect differentially expressed genes in the hippocampus of rats and quantitative real-time polymerase chain reaction (qRT-PCR) was used to validate the results of RNA-Sequencing. The status of HCRT promoter methylation was assessed by methylation specific polymerase chain reaction.

Results: Behavioral tests showed that rats exposed to CUMS had significant depressive-like behaviors. The number of liver tumors and tumor load in depressed rats exposed to CUMS was higher than in SD rats without CUMS. RNA-Sequencing revealed that HCRT was one of the most siginificantly downregulated gene in the hippocampus of SD rats with CUMS compared to non-stressed group, which was validated by qRT-PCR. HCRT mRNA expression was downregulated and the promoter for HCRT was hyper-methylated in those with depression.

Conclusion: These results identified a critical role for chronic psychological stressors in tumorigenesis and cancer progression, via epigenetic HCRT downregulation. Such epigenetic downregulation may be the molecular basis for the association of cancer with depression.

160. Bevacizumab-containing Neoadjuvant Therapy Improves Specific Patients' Survival in Non-metastatic Breast Cancer: A Systemic Review and Meta-Analysis

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Background: Neoadjuvant Therapy (NAT) is an important part of the treatment of non-metastatic breast cancer. Bevacizumab (Bev), a monoclonal antibody against vascular endothelial growth factor (VEGF) to target angiogenesis, is selected as a component of NAT in some trials. However, whether NAT with Bev provides a greater benefit to patients thant NAT without Bev is debatable, owing to

multiple clinical trials showing different results. Our study aimed to review Bev's role in NAT in non-metastatic breast cancer (NMBC) and identify predictive markers associated with Bev-specific outcomes. **Methods:** Prior to April 2020, eligible trials were retrieved from the Pubmed, EMBASE, and Cochrane Library. Random or fixed effects model to synthesis data were applied. Clinical or biological predictive markers were identified by subgroup analyses and summary of literature. Power of pCR to predict DFS or OS was evaluated at trial level by nonlinear mixed effect model and at individual level by merging corresponding data. Publication bias was detected using funnel plots. **Results:** In NMBC, Bev significantly improved the rate of patients achieving pCR, especially for those with specific biomarkers, but the trend discontinued in DFS or OS. PAM50 intrinsic subtype, VEGF overexpression, regulation of VEGF signaling pathway, hypoxia-related genes, BRCA1/2 mutation, P53 mutation, and immune genes can be used to predict Bev-inducing pCR. Among these, serum CAIX level and BRCA1/2 mutation status were powered to predict Bev-related DFS. Subgroup analyses found Bev prolonged patients' OS (and DDFS) in a trial where Bev was given pre- and post-surgery although HER2 or HR status failed to classify Bev sensitive and non-sensitive patients. Lastly, adding Bev resulted in significantly increased adverse effects, which should be taken into consideration in subsequent applications. Conclusion: In biomarkers - identified subgroup, Bev-induced pCR can be elevated by a wide margin so that pCR could be powered to translate to survival benefit although it offered limited effect for patients with NMBC in an unscreened population. However, with proper dose and course, Bev could be promising to ameliorate the prognosis of specific patients with NMBC.

161. 甲状腺良恶性结节的基因变异谱比较

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背景：甲状腺结节是内分泌系统的多发病和常见病，5~15%的甲状腺结节为恶性，即甲状腺癌。良恶性甲状腺结节的临床处理方式不同，因此，甲状腺结节的评估要点是良恶性鉴别。甲状腺癌是单克隆基因选择性疾病，RET、RAS、BRAF、TERT 等基因突变和融合均可能导致甲状腺癌发生，但不同类型的甲状腺癌存在不同的致瘤性时间和不同的信号转导通路。本研究通过对甲状腺结节样本的基因检测与变异分析，从基因学角度探究甲状腺癌的发生发展。

方法：本研究收集了 197 例甲状腺结节样本，通过 B 超和细针穿刺活检结果将样本分为甲状腺癌、良性结节和性质不明确的结节。甲状腺癌经过术后病理学检测证实。结果 197 例样本提取到 RNA，187 例样本提取到 DNA。同时收集了 81 例正常甲状腺样本，提取到了 DNA 和 RNA。通过二代测序技术，对 DNA 样本进行了基因变异检测，对 RNA 样本进行了融合基因

检测。

结果：268 例 DNA 样本共检出变异 476 个，累及基因 40 个，主要包括驱动基因、DNA 损伤修复基因、免疫相关基因、染色体重塑相关基因和激素相关基因等，包括错义突变、框移突变、插入突变、缺失突变和无义突变。187 例 DNA 样本分为癌组织组和良性结节组两组，癌组织和良性结节的基因突变谱比较类似，癌组织组共检出突变基因 38 个，包含突变位点 240 个；良性结节组共检出突变基因 37 个，包含突变位点 200 个。且 90%以上（175/187）的样本中，一个样本同时会有多个基因的突变同时存在。而正常组织中共检出突变基因 23 个，包含突变位点 74 个；且除 RET 外无其他驱动基因的突变。197 例 RNA 共检测出 14 例融合样本，其中 13 例见于癌组织（13/139，9.35%）。正常组织中未检出融合。

结论：甲状腺癌是一类突变多发的肿瘤，一个甲状腺癌患者往往会有多个基因突变的同时存在，且单个基因常有不同位点和不同突变类型同时存在；除驱动基因外，DNA 损伤修复基因、免疫相关基因和染色体重塑相关基因等与驱动基因协同，共同参与甲状腺癌的发生发展。而良性结节中已有多个基因的突变，说明分子事件在表型改变前已经启动。

关键词：甲状腺癌，基因突变，基因融合，二代测序

162. Dysregulated Glutamate Transporter SLC1A1 Propels Cystine Uptake via Xc- for Glutathione Synthesis in Lung Cancer (Cancer Research，2020. 10，IF=9.7)

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Cancer cells need to generate large amount of glutathione (GSH) to buffer oxidative stress during tumor development. A rate limiting step for GSH biosynthesis is cystine uptake via a cystine/glutamate antiporter Xc-. Xc- is a sodium-independent antiporter, passively driven by the concentration gradients from extracellular cystine and intracellular glutamate across membrane. Thus, increased uptake of cystine via Xc- in cancer cells would increase the level of extracellular glutamate, which would restrain cystine uptake via Xc-. Cancer cells must therefore evolve a mechanism to overcome this negative feedback regulation since increased extracellular glutamate via Xc- would inhibit the driving force for cystine uptake. While studying the metabolism in lung tumorigenesis, we unexpectedly found that glutamate transporters, in particular SLC1A1, are in tightly intertwined with cystine uptake and GSH biosynthesis in lung cancer cells. Mechanistically, dysregulated SLC1A1, a sodium-dependent glutamate carrier, can actively recycle extracellular glutamate into cells, which enhances the efficiency of cystine uptake via Xc- and GSH biosynthesis, as measured by stable

isotope-assisted metabolomics. On contrary, knockdown of glutamate transporter SLC1A1 increases extracellular glutamate, which inhibits cystine uptake, blocks GSH synthesis, and induces oxidative stress-mediated cell death and/or growth inhibition. Moreover, glutamate transporters were frequently upregulated in the tissue samples of non-small cell lung cancer. Taken together, active uptake of glutamate via SLC1A1 propels cystine uptake via Xc-, for GSH biosynthesis in lung tumorigenesis.

163. Prognostic significance of GRINA in Colorectal cancer: an integrated bioinformatics analysis

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GRINA, has been deemed to have oncogenic activities in gastric cancer. However, the role and molecular mechanisms of GRINA in colorectal cancer (CRC) remain largely unknown. We evaluated its prognostic value in CRC by an integrated bioinformatics analysis. $\chi 2$ test and Wilcoxon rank sum test were performed to evaluate the connection between GRINA expression and clinical features. Kaplan-Meier's analysis was used to assess the correlation between GRINA expression and clinical outcomes. GO annotation, PPI network and GSEA were utilized to explore the underlying function of GRINA. GRINA expression was upregulated in diverse human cancer types and especially in CRC. Higher GRINA expression was closely related to unfavorable clinical outcomes. Functional enrichment analyses suggested that GRINA is involved in the most significant terms including cell proliferation related pathways, metabolic pathways. GRINA may be a potential prognostic biomarker and therapeutic target in CRC. Moreover, GRINA might accelerate CRC development and EMT by regulating the crosstalk of WNT and MYC signaling which contribute to the unfavorite survival rate.

164. Identification of tumor infiltrating immune cells and prognostic validation of tumor infiltrating mast cells in adrenocortical carcinoma: results from bioinformatics and real-world data

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Objective: The purpose of this study was to explore the composition of tumor infiltrating immune cells (TIIC) and prognostic significance of tumor infiltrating mast cells (TIMC) in adrenocortical carcinoma (ACC).

Methods: The gene expression profiles of ACC were downloaded from the Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GSE90713, GSE12368). The abundance of TIICs in ACC

samples was calculated by CIBERSORT algorithm and immunohistochemistry was used to identify mast cells of 39 tumor samples from Fudan University Shanghai Cancer Center (FUSCC). Differentially expressed genes (DEGs) were analyzed by LIMMA package using R software. Survival analysis was analyzed by Kaplan-Meier method and Cox regression models. **Results**: The abundance of mast cells (p=0.008) was positively correlated with ACC patients' outcome in TCGA cohort and was also positively correlated with both overall survival (p<0.05) and progression-free survival (p<0.05) in FUSCC cohort. Different TIMC infiltration showed significant changes in signaling pathways including DNA replication, nuclear chromosome segregation, and meiotic cell cycle process of ACC. In addition, elevated expression of eight hub genes (KIF18A, CDCA8, SKA1, CEP55, BUB1, CDK1, SGOL1, SGOL2) related to the abundance of TIMC in ACC were significantly correlated with the poor prognosis of the patients.

Conclusion: In conclusion, higher TIMC infiltration was positively correlated with ACC patients' outcome in both TCGA and FUSCC cohort. Lower TIMC infiltration and elevated expression of hub genes (KIF18A, CDCA8, SKA1, CEP55, BUB1, CDK1, SGOL1, SGOL2) markedly correlated with aggressive progression and poor prognosis, which might shed lights on novel targets for treatment strategies.

165. Construction of a robust prognostic model for adult adrenocortical carcinoma: results from multiomics and real-world data

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Objective: This study aims to construct a robust prognostic model for adult adrenocortical carcinoma (ACC) by large-scale multiomics analysis and real-world data.

Methods: The RPPA data, gene expression profiles and clinical information of adult ACC patients were obtained from The Cancer Proteome Atlas (TCPA), Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA). Integrated prognosis-related proteins (IPRPs) model was constructed. Immunohistochemistry was used to validate the prognostic value of the IPRPs model in Fudan University Shanghai Cancer Center (FUSCC) cohort. 76 ACC cases from TCGA and 22 ACC cases from GSE10927 in NCBI's GEO database with full data for clinical information and gene expression were utilized to validate the effectiveness of the IPRPs model.

Results: Higher FASN (p=0.039), FIBRONECTIN (p<0.001), TFRC (p<0.001), TSC1 (p<0.001) expression indicated significantly worse overall survival for adult ACC patients. Risk assessment suggested significantly a strong predictive capacity of IPRPs model for poor overall survival (p<0.05). IPRPs model showed a little stronger ability for predicting prognosis than Ki-67 protein in FUSCC

cohort (p=0.003, HR=3.947; p=0.005, HR=3.787). In external validation of IPRPs model using gene expression data, IPRPs model showed strong ability for predicting prognosis in TCGA cohort (p=0.005, HR=3.061) and it exhibited best ability for predicting prognosis in GSE10927 cohort (p=0.0898, HR=2.318).

Conclusion: This research constructed IPRPs model for predicting adult ACC patients' prognosis using proteomic data, gene expression data and real-world data and this prognostic model showed stronger predictive value than other biomarkers (Ki-67, Beta-catenin, etc.) in multi cohorts.

166. Correlation of CCL2 gene polymorphism and clinicopathological characteristics of prostate cancer

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Objective: To evaluate the correlation between CCL2 gene polymorphism and clinicopathological characteristics of prostate cancer, and to compare the difference in CCL2 gene mutation frequency between the Chinese and Caucasians. **Methods**: The clinical data of 182 patients from June 2014 to June 2019 treated in Fudan University Shanghai Cancer Center were included in the study. The average age was 65.3 years old (46~85 years).Median prostate specific antigen (PSA) was 45 ng/ml(0.06~180 ng/ml).There are 38 patients with biopsy Gleason scores ≤7 and 142 patients with biopsy Gleason scores＞7.There were 76 in high-volume metastatic disease group and 50 in low-volume metastatic disease group. Clinical M stage was also evaluated, including 55 diagnosed as M0 stage,126 diagnosed as M1 stage. DNA samples of 182 prostate cancer patients were sequenced for CCL2 gene. According to the results of genetic testing, the patients were divided into variant and normal groups. A study involving 1765 patients was enrolled. Statistical methods were used to evaluate the correlation between clinicopathological characteristics of prostate cancer and CCL2 gene polymorphism. Meanwhile, the differences of CCL2 gene mutation frequency between the Chinese and Caucasians were compared. **Results**: Of the 182 patient samples analyzed, 33(18.1%) harbored a mutational variant(1245C): 81.9% in AA, 17.6% in AG, 0.5% in GG. The Mutation frequency of Caucasians in enrolled literature was 6.8%（120/1765),which was lower than it in our study (P＜0.001). The CHI-square test revealed the patient of high-volume metastatic disease in normal group was higher than variant group（P=0.023）.**Conclusions**: Genotype of CCL2 gene is a independent factor for low-volume and high-volume metastatic disease, which validate the role of CCL2 genetic polymorphisms in prostate cancer progression and metastases. And the predictive ability of genotype of CCL2 to the ADT efficacy in Chinese is further than it in Caucasians theoretically.

167. Correlation of HSD3B1 gene polymorphism and clinicopathological characteristics of prostate cancer

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Background and purpose:HSD3B1 (1245A>C) is linked to castration-resistant prostate cancer (CRPC), andcould be a powerful genetic biomarker of the effectiveness of androgen deprivation therapy (ADT) in prostate cancer patients. This study aimed to compare the difference in HSD3B1 gene mutation frequency between the Chinese population and other races, and to explore the correlation between HSD3B1 gene polymorphism and clinicopathological characteristics of prostate cancer. Methods: A total of 180 prostate cancer patients in Fudan University Shanghai Cancer Center from Jun. 2014 to Jun. 2019 were retrospectively enrolled, and germline DNA samples of 180 prostate cancer patients were sequenced for HSD3B1 gene. To compare the difference inHSD3B1 mutation frequency between the Chinese population and other races, meanwhile, statistical methods were used to analyze the association between germline mutation status and clinical relevance. Results: Of the 286 patient samples analyzed, 38 harbored a mutational variant (1245C): 86.7% in AA, 13.0% in AC, 0.3% in CC. The frequency of mutation in HSD3B1 among Chinese prostatecancer patients was significantly lower compared with the figure reported by the American (13.3% vs 55.8%, P=0.01). In addition,the mean age of onset was significantly lower in the mutated group than in the normal group: 61±8 vs 66±7 (P<0.05). However,there was no difference in mutation frequencies according to prostate-specific antigen (PSA) level, Gleason score, metastases volume or clinical pathological stage (P>0.05). Conclusion: The age of onset of the HSD3B1 gene mutated group is lower than that of the normal group. Meanwhile, due to the low frequency of mutations in the Chinese population, HSD3B1 (1245A>C) cannot play a rolein predicting the efficacy of ADT as it does in the American and European populations.

168. Genomic and transcriptomic alterations associated with drug vulnerabilities and prognosis in adenocarcinoma at the gastroesophageal junction

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Adenocarcinoma at the gastroesophageal junction (ACGEJ) has dismal clinical outcomes and there are currently few specific effective therapies because of limited knowledge on its genomic and transcriptomic alterations. The present study investigates genomic and transcriptomic changes in ACGEJ from Chinese patients and analyzes their drug vulnerabilities and associations with the survival time. Here we show that the major genomic changes of Chinese ACGEJ patients are chromosome instability promoted tumorigenic focal copy-number variations and COSMIC Signature 17-featured single nucleotide variations. We provide a comprehensive profile of genetic changes that are potentially vulnerable to existing therapeutic agents and identify Signature 17-correlated IFN-a response pathway as a prognostic marker that might have practical value for clinical prognosis of ACGEJ. These findings further our understanding on the molecular biology of ACGEJ and may help develop more effective therapeutic strategies.

169. Lutein inhibits proliferation, invasion and migration of hypoxic breast cancer cells via downregulation of HES1

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An intratumoral hypoxic microenvironment is frequently observed in solid tumors, including breast cancer. Lutein, a plant-derived compound and non-vitamin A carotenoid, has been demonstrated to possess multiple protective properties including anti-inflammation, anti-oxidative stress and antitumor effects. The main objective of the present research was to elucidate the involvement of lutein in the production of reactive oxygen species (ROS) under hypoxia, the activation of hairy and enhancer of split 1 (HES1), and the proliferation, invasion and migration of breast cancer cells. The human breast cancer cell lines MDA-MB-157 and MCF-7 were exposed to hypoxic conditions and various concentrations of lutein. An MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was performed to examine cell proliferation, and Annexin V-fluorescein isothiocyanate/propidium iodide staining was performed to analyze the apoptosis ratio. The levels of hypoxia inducible factor-1α (HIF-1α), NOTCH signaling molecules, HES1 and epithelial-mesenchymal transition (EMT)-associated factors were examined by reverse transcription-quantitative polymerase chain reaction and western blot analysis. Wound healing and Transwell invasion assays were used to detect the invasion and migration of breast cancer cells. Intracellular ROS levels were examined using 2,7-dichlorodihydrofluorescein-diacetate and flow cytometry. The results revealed that cell proliferation was inhibited by lutein in a dose-dependent manner, and the apoptosis ratio gradually increased with lutein treatment under hypoxia as evident from flow cytometry-based analysis. Exposure to lutein inhibited hypoxia-mediated activation of HIF-1α, NOTCH signaling and HES1 expression, and suppressed the hypoxia-induced expression of EMT-associated factors. Lutein markedly inhibited the invasion and migration of breast cancer cells under hypoxia. Hypoxia-induced production of ROS was also decreased by lutein. Furthermore, the ROS scavenger N-acetylcysteine also suppressed hypoxia inducible factor 1α and HES1 expression in breast cancer cells during hypoxia, but hydrogen peroxide (H2O2) levels were increased. Taken together, the results of the present study suggested that lutein may be a novel candidate for the chemoprevention of breast cancer. Furthermore, HES1 may be crucial in mediating the involvement of lutein in the suppression of hypoxia-driven ROS-induced breast cancer progression.

170. 血清 TK-1 水平在肝癌中的诊断及预后价值研究

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目的：研究 TK-1（胸苷激酶-1），作为潜在的肿瘤标志物在肝癌中的诊断及预后价值。

方法：我们总共收集了 123 名肝细胞肝癌（HCC）确诊患者，80 名肝良性病变患者，98 名健康人群血清标本，检测并比较了不同人群的 TK-1 水平（TK-1 大于等于 2.00pmol/L 的比例），分析 TK-1 在肿瘤诊断中的特异性和敏感性；收集 HCC 患者 AFP，CA19-9 等数据，使用 ROC 曲线建立模型，对 TK-1 在 HCC 中的诊断价值进行分析；检测肝癌患者术前、术后、术后 1 个月、3 个月、6 个月的 TK-1 水平，并长期随访，分析 TK-1 在肝癌患者手术疗效评价和预后管理中的作用。

结果：肝癌患者 TK-1 水平中位数为 2.38pM，阳性率为 55.3%，显著高于肝良性病变组和健康人对照组（P 均=0.000）；肝癌患者 TK-1 的 AUC 为 0.7983，接近于 AFP，两者联合诊断 AUC 为 0.9221；对肝癌患者 TK-1 水平动态监测中，肝癌患者术后 TK-1 水平比术前有明显的下降（P=0.000），术后复发或转移患者的 TK-1 水平在术后 6 个月内显著高于术后无进展患者（P=0.000）；术前 TK-1 阴性患者的 PFS 显著高于 TK-1 阳性患者（P=0.000）。

结论：TK-1 能够辅助诊断肝癌，TK-1 联合 AFP 检测可以进一步提高肝癌诊断的特异性及敏感性。术前到术后半年内 TK-1 水平的动态变化能够帮助肝癌患者评价手术疗效和进行预后分层。

171. ImmuCellAI: a unique method for comprehensive T-cell subsets abundance prediction and its application in cancer immunotherapy

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The distribution and abundance of immune cells, particularly T-cell subsets, play pivotal roles in cancer immunology and therapy. T cells has many subsets with specific function and current methods are limited in estimating them, thus, a method for predicting comprehensive T-cell subsets is urgently needed in cancer immunology research. Here we introduce Immune Cell Abundance Identifier (ImmuCellAI), a novel gene set signature-based method, for precisely estimating the abundance of 24 immune cell types including 18 T-cell subsets, from gene expression data. Performance evaluation on both our sequencing data with flow cytometry results and public expression data indicated that

ImmuCellAI can estimate the abundance of immune cells with superior accuracy than other methods especially on many T-cell subsets. Application of ImmuCellAI to immunotherapy datasets revealed that the abundance of dendritic cells (DC), cytotoxic T, and gamma delta T cells was significantly higher both in comparisons of on-treatment vs. pre-treatment and responders vs. non-responders. Meanwhile, we built an ImmuCellAI result-based model for predicting the immunotherapy response with high accuracy (AUC 0.80~0.91). These results demonstrated the powerful and unique function of ImmuCellAI in tumor immune infiltration estimation and immunotherapy response prediction. The ImmuCellAI online server is freely available at http://bioinfo.life.hust.edu.cn/web/ImmuCellAI/.

172. 抗肿瘤顺铂耐药新靶点--HDAC/RXR/HtrA1 信号轴的发现及靶向治疗研究

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目的: 顺铂是用于治疗人类非小细胞肺癌（NSCLC）的一线药物；然而，大多数患者在治疗后会产生耐药性。为了克服顺铂耐药性，阐明非小细胞肺癌顺铂耐药的新机制迫在眉睫。

方法:

（1）使用基因芯片在 NSCLC 细胞系筛选顺铂耐药相关基因，随后使用基因操控验证 NSCLC 中 HDAC，RXR 和 HtrA1 基因之间的相关性。

（2）使用免疫组织化学染色检测 NSCLC 病人样本中的 HDAC，RXR 和 HtrA1 表达，考察三个基因之间的相关性。

（3）在体内外进行了增殖，迁移和侵袭试验，以确定 HDAC/RXR/HtrA1 信号轴在顺铂耐药中的确切作用。

（4）使用荧光素酶报告基因分析和 ChIP 实验研究 HDAC 和 RXR 调控 HtrA1 表达的潜在机制。

（5）此外，在顺铂耐药的非小细胞肺癌中使用体内外实验考察小分子化合物 DW22 靶向 HDAC/RXR/HtrA1 信号轴的作用。

结果: HtrA1 被确定为 NSCLC 细胞中与顺铂耐药相关的基因。HDAC 和 RXR 调控 HtrA1 显着降低了 NSCLC 细胞对顺铂的敏感性。免疫组织化学结果显示，NSCLC 患者组织中 HDAC1 与 HtrA1 呈负相关，RXRα 与 HtrA1 呈正相关。值得注意的是，HDAC1 和 HtrA1 的表达可被认为是 NSCLC 患者铂类药物疗效和预后的生物标志物。从机制上讲，核受体 RXR 的异源二聚体与组蛋白去乙酰化酶 HDAC 协同调控 NSCLC 细胞中 HtrA1 的转录。通过小分子化合物 DW22 双重靶向 HDAC 和 RXR 来重获 HtrA1 表达，可显着抑制顺铂耐药的 NSCLC 细胞的增殖，迁

移和侵袭能力，并诱导其凋亡。

结论: 我们的结果表明，在 NSCLC 中顺铂耐药相关基因 HtrA1 受 HDAC 和 RXR 协同调控。靶向 HDAC/RXR/HtrA1 信号轴可以重获 HtrA1 表达并逆转 NSCLC 的顺铂耐药性。

173. Molecular and clinical characterization of PD-1 in breast cancer through large-scale transcriptome data

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Abstract

Despite the impressive impact of PD-1-targeted cancer immunotherapy, a large proportion of cancer patients remains fail to respond. The impact of PD-1 on other immune cells except for T cells and synergistic role of PD-1 with other immune modulators remain largely unknown. To fill this gap, we systematically investigated PD-1 related transcriptome data and relevant clinical information derived from a total of 2994 breast cancer patients recorded in The Cancer Genome Atlas (TCGA) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC). Our results revealed the relationship between PD-1 and major molecular and clinical characteristics in breast cancer. More importantly, we depicted the landscape of associations between PD-1 and other immune cell populations. Gene ontology analyses and Gene Set Variation Analysis (GSVA) of genes correlated with PD-1 revealed that PD-1were mainly involved in immune response and inflammatory activities. We also elucidated the association of PD-1 and other immune modulators in pan-cancer level, especially the potential synergistic relationship between PD-1 and other immune checkpoints members in breast cancer. In short, PD-1 expression was closely related to malignancy of breast cancer and might serve as a potential biomarker; PD-1 might manipulate anti-tumor immune response by impacting not only T cells but also other immune cells, and this might vary with different tumors. Furthermore, PD-1 might synergize with other immune checkpoint members to modulate the immune microenvironment in breast cancer. To the best of our knowledge, this is by far the most comprehensive and largest study characterizing the molecular and clinical features of PD-1 in breast cancer using large-scale transcriptome data.

174. 血清自身抗体检测在早期恶性肿瘤中应用的研究进展

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摘要：研究表明血清肿瘤相关抗原自身抗体直接参与肿瘤进展的观点，即各种恶性肿瘤细胞分泌的一些抗体可以促进其增殖和转移已经得到了广泛的支持。由于肿瘤细胞产生了细胞抗原的变换，使得细胞出现了新抗原，从而诱导免疫系统产生自身抗体，因此人们对建立针对肿瘤相关抗原的血清自身抗体作为新型的特异性肿瘤标志物进行了深入的研究。作为恶性肿瘤早期诊断中的肿瘤标志物，自身抗体不仅比抗原更敏感和特异，而且还可以在以肺癌为代表的多种癌症临床指征出现之前更好的做出提示。血清肿瘤相关抗原自身抗体在恶性肿瘤的治疗中有着较大的现实价值。本文总结了自身抗体在早期恶性肿瘤检测与诊断中的应用，并讨论了自身抗体的检测在恶性肿瘤中潜在的价值。迄今为止的研究表明，自身抗体不仅可以调节恶性肿瘤进展，而且有望成为提示早期癌症的重要工具。本文特别强调了几种癌症中自身抗体特征的临床应用以及临床验证所面临的挑战。

175. Infiltrating immune cells serve as diagnosis and prognosis biomarker in prostate cancer

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Background: This study was to explore the infiltration pattern of immune cells in prostate cancer(PCa) microenvironment and evaluate the possibility of specific infiltrating immune cells as potential prognostic biomarkers in PCa.

Methods: Infiltrating percentage of 22 immune cells were extracted from 27 normalized datasets by CIBERSORT algorithm. Samples with CIBERSORT p-value < 0.05 were subsequently merged and divided into normal or tumor groups. The differences of 22 immune cells between normal and tumor tissues were analyzed along with potential infiltrating correlations among 22 immune cells and Gleason grades. SNV data from TCGA was used to calculate the TMB score. A univariate and multivariate regression were used to evaluate the prognostic effects of immune cells in PCa.

Results: 10 immune cells with significant differences were identified, including seven increased and three decreased infiltrating immune cells from 190 normal prostate tissues and 537 PCa tissues. Among them, the percentage of infiltration of resting NK cells rank the top increased, whereas the percentage of infiltration of resting mast cells decreased the most. In the normal tissues, CD8+ T cells

had the strongest infiltrating correlation with monocytes, while activated NK cells and naive B cells were the highest in PCa tissues. Moreover, the infiltration of five immune cells was significantly associated with TMB score and mutations of immune gene change the infiltration of immune cells. The Area Under Curve(AUC) of the multivariate regression model for the five- and ten-year survival prediction of PCa reached 0.796 and 0.862. The validation cohort proved that the model was reproducible.

Conclusions: This study demonstrated that different infiltrating immune cells in prostate cancer, especially higher infiltrating M1 macrophages and neutrophils in PCa tissue are associated with patients' prognosis, suggesting that these two immune cells might be potential targets for PCa diagnosis and prognosis of treatment.

176. Alternative splicing implicated in immunity and prognosis of colon adenocarcinoma

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Dysregulation of immune system is the hallmark of colon adenocarcinoma (COAD) patients. Aberrant alternative splicing(AS) is closely related to progression and immunotherapy of COAD. However, the intrinsic correlation of immune system with AS have not been elucidated. Here we identified 640 AS events related to immunescore by multi-omics data analysis. 7 key AS events were screened out and used to develop a riskscore model, the area under the ROC curve of riskscore model predicting 3-, 5-year survival probability was 0.750, 0.768. Also, the riskscore based on 7 key AS events is an independent prognostic factor. The AUC of the nomogram composed of riskscore and TMN grade reached to 0.872(3-year) and 0.841(5-year). Moreover, 11 AS events were identified to be associated with the infiltration of 8 types of immune cells. Interestingly, M1 macrophages and memory B cells had a higher infiltration in high-riskscore patients, and higher infiltration of M1 macrophages and memory B cells were significantly associated with worse prognosis. In conclusion, AS are closely related to immunescore, immunity stage and infiltrating immune cells. The riskscore is an effective diagnostic and prognostic indicator better than TMN grade, and AS events related to the immune system may be potential therapeutic targets for COAD.

177. Low expression of F9 is a novel biomarker and associated with immune infiltration in hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is one of the most common leading causes of cancer morbidity and mortality worldwide, and identification of the specific biomarkers of HCC continues to face enormous challenges. Factor IX gene (F9), encoded by the blood coagulation factor IX, is predicted to alter RNA splicing and to lead to production of a truncated form of factor IX. However, its expression levels have not been reported in HCC. The present study aimed to reveal the F9 expression and its underlying molecular in HCC.

Methods: The levels of F9 expression in HCC were analyzed with Oncomine and HCCDB database. The correlations between F9 expression and the clinical characteristics of HCC were identified using the UALCAN database. The prognostic value of F9 was evaluated using Kaplan-Meier plotter. Meanwhile, the functional enrichment analysis of genes co-expressed with F9 and its relevant kinase, miRNA and transcription factor target networks were created on LinkedOmics and GeneMANIA. In addition, the relationship between F9 expression and immune infiltration level was explored using Tumor Immune Estimation Resource (TIMER) and TISIDB database; the correlation between F9 and gene signature pattern of immune infiltration were checked using TIMER and Gene Expression Profiling Interactive Analysis (GEPIA) database. Aadditionally, The Kaplan-Meier plotter to identify the prognostic value in gene signature pattern of immune infiltration. Finally, we present a web server named Gene Set Cancer Analysis (GSCALite) to analyze a set of genes in HCC with the gene expression associated cancer pathway activity.

Results: We found that F9 was significantly lowly expressed in HCC than their normal tissues, and its expression might be correlated with clinical characteristics of age, stage, and grade status in HCC. Meanwhile, the decreased F9 expression levels were associated with poorer overall survival (OS), recurrence-free survival (RFS), progression-free survival (PFS), and disease-free survival (DFS) in in patients with HCC (OS HR=0.5, p=0.00025; RFS HR=0.57, p=0.00065; PSF HR= 0.6, p=0.00049; DFS HR= 0.68, p=0.012). The functions analyses revealed that F9 and its associated regulators may largely regulate the microtubule cytoskeleton organization involved mitosis, telomere organization, regulation of cell cycle phase transition, and cell cycle pathways. Moreover. F9 showed strong correlation with tumor-infiltrating B cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells. Whereas, F9 expression in HCC significantly was considerably associated with several immune markers, including exhausted CD2, CD3E, TNF, GATA3, STAT5A, FOXP3, TGFB1, LAG3, and GZMB, meanwhile these immune cell markers were associated with poorer overall OS in HCC, suggesting its role in regulating tumor immunity. In addition, the expression of F9 may be inhibit the

pathway activity of the apoptosis, DNA damage response, and EMT pathway activity, while active the pathway activity of the TSC/mTOR.

Conclusions: F9 is a key gene whose expression level is significantly correlated with HCC prognosis and infiltration levels of B cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells in HCC. Our findings demonstrate that F9 may be a novel potential prognostic target for future treatment of HCC.

Keywords: hepatocellular carcinoma, Factor IX gene, prognostic value, immune infiltration, biomarker

178. Improved EGFR mutation detection sensitivity after enrichment by Cas9/sgRNA digestion and PCR amplification

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In the present study, we aimed to improve the sensitivity of downstream mutation detection of next-generation sequencing using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system to selectively target wild-type fragments but with low or no cleavage activity to mutant fragments, followed by amplification using polymerase chain reaction. We selected different mutant sites of epidermal growth factor receptor gene (EGFR)-exon19 deletions in patients with lung cancer and constructed mixed templates of mutant and wildtype DNA comprising ratios of 10% to 0.01% to test the effectiveness of the enrichment method. The results showed that after CRISPR/Cas9 enrichment, a low concentration of mutant DNA fragments (0.01%) could be detected by Sanger sequencing, which represented a 1000-fold increase compared with the untreated samples. We further verified the feasibility of the introduced method an obtained similar results in clinical samples from patients with non-small cell lung cancer, indicating that this method has the potential to detect low copy number mutations at the early stage.

179. Development and external validation of a novel four-gene-pair signature for predicting clinical response to anti-PD-1 immunotherapy in patients with advanced NSCLC

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Background: Treatment of advanced non–small-cell lung cancer (NSCLC) with immune checkpoint inhibitors (ICIs) is characterized by durable responses and improved survival in a subset of patients. A clinically feasible tool is urgently needed to predict the patients who might benefit from ICIs.

Methods: In this multicohort analysis, 76 patients with advanced NSCLC treated with ICIs from three independent cohorts were included in our study. Using transcriptome data analysis of a training set (n=35), we constructed a predictive signature consisting of immune-related gene pairs (IRGPs). The predictive signature was first validated in the test set (n=20) and then validated in an independent cohort containing 21 patients recruited from the Cancer Hospital/Institute, Chinese Academy of Medical Sciences (CICAMS).

Results: Based on a gene expression profile from the GSE93157 database, we proposed the IRGP index (IRGPI) represented by four IRGPs significantly associated with progression-free survival (PFS) of NSCLC patients treated with ICIs, which was also well-validated in a test set. Furthermore, the prognostic performance of the IRGPI was further verified at protein levels in an additional independent set. Stratification analysis and multivariate Cox regression analysis revealed that the IRGPI was an independent prognostic factor.

Conclusion: Our study highlights the potential predictive value of IRGPI for immunotherapeutic benefit in advanced NSCLC. This signature may be a powerful prognostic tool and help further optimize the use of ICIs.

180. Genome-wide analysis reveals prognostic value of novel signature CLU for malignant meningioma patients based on large-scale cohorts

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Background: Meningioma is one of the most common tumors of central nervous system. Although genetic alterations have been linked to elevated risk of malignancy for meningioma patients, the incongruence between clinical outcomes and WHO grade classification still exist. Therefore, large-scale genome-wide expression profiles identifying reliable biomarkers remains incompletely investigated.

Methods: In order to identify genes related to invasion and metastasis process in meningiomas, genome-wide profiles in 145 meningioma patients were identified using microarray datasets GSE12530, GSE16581 and GSE43290 from the Gene Expression Synthesis (GEO) database based on differential tissues expression. Protein-protein interaction (PPI) network were constructed and functional annotations of DEGs were evaluated using R software. In addition, differential expression and prognostic value of CLU on meningioma was evaluated using immunohistochemistry in WHO grade II-III meningioma from AHYMUN, a real-world cohort.

Results: A total of 58 DEGs were significantly associated with malignant behaviours of meningioma. Next, CLU were identified as hub gene in the PPI network, showing markedly prognostic implications in 67 meningioma patients. Expression level of CLU significantly climbed with elevated WHO risk classification. Interestingly, 40 genes were screened according to differential CLU expression. Additionally, significant high expression level of CLU were found in meningiomas tissue than normal tissues, predicting significant poor prognosis for 100 meningiomas patients from AHYMUN cohort.

Conclusion: In conclusion, this study first reveals novel role of CLU using genome-wide expression profiles in high-risk WHO grade of meningioma and significant prognostic value based on large-scale cohorts. This work laid the foundation for the targeted molecular therapies and provided new insights into the treatment and prognostic srategies of meningiomas.

181. Genome-wide analysis of the prognosis-related mRNA alternative splicing event and splicing factors in glioblastoma

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Background: This study aimed to explore differential RNA splicing patterns and elucidate the role of splice variants as prognostic biomarkers in glioblastoma multiform (GBM).

Methods: RNA-seq data from the Cancer Genome Atlas (TCGA) program was utilized to genetically analyze prognostic splicing (AS) events across the genome to assess seven AS patterns in a cohort of 599 polymorphic glioblastoma. The prognostic model was assessed by comprehensive Cox proportional hazard regression. Built on the correlation between survival-related AS events and SFs, a splicing network was established.

Results: A total of 1,434 AS-related survival events related to GBM were identified. Interestingly, the majority of these 20 survival-related AS events were poor prognostic factors. Establishing a prognostic model according to each splicing mode has a beneficial effect on the risk stratification of GBM patients. The area under the curve (AUC) of the receiver operating characteristic (ROC) of the

combined prognosis prediction model can reach 0.854. The splicing network also suggested that there was an important correlation between the SFs genes and AS events in GBM patients.

Conclusion: An ideal prognostic model for risk stratification in patients with GBM was constructed by differential splicing patterns of 58 genes.

182. Network Pharmacological System Study of Huang-lian-tang in the Treatment of Glioblastoma Multiform

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Background: Glioblastoma multiforme (GBM) has a poor prognosis, its recurrence rate and mortality is high. There is no effective clinical method to control its progress and recurrence at prensent.Chinese medicine has a high status not only in China, but also in the world. Some drugs are also used in clinical treatment of tumor diseases. In clinical practice, Huang-Lian-Tang (HLT) has the effects of treating brain diseases and preventing tumor recurrence. However, we are not clear about its drug mechanism. This study explores the potential mechanism of HLT in the treatment of gliomas based on network pharmacology.

Patients and methods: We first obtained the composition information of HLT from the TCMSP database, then analyzed the composition and target of the compound drug, after that, we build a pharmacological interaction network for HLT. At the same time, we obtained the expressed genes of GBM patients from the TCGA database and screened them. We then constructed a protein-protein interaction (PPI) network for both sets of data and combined them with a topology method for analysis. Finally, the screened genes were subjected to enrichment analysis and pathway analysis.

Results: We finally screened 38 related targets and 7 KEGG pathways, they are mainly related to various amino acid metabolism. GO enrichment analysis and KEGG signal pathway analysis indicate that these targets are related to anti-apoptosis, antioxidant stress, multicellular biological processes, and other physiological and pathological processes related to the occurrence and development of GBM.

Conclusion: In summary, we found that the mechanism of HLT for GBM involves multiple targets and signaling pathways that are related to tumorigenesis and development. Our research not only provides novel theoretical basis for traditional Chinese medicine to treat tumors, but also provides new ideas for the treatment of GBM.

Keywords: huang-lian-tang, network pharmacological system, glioblastoma multiform

183. Quantitative proteomics reveals clinical candidate protein biomarkers and prognosis-related proteins model in brain lower grade glioma

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Objective: Lower grade glioma (LGG) is a more common malignant brain tumor, often with high risk of relapse, poor survival and limited treatment options. This study aims to identify potential biomarkers by first large-scale proteomic analysis of LGG with reverse-phase protein arrays (RPPA)data.

Methods: The RPPA data, gene expression profiles and clinical information of 625 LGG patients were obtained from The Cancer Proteome Atlas (TCPA) and The Cancer Genome Atlas. Lasso and multivariate Cox regression were used to screen for candidate proteins and construct the integrated prognosis-related proteins (IPRPs) model. Receiver operating characteristic curve was constructed to evaluate stability and differentially expressed genes (DEGs) were extracted based on IPRPs model using R software.

Results: By TCPA mining candidate protein biomarkers related to the low survival rate of LGG patients, a total of 101 important proteins were found. Higher expressions of MSH6, AKT, TIGAR and CRAF indicate that the prognosis of patients with LGG is significantly worse. Low expressions of CD31, PKCα, PKCβ and MRE11 indicate that the prognosis of patients with LGG is significantly worse. Risk assessment showed that the IPRPs model has a strong predictive ability for poor survival ($p < 0.05$). It is worth noting that the maximum area under the ROC curve is 0.899, indicating its diagnostic accuracy and consistent predictive power. In addition to the LGG progressive phenotype, significant changes in the IPRPs model are also involved in the cancer pathway, cellular senescence, and PI3K-Art signaling pathway.

Conclusion: In conclusion, this study first constituted the large-scale LGG proteomic analysis using RPPA data and described clinical candidate protein landscape for LGG patients. These findings construct a novel predictive model of IPRP and distinguish it from previously identified tumor promoters, which is superior to the currently established prognostic parameters for predicting disease progression and better treatment of LGG.

184. CD3E Has Potential to Be a Prognostic Factor for Low Grade Glioma and an Indicator for Tumor Microenvironment Remodeling

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Background: Tumor microenvironment (TME) plays a crucial role in the initiation and progression of low grade glioma (LGG); however, there is still a challenge in understanding the dynamic modulation of the immune and stromal components in TME Methods: In the presented study, we applied CIBERSORT and ESTIMATE computational methods to calculate the proportion of tumor-infiltrating immune cell (TIC) and the amount of immune and stromal components in 161 LGG cases from The Cancer Genome Atlas (TCGA) database. The differentially expressed genes (DEGs) were analyzed by COX regression analysis and protein–protein interaction (PPI) network construction. Results: CD3E was determined as a predictive factor by the intersection analysis of univariate COX and PPI. Further analysis revealed that CD3E expression was negatively correlated with the clinical pathologic characteristics (clinical stage, distant metastasis) and positively correlated with the survival of LGG patients. Gene Set Enrichment Analysis (GSEA) showed that the genes in the highexpression CD3E group were mainly enriched in immune-related activities. CIBERSORT analysis for the proportion of TICs revealed that B-cell memory and CD8+ T cells were positively correlated with CD3E expression, suggesting that CD3E might be responsible for the preservation of immunedominant status for TME. Conclusion: The levels of CD3E might be useful for outlining the prognosis of LGG patients and especially be a clue that the status of TME transition from immunedominant to metabolic activity, which offered an extra insight for therapeutics of LGG.

185. Quantitative proteomics reveals clinical candidate protein biomarkers and prognosis-related proteins model in Glioblastoma multiform

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Objective: Glioblastoma multiform (GBM) is a more common malignant brain tumor, often with high risk of relapse, poor survival and limited treatment options. This study aims to identify potential biomarkers by first large-scale proteomic analysis of GBM with reverse-phase protein arrays (RPPA)data.

Methods: The RPPA data, gene expression profiles and clinical information of 625 GBM patients

were obtained from The Cancer Proteome Atlas (TCPA) and The Cancer Genome Atlas. Lasso and multivariate Cox regression were used to screen for candidate proteins and construct the integrated prognosis-related proteins (IPRPs) model. Receiver operating characteristic curve was constructed to evaluate stability and differentially expressed genes (DEGs) were extracted based on IPRPs model using R software.

Results: TCPA mining for candidate protein biomarkers associated with poor survival of ACC patients revealed totally 115 significant proteins. Higher BETACATENIN ($p = 0.032$), CHK2 ($p = 0.013$), and NDRG1_pT346 ($p < 0.001$) expression indicated significantly worse outcomes for ACC patients. Risk assessment suggested significantly a strong predictive capacity of IPRPs model for poor survival ($p<0.05$). Notably, area under curve value of ROC curve was up to 0.656, indicating the diagnostic accuracy and consistent predictive ability. Besides GBM progressive phenotype, significant alteration of IPRPs model involved in the cancer pathway, the PI3K-Akt signaling pathway, and cell aging. Hub genes with prognostic implications associated with IPRPs model mostly involved in regulation of cell-cycle pathways.

Conclusion: In conclusion, this study first constituted the large-scale GBMproteomic analysis using RPPA data and described clinical candidate protein landscape for GBM patients. These finding distinguished BETACATENIN, CHK2, and NDRG1_pT346 from previously identified tumor promoters and revealed novel prediction model IPRPs, outperforming the currently established prognostic parameters for anticipating disease course and better clinical management of glioblastoma multiform.

186. Identification and validation of novel metastasis-related signatures of clear cell renal cell carcinoma using gene expression databases

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Patients with clear cell renal cell carcinoma (ccRCC) typically face aggressive disease progression when metastasis occurs. Here, we screened and identified differentially expressed genes in three microarray datasets from the Gene Expression Omnibus database. We identified 112 differentially expressed genes with functional enrichment as candidate prognostic biomarkers. Lasso Cox regression suggested 10 significant oncogenic hub genes involved in earlier recurrence and poor prognosis of ccRCC. Receiver operating characteristic curves validated the specificity and sensitivity of the Cox regression penalty used to predict prognosis. The area under the curve indexes of the integrated genes scores were 0.758 and 0.772 for overall and disease-free survival, respectively. The prognostic values

of ADAMTS9, C1S, DPYSL3, H2AFX, MINA, PLOD2, RUNX1, SLC19A1, TPX2, and TRIB3 were validated through an analysis of 10 hub genes in 380 patients with ccRCC from a real-world cohort. The expression levels of were of high prognostic value for predicting metastatic potential. These findings will likely significantly contribute to our understanding of the underlying mechanisms of ccRCC, which will enhance efforts to optimize therapy.

187. Large-scale transcriptome profiles reveal robust 20-signatures metabolic prediction models and novel role of G6PC in clear cell renal cell carcinoma

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Clear cell renal cell carcinoma (ccRCC) is the most common and highly malignant pathological type of kidney cancer. We sought to establish a metabolic signature to improve postoperative risk stratification and identify novel targets in the prediction models for ccRCC patients. A total of 58 metabolic differential expressed genes (MDEGs) were identified with significant prognostic value. LASSO regression analysis constructed 20-mRNA signatures models, metabolic prediction models (MPMs), in ccRCC patients from two cohorts. Risk score of MPMs significantly predicts prognosis for ccRCC patients in TCGA ($p<0.001$, HR=3.131, AUC=0.768) and CTPAC cohorts ($p=0.046$, HR=2.893, AUC=0.777). In addition, G6PC, a hub gene in PPI network of MPMs, show significantly prognostic value in 718 ccRCC patients from multiply cohorts. Next, G6Pase was detected high expressed in normal kidney tissues than ccRCC tissues. It suggested that low G6Pase expression significantly correlated with poor prognosis ($p<0.0001$, HR=0.316) and aggressive progression ($p<0.0001$, HR=0.414) in 322 ccRCC patients from FUSCC cohort. Meanwhile, promoter methylation level of G6PC was significantly higher in ccRCC samples with aggressive progression status. G6PC significantly participate in abnormal immune infiltration of ccRCC microenvironment, showing significantly negative association with check-point immune signatures, dentritic cells, Th1 cells, etc. In conclusion, this study first provided the opportunity to comprehensively elucidate the prognostic MDEGs landscape, established novel prognostic model MPMs using large-scale ccRCC transcriptome data and identified G6PC as potential prognostic target in 1,040 ccRCC patients from multiply cohorts. These finding could assist in managing risk assessment, and shed valuable insights into treatment strategies of ccRCC.

188. Systematic identification and prognostic implications of splicing regulator DDX21 in aggressive progression of adrenocortical carcinoma

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Background: Recently, the role of alternative splicing (AS) in tumor biologic process provides a novel perspective on better deciphering diverse post-transcriptional regulation in carcinogenesis. However, the clinical implications and in-depth investigations of individual AS pattern in adrenocortical carcinoma (ACC) have merely been far underestimated.

Methods: Genome-wide profiles of AS events in 76 ACC patients were identified based on RNA-Seq data from TCGA; methodology included samples from TCGA SpliceSeq and SpliceAid in 76 ACC patients and 39 ACC samples from Fudan University Shanghai Cancer Center (FUSCC). Prognosis-related AS events (PASEs) were evaluated after matching Splice-sequence data and clinicopathological information. Survival analysis was performed after predictive models were constructed using LASSO regression analysis and unsupervised clustering assessment of the PASEs.

Results: A total of 23,984 AS events and 3,614 PASEs were detected in ACC patients. The risk scores of each ACC patients were predicted, suggesting that eight PASEs groups significantly correlated with clinical outcomes of ACC patients ($P<0.001$); based on these, prognostic models showed AUC value of 0.907 in all PASEs group. A total of 8 SFs, including BAG2, CXorf56, DDX21, HSPB1, MBNL3, MSI1, RBMXL2, SEC31B, were identified and matched as significant splicing factors in close relation to regulation of PASEs in regulatory networks of ACC. Functional enrichment analysis revealed eight splicing factors network as essential regulatory elements of mRNA splicing process, VEGF signaling pathway (FDR<0.001) and other splicing pathway mechanisms. Next, DDX21 were identified and validate as a novel clinical signature and therapeutic targets in 115 ACC patients from TCGA and FUSCC cohorts.

Conclusions: The implementation of strict standards ensures the systematic profiles of AS events based on genome-wide cohort. These findings first provided the opportunity to comprehensively elucidate the landscape and underlying mechanism of alternative splicing, and shed valuable insights into value of DDX21 in predicting prognosis for ACC patients.

189. Elevated double-strand break repair protein RAD50 predicts poor prognosis in hepatitis B virus-related hepatocellular carcinoma: A study based on Chinese high-risk cohorts

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Objective: Increasing evidence indicates that RAD50, which is involved in the repair process of DNA double-strand break (DSB), is also involved in cancer outcomes. However, its role in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) remains unclear. This study was designed to investigate the expression of RAD50 and its prognostic value in HBV-related HCC patients.

Methods: 107 and 100 patients with HBV-related HCC from the Affiliated Hospital of Youjiang Medical University of Nationalities (AHYMUN) and the Affiliated Hospital of Nantong University (AHNU), respectively, were enrolled in the study. The distribution of the categorical clinical-pathological data and the levels of RAD50 expression were compared with a $\chi 2$ test. Immunohistochemistry (IHC) staining of RAD50 was performed. A partial likelihood test based on univariate and multivariate Cox regression analysis was developed to address the influence of independent factors on disease-free survival (DFS) and overall survival (OS). The Oncomine online database was used to analyse and validate the differential expression of RAD50. The Kaplan-Meier method and a log-rank test were performed to assess the influence of RAD50 on survival at different levels.

Results: RAD50 was highly expressed in HCC tissues compared to normal tissues and was significantly correlated with OS in the Cancer Genome Atlas (TCGA) cohort. The validation analysis indicated that significantly increased levels of RAD50 were expressed in HCC tissues in the two independent cohorts. In addition, HCC patients with elevated RAD50 expression levels showed poor OS and DFS in the AHYMUN cohort and decreased OS and DFS in the AHNTU cohort.

Conclusion: In conclusion, our study reveals that elevated RAD50 expression is significantly correlated with cancer progression and poor survival in HBV-related HCC patients. These data suggest that RAD50 may act as an oncogene and may serve as a promising target for the therapy of HBV-related HCC patients.

190. Genome-wide analyses of the prognosis-related mRNA alternative splicing landscape and novel splicing factors based on large-scale low grade glioma multiform cohort

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Alternative splicing (AS) changes are considered to be critical in predicting treatment response. Our study aimed to investigate differential splicing patterns and to elucidate the role of splicing factor (SF) as prognostic markers of low-grade glioma (LGG). We downloaded RNA-seq data from a cohort of 516 LGG tumors in The Cancer Genome Atlas and analyzed independent prognostic factors using LASSO regression and Cox proportional regression to build a network based on the correlation between SF-related survival AS events. We collected 100 patients from our center for immunohistochemistry and analyzed survival using $\chi 2$ test and Cox and Kaplan-Meier analyses. A total of 9,616 AS events related to LGG were screened and identified as well as established related models. Through analyzing specific splicing patterns in LGG, we screened 16 genes to construct a prognostic model to stratify the risk of LGG patients. Validation revealed that the expression level of the prognostic model in LGG tissue was increased, and patients with high expression showed worse prognosis. In summary, we demonstrated the role of SFs and AS events in the progression of LGG, which may provide insights into the clinical significance and aid the future exploration of LGG-associated AS.

191. Circular RNA circCCDC9 acts as a miR-6792- 3p sponge to suppress the progression of gastric cancer through regulating CAV1 expression

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Background: As a novel type of noncoding RNAs, covalently closed circular RNAs (circRNAs) are ubiquitously expressed in eukaryotes. Emerging studies have related dysregulation of circRNAs to tumorigenesis. However, the biogenesis, regulation, function and mechanism of circRNAs in gastric cancer (GC) remain largely unclear.

Methods: The expression profile of circRNAs in 6 pairs of GC tissues and adjacent non-tumor tissues was analyzed by RNA-sequencing. Quantitative real-time PCR was used to determine the expression level of circCCDC9 in GC tissues and cell lines. Then, functional experiments in vitro and in vivo were employed to explore the effects of circCCDC9 on tumor growth and metastasis in GC. Mechanistically, dual luciferase reporter, fluorescence in situ hybridization (FISH), RNA

immunoprecipitation (RIP) and RNA pull-down assays were performed to confirm that circCCDC9 directly sponged miR-6792-3p and alleviated suppression on target CAV1 expression.

Results: Evidently down-regulated expression of circCCDC9 was observed in both GC tissues and cell lines. Expression of circCCDC9 was negatively correlated with tumor size, lymph node invasion, advanced clinical stage as well as positively correlated with overall survival in GC patients. Functionally, overexpression of circCCDC9 significantly inhibited the proliferation, migration and invasion of GC cell lines in vitro and tumor growth and metastasis in vivo, whereas miR-6792-3p mimics counteracted these effects. Mechanistic analysis demonstrated that circCCDC9 acted as a "ceRNA" of miR-6792-3p to relieve the repressive effect of miR-6792-3p on its target CAV1, then suppressed the tumorigenesis of GC.

Conclusions: CircCCDC9 functions as a tumor suppressor in inhibiting the progression of GC through miR-6792-3p/CAV1 axis, which has provided an exploitable biomarker and therapeutic target for patients with GC.

192. 星形细胞瘤生存预后相关 miRNA-mRNA 调控关系对筛选

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【摘要】 **目的：**利用 GEO 数据库中的芯片数据，筛选与星形细胞瘤生存预后相关的 miRNA-mRNA 调控关系对，为后续研究提供理论支持。**方法：**下载芯片数据利用 R 语言进行差异表达分析，得到星形细胞瘤较正常组织表达显著改变的 miRNA 与 mRNA；通过 miRNA 靶基因预测，将靶基因与差异表达 mRNA 取交集，明确 mRNA 与 miRNA 之间的关系；利用 GEPIA2.0 工具在 TCGA 数据库中筛选有生存价值的 mRNA 并验证表达情况，利用 OncoLnc 工具对相应 miRNA 进行生存分析。 **结果：**筛选到差异表达的 miRNA 90 个（表达上调 22 个，下调 68 个）；差异表达的 mRNA 644 个（表达下调 476 个，上调 168 个）；根据 miRNA 靶基因预测结果，整理出 miRNA-mRNA 关系对 30 个，对其中的 mRNA 与 miRNA 进行生存分析，共得到 7 个 miRNA-mRNA 关系对与 LGG 患者生存预后明显相关，未筛选到与 GBM 患者生存预后有关的调控关系对。 **结论：**本研究筛选到的 7 个 miRNA-mRNA 调控关系对与 LGG 患者生存预后显著相关，可为相关研究与治疗提供靶点和参考方向。

193. 多形性胶质母细胞瘤患者自噬相关 mRNA 与 lncRNA 的预后作用

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【摘要】 目的 分别构建由自噬相关 mRNA 与 lncRNA 组成的预后模型，预测多形性胶质母细胞瘤（GBM）患者的生存预后情况，为其个性化诊疗和基础研究提供依据。 **方法** 利用 TCGA 数据库中 GBM 的测序信息与人类自噬数据库联合，筛选差异表达的自噬相关 mRNA，通过共表达分析筛选自噬相关 lncRNA；通过单因素与多因素 Cox 分析筛选与患者生存预后明显相关的风险因子，构建预后风险评分模型；根据模型计算患者风险值并验证模型。 **结果** GBM 肿瘤组织相较正常组织共筛选到 77 个差异表达的自噬相关 mRNA（表达上调 56 个，下调 21 个）和 181 个自噬相关 lncRNA；单因素 Cox 分析共筛选到 18 个与患者生存预后相关的 mRNA 与 17 个相关的 lncRNA；多因素 Cox 分析后各有 3 个 mRNA 与 lncRNA 被分别纳入预后风险评分模型，mRNA 分别是组织蛋白酶 B（CTSB）、微管相关蛋白 1 轻链 3α（MAP1LC3A1）和整合素亚基 3（ITGA3），计算公式为：风险值（risk score）=CTSB 表达量*0.270+MAP1LC3A 表达量*0.458+ITGA3 表达量*0.190；lncRNA 相关计算公式为：风险值（risk score）=AC025857.2 表达量*0.176-AC126407.1 表达量*0.182+AC114803.1 表达量*0.105。K-M 生存曲线显示高风险组生存率低于低风险组，风险曲线提示 mRNA 与 lncRNA 均与患者不良预后密切相关，ROC 曲线证明模型具有预测意义。**结论** 所构建的 2 个预后风险评分模型可有效预测患者生存预后情况，并提供个性化诊疗策略。

194. 利用 TCGA 数据库构建肾透明细胞癌相关 miRNA 预后模型

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摘要：目的：利用 TCGA 数据库中肾透明细胞癌的 miRNA 与 mRNA 数据及临床信息，构建由 miRNA 组成的预后风险评分模型，并筛选与生存预后相关的 miRNA-mRNA 调控关系对，为研究提供理论依据。**方法：**下载并整理 TCGA 数据库中肾透明细胞癌的 miRNA 与 mRNA 数据；对数据进行差异分析，将差异表达的 miRNA 与临床信息进行合并，利用单因素与多因素 Cox 回归分析，构建预后模型并进行模型评价；对模型中的 miRNA 进行靶基因预测，结果与差异表达的 mRNA 进行取交集，构建 miRNA-mRNA 调控网络；对网络中的 mRNA 进行生存

分析，筛选生存相关的 miRNA-mRNA 调控关系对。**结果：**共得到 49 个差异表达的 miRNA 与 3 613 个差异表达的 mRNA；预后模型计算公式为：风险值（risk score）=hsa-miR-21-5p 表达量×0.603＋hsa-miR-1251-5p 表达量×-0.093；调控网络中共纳入 31 个 miRNA-mRNA 调控关系对；对 mRNA 进行生存分析，共得到 7 个有价值的关系对。**结论：**所构建预后模型可有效预测肾透明细胞癌患者生存预后情况，筛选到的 miRNA-mRNA 调控关系对可为相关研究与治疗提供参考。

195. mRNA and protein of p33ING1 in normal and cancer tissues

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Background: Inhibitor growth protein 1 (ING1) is a tumor suppressor, and its down-regulation is involved in the progression and aggressive phenotypes of human malignancies through its interactions with the H3K4me3 and p53.**Methods:**We collected datasets to analyze the relationship between ING1b mRNA expression and accumulative survival rate, and carried out immunohistochemistry analyses to determine the expression profiles of the p33ING1 protein on the mouse, normal human, and human cancer tissue microarrays.**Results:** Compared with normal tissues, the ING1bmRNA was highly expressed in various types of cancer tissues, including gastric,colorectal, liver, breast and lung cancers, and was positively correlated with the overall survival rate of gastric cancer patients. In mouse tissues, the subcellular location of p33ING1 was frequently nuclear; however, it was occasionally cytoplasmic or nucleocytoplasmic.There was a positive detection in the neuron body, a part of glial cells, the glandular epithelium of the stomach, intestines, breast, hepatocytes, heart, skeletal muscle cells, the bronchial and alveolar epithelium, and nephric tubules. In human tissues, the p33ING1 protein,apart from its cytoplasmic distribution,was distributed in the nuclei of the tongue, esophagus, stomach, intestine, lung, trachea, skin, appendix, cervix, endometrium, ovary, and breast. p33ING1 immunoreactivity was strongly detected in the stomach, trachea, skin, cervix, and breast, while it was weak in the other tissues. The positive rate of p33ING1 was 41.0% in the tested cancer entities (489/1194). In general, p33ING1 expression was restricted to only the cytoplasm for all cancers, whereas it was found in the nucleus of renal clear cells, and ovarian and colorectal cancers. Among them, p33ING1 was expressed in more than half of squamous cell carcinomas derived from the esophagus and cervix, while it was rarely expressed in hepatocellular (21.0%) and renal clear cell carcinoma (19.4%). **Conclusions:**The findings suggest that p33ING1 might be participated in the repair and regeneration of organs or tissues the repair and regeneration of organs or tissue, and the carcinogenesis of the highly proliferative epithelium.Down-regulated Beclin 1 expression is closely linked to lung carcinogenesisby reversing aggressive phenotypes

196. Down-regulated Beclin 1 expression is closely linked to lung carcinogenesisby reversing aggressive phenotypes

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Here, Beclin 1 overexpression suppressed cell viability, glycolysis and mitochondrial respiration, migration,invasion and lamellipodia formation, induced apoptosis, S or G2 arrest, fat accumulation, autophagy, and senescence in SQ-5 and KJ cells with Bcl-2, HSP90 and β-catenin hypoexpression, LC-3B, ADFP, p-p38, and cytochrome c hyperexpression. The effect of Beclin 1 silence was opposite in H446 cells. In vivo and vitro Beclin 1-mediated chemoresistance to cisplatin was closely with the apoptotic level and NF-κB activation. Beclin 1 overexpression suppressed tumor growth of lung cancer by decreasing proliferation, and inducing apoptosis and autophagy. Beclin 1 expression was down-regulated in lung cancer at both mRNA and protein level. A higher level of Becn1 mRNA was detectable in adenocarcinoma than squamous cell carcinoma ($p<0.05$), while versa for its protein. Becn1 mRNA expression was positively correlated with overall or post-progression survival rates of all cancer patients, even stratified by aggressive behaviors ($p<0.05$). These finding suggested that down-regulated Beclin1 expression was closely linked to the tumorigenesis and histogenesis of lung cancer. Beclin 1 might be employed as a potential target for the gene therapy of lung cancer if its chemoresistance can be ameliorated or avoided.

197. BTG1 overexpression might promote invasion and metastasis of colorectal cancer via decreasing adhesion and inducing epithelial-mesenchymal transition

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BTG (B-cell translocation gene) could inhibit cell proliferation, metastasis and angiogenesis, and regulate cell cycle progression and differentiation in a variety of cancer cell types. To clarify the role of BTG1 in invasion and metastasis, its expression was compared with the clinicopathological parameters of colorectal cancer by immunohistochemistry. We also overexpressed BTG1 in HCT-15 cells and examined its effects on adhesion, migration and metastasis with their related molecules screened. BTG1 mRNA expression was negatively correlated with its promoter methylation in colorectal cancer ($P<0.05$). Among them, cg08832851 and cg05819371 hypermethylation, and mRNA expression of BTG1 was positively related with poor prognosis of the colorectal cancer patients ($P<0.05$). BTG1 expression was found to positively correlate with depth of invasion, venous invasion, lymph node metastasis, distant metastasis and TNM staging of colorectal cancer ($P<.05$), but negatively with serum level of CEA and CA19-9 ($P<.05$). According to TCGA database, BTG1

mRNA expression was lower in well-, moderately and poorly-differentiated than mucinous adenocarcinomas (P<.05). Kaplan-Meier analysis showed the negative correlation between BTG1 mRNA expression and overall survival rate of all cancer patients (P<.05). BTG1 overexpression weakened adhesion and strengthened migration and invasion of HCT-15 cells (P<.05). There was E-cadherin hypoexpression, N-cadherin and MMP-9 hyperexpression, Zeb1 and Vimentin mRNA overexpression, a high expression of CEA mRNA and protein, and a strong secretion of CEA in BTG1 transfectants, compared with the control or mock. It was suggested that BTG1 expression might promote invasion and metastasis by decreasing adhesion, and inducing epithelial-mesenchymal transition.

198. 卵巢癌中 REG4 的表达及其作用机制

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目的 探讨卵巢癌中再生基因 4（REG4）表达的临床病理意义及其作用机制。方法 利用 UCSC Xena 数据库分析卵巢癌中 REG4 mRNA 及相关基因的表达情况；采用 Kaplan-Meier Plotter 分析卵巢癌中 REG4 mRNA 表达与生存的关系；稳定转染 pcDNA3.1-REG4 真核表达质粒和 pcDNA3.1 空载体至 SKOV3 卵巢癌细胞，采用实时 PCR 和 Western blotting 筛选 REG4 过表达细胞株；通过 MTT 法、流式细胞术、Transwell 法分别检测 REG4 对卵巢癌细胞增殖、凋亡和侵袭的影响；应用 TCGA 数据库对 REG4 表达的卵巢癌进行基因富集分析。结果 与正常卵巢组织相比，复发性卵巢癌中 REG4 mRNA 表达最高（P < 0.05），卵巢癌中次之（P <0.05），REG4 高表达与卵巢癌的总体生存率、无进展生存率和后进展生存率降低相关（P < 0.05） ；REG4 过表达可抑制 SKOV3 细胞凋亡并促进 SKOV3 细胞增殖和侵袭（P < 0.05） ；REG4 与凋亡相关基因呈负相关富集（P < 0.05），与药物代谢细胞色素 P450 相关基因呈正相关富集（P < 0.05）。结论 卵巢癌中 REG4 表达上调，且与卵巢癌不良预后相关，它通过调节细胞的增殖、凋亡和侵袭促进卵巢癌的发生发展，可作为卵巢癌预后评估和基因治疗的分子靶标。

199. SAHA 联合 MG132 对神经母细胞瘤的抗肿瘤作用及分子机制

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目的 研究 SAHA 和 MG132 对神经母细胞瘤的抗肿瘤作用及其相关分子机制。**方法** 用 SAHA 和 MG132 共同处理 SH-SY5Y 细胞，检测其增殖、细胞周期、凋亡、迁移、侵袭和表型相关蛋白。**结果** SAHA 和 MG132 可协同抑制 SH-SY5Y 细胞的增殖(P<0.05)、糖代谢(P<0.05)、细胞迁移和侵袭(P<0.05)，诱导 G1 期阻滞和凋亡(P<0.05)，并呈现出时间和剂量依赖性。SAHA 和/或 MG132 能上调 ING5、PTEN、p53、Caspase-3、Bax、p21 和 p27 的表达，下调 14-3-3、MMP-2、MMP-9、c-myc、CyclinD1 的表达。**结论** SAHA 和 MG132 联合应用可通过抑制增殖、迁移、侵袭、糖代谢和诱导细胞凋亡，有效逆转神经母细胞瘤恶性表型，二者联合使用现实高效低毒的杀伤效果。

200. Plasma metabolomic signatures associated with the progression of precancerous gastric lesions and development of gastric cancer

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Objective: Gastric cancer (GC) is among the most lethal malignancies with multistep gastric carcinogenesis process. The etiology of GC is still less clarified and biomarkers for the progression of precancerous gastric lesions and development of GC are still limited. Deregulating cellular energetics is one of the core hallmarks of cancer cells, and metabolic deregulation plays a vital role in the development of GC. However, no studies have comprehensively explored the metabolomic profiling associated with the cascade of precancerous gastric lesions and GC. This study aimed to draw a metabolomic landscape along the cascade of dynamic evolution of precancerous gastric lesions and GC development and define the metabolomic signatures associated with the progression of gastric lesions and risk of GC.

Methods: Based on a high-risk population for GC in Linqu, Shandong Province of China, plasma untargeted metabolomics were conducted using ultra-high performance liquid chromatography-mass spectrometry, initially in a discovery stage among a total of 200 subjects with superficial gastritis (SG), chronic atrophic gastritis (CAG), intestinal metaplasia (IM), dysplasia (DYS) or GC. For identified key metabolomic biomarkers, the validation stage prospectively enrolled 152 subjects with different gastric lesions which were followed up for 118 to 1063 days, as well as 48 subjects with GC.

Results: Our study demonstrated clearly differential metabolomic profiles in subjects with precancerous gastric lesions and GC. Compared with those with mild gastric lesions (SG or CAG), a total of 6 metabolites, including alpha-linolenic acid, linoleic acid, palmitic acid, arachidonic acid, sn-1 LysoPC(18:3), and sn-2 LysoPC(20:3) were significantly inversely associated with the risk of GC even after multivariate adjustment in the discovery stage (FDR < 0.05) and further in the validation stage (P < 0.05). Among them, alpha-linolenic acid, linoleic acid, and palmitic acid were also significantly inversely associated with the risk of gastric lesion progression, especially for the progression of IM (P < 0.05). Compared with the model combining age, sex, Helicobacter pylori infection, and baseline gastric histology, integrating three validated metabolites significantly improved the performance for predicting the progression of precancerous gastric lesions and GC development with the area under the curve of 0.86 vs. 0.69 (Delong's test P = 0.02).

Conclusion: Based on a high-risk population of GC in China, our study portraited the distinct plasma metabolomic profiles and defined metabolomic signatures for precancerous gastric lesions and GC. Based on prospective endoscopic follow-up of study subjects, we defined a set of plasma metabolites associated with the risk of gastric lesion progression and GC and constructed a risk prediction model for the evolution potential of precancerous gastric lesions, which may have translational implications for risk assessment of GC high-risk populations. The identified metabolites may serve as critical biomarkers for the progression of gastric lesions and development of GC. Our study on metabolic signatures may also shed light on the etiology of GC carcinogenesis, providing important insights into potential intervention targets for GC prevention.

201. 肝细胞癌患者自噬相关基因的预后作用

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目的：构建由自噬相关基因组成的预后模型，预测肝细胞癌（HCC）患者的生存预后情况，为其个性化诊疗和临床研究提供依据。 **方法：**利用 TCGA 数据库中 HCC 的测序信息与人类自噬数据库联合，筛选差异表达的自噬相关基因，对其进行 GO 富集与 KEGG 通路分析；通过单因素与多因素 Cox 分析筛选与患者生存预后明显相关的风险基因，构建预后风险评分模型；根据模型计算患者风险值并验证模型，利用 GEPIA2.0 网页工具与 HPA 数据库对风险基因在 HCC 中的表达情况以及与生存预后的关系进行验证。 **结果：**HCC 肿瘤组织相较正常组织共筛选到 61 个差异表达的自噬相关基因（表达上调 57 个，下调 4 个），GO 富集与 KEGG 通路分析显示均与自噬有关；单因素 Cox 分析共筛选到 12 个与患者生存预后相关的基因，多因素 Cox 分析后共有 4 个基因被纳入预后风险评分模型，分别是 SQSTM1、HDAC1、RHEB 和 ATIC，计算公式为：风险值（risk score）=SQSTM1 表达量×0.185＋HDAC1 表达量×0.382＋

RHEB 表达量×0.423＋ATIC 表达量×0.438；K-M 生存曲线显示高风险组生存率低于低风险组，风险曲线提示 4 个基因与不良预后密切相关，ROC 曲线证明模型具有预测意义；GEPIA2.0 网页工具以及 HPA 数据库表明高表达 4 个基因均导致患者生存率降低。 **结论：**所构建预后风险评分模型可有效预测 HCC 患者生存预后情况，并提供个性化诊疗策略。

202. ROS/JNK/c-Jun pathway is involved in chaetocin induced colorectal cancer cells apoptosis and macrophage phagocytosis enhancement

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Colorectal cancer (CRC) is one of the most common cancers worldwide. Novel agents for CRC treatment are urgently needed. In this study, we investigated the cytotoxic effect of chaetocin in both 5-FU-sensitive and 5-FU-resistant CRC cells. We showed that chaetocin induced proliferation inhibition, G2/M phase arrest and caspase-dependent apoptosis in both 5-FU-sensitive and 5-FU-resistant CRC cells. The c-Jun N-terminal kinase (JNK)/c-Jun pathway is involved in chaetocin-induced CRC cell apoptosis because chaetocin activated JNK/c-Jun pathway and the JNK inhibitor SP600125 restored chaetocin-induced apoptosis in CRC cells. Moreover, chaetocin induced reactive oxygen species (ROS) accumulation in CRC cells, and the ROS scavenger N-acetyl-L-cysteine (NAC) reversed both the apoptotic effect and the activation of the JNK/c-Jun pathway induced by chaetocin. Additionally, this study indicated that chaetocin could down-regulate the expression of CD47 at both mRNA and protein levels, and enhance macrophages phagocytosis of CRC cells. Chaetocin also inhibited tumor growth in CRC xenograft models. Taken together, these data reveal that chaetocin induces apoptosis through the ROS/JNK/c-Jun pathway in CRC cells, overcomes 5-FU resistance, and

enhances macrophages phagocytosis, indicating that chaetocin is a potential agent for CRC treatment.

203.组蛋白去甲基化酶 JMJD2D 通过拮抗 p53 蛋白的转录活性促进肝癌的起始和进展

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作为组蛋白去甲基化酶，JMJD2D 可通过特异性去除 H3K9me2/3 的甲基来增强基因表达，已有研究表明 JMJD2D 在促进大肠癌进展中起着重要作用。然而，其在肝癌中的作用尚不清楚。我们的研究显示，与癌旁组织相比较，JMJD2D 在人肝癌组织中高频率的上调表达。与低表达 JMJD2D 的肝癌患者相比较，JMJD2D 高表达患者的总生存率显著降低。下调 JMJD2D 蛋白表达显著抑制肝癌细胞的增殖和异种移植瘤的生长，促进细胞对化疗药物诱导凋亡的敏感性，并且增加细胞周期抑制因子 p21 和促凋亡基因 PUMA 的表达。在遗传学方面，敲除 JMJD2D 抑制 DEN 诱导的小鼠原位肝癌的起始和进展。敲除抑癌基因 p53 显著降低下调 JMJD2D 对细胞增殖、凋亡以及 p21 和 PUMA 表达的影响，提示 JMJD2D 部分通过抑制 p53 信号通路来调节肝癌细胞的功能。既往对 JMJD2D 的研究都是聚焦在“JMJD2D 作为组蛋白去甲基化酶特异性激活基因转录”这一概念上，而且目前发展的 JMJD2D 小分子抑制剂均是针对其酶活结构域。我们的研究首次发现一种 JMJD2D 促进肿瘤进展的新分子机制，即 JMJD2D 以非酶活依赖的模式直接与 p53 蛋白 DNA 结合结构域相结合，这种相互作用可以有效的封闭 p53 蛋白与特异性 DNA 的结合，进而抑制多种 p53 靶基因的表达。鉴于我们发现的分子机制以及 p53 蛋白重要的抗肿瘤作用，开发能够下调 JMJD2D 表达或阻断 JMJD2D 与 p53 相互作用的 JMJD2D 抑制剂可能是恢复野生型 p53 在肝癌治疗中转录活性的新策略。另外，我们的研究也显示，JMJD2D 可以以组蛋白去甲基化酶依赖的方式激活 Wnt/β-catenin 信号通路，并且促进肝癌细胞的增殖。总之，我们的研究显示 JMJD2D 同时通过拮抗肿瘤抑制因子 p53 和激活致癌信号通路 Wnt/β-catenin 来促进肝癌的发生和发展，这些结果表明 JMJD2D 可能是肝癌治疗的新靶点。

204. Development of a DNA methylation-Classification Model for Brain Tumors

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Abstract

Objective: This study aims to develop a classification model for solid brain tumors into biologically defined subtypes by incorporating differences at the epigenetic level for more accurate classification of the tumors.

Materials and methods: Tumor samples from three cohorts were used in the study: the first cohort (GSE90496, n = 2801) and the second cohort (GSE109387, n = 1104) were downloaded from the Gene Expression Omnibus (GEO) database including seven kind of brain tumors and 91 subtypes from central nervous system. The two cohorts comprise both formalin-fixed, paraffin-embedded (FFPE) and snap-frozen tumor specimens. All the genome-wide DNA methylation profiles were generated using the Infinium HumanMethylation 450K BeadChip array. The third cohort comprised the DNA methylation profiles of the FFPE tumor tissues from 94 craniopharyngiomas (including two subtypes in pathological diagnosis) profiled by us using the Infinium HumanMethylation EPIC BeadChip array. The first cohort and two thirds of the third cohort were used as the training datasets. After preprocessing with the ChAMP package, 411,605 methylation probes were left. Pairwise Pearson correlation was calculated for all samples and the 32,000 probes were selected with the highest variances in their beta values. These probes were further selected by the permutation-based variable importance measure as implemented in the random forest algorithm. The top 900 probes were used as features to develop a classifier based on the multilayer perceptron model (MLP). The performance of the classifier was evaluated on the second cohort and the remaining one third samples of the third cohort.

Result: We selected the most important 900 probes by the random forest algorithm as the input features for model development. The MLP classifier was trained on the beta values of these 900 probes. The accuracy of the MLP model with the accompanying calibration model was evaluated by a ten-fold cross-validation on the training datasets. The accuracy is 99% in the training cohorts. In the independent validation cohorts, the accuracy is 88%. This misclassified samples belong to the subtypes which resemble to each other molecularly.

Conclusion: The classification model allows researchers and clinicians to predict the subtypes of brain tumors accurately with a single DNA methylation profile. Further optimization and application of the classifier complement the current pathological tests and offer ideas for better

treatment decisions.

Keywords: DNA methylation, Random Forest, Multilayer Perceptron Model, Brain Tumors.

205. 长非编码 RNA LINC02006 对食管癌细胞 EC9706 增殖和侵袭的影响

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[摘要] 背景与目的：长链非编码 RNA（LncRNA）与肿瘤的发生发展密切相关，对肿瘤细胞具有重要的调控作用。本研究旨在探讨长链非编码 RNA LINC02006 在食管癌细胞 EC9706 中的表达及沉默 LINC02006 表达对 EC9706 细胞增殖和侵袭的影响。**方法：**荧光定量 RT-PCR 检测 57 例食管癌和癌旁组织中 LINC02006 的表达水平。食管癌细胞 EC9706 分为空白组（未转染的细胞）、对照组（转染 si-NC）和 si-LINC02006 组（转染沉默 LINC02006 表达），分别采用 CCK-8、细胞克隆形成实验和 Transwell 方法检测沉默 LINC02006 表达对各组细胞增殖和侵袭的影响。运用双荧光素酶报告实验和 qRT-PCR 检测 LINC02006 对 mi-R-214-3p 的调控作用。**结果：** LINC02006 在食管癌组织中的表达水平显著高于在对应的癌旁组织中的表达水平（P<0.001）。si-LINC02006 inhibitor 组 EC9706 细胞中 LINC02006 的表达量和细胞克隆数均显著低于空白组（P<0.001）和对照组 （P<0.001）。LINC02006 通过吸附 mi-R-214-3p 负调控其表达。**结论：**LINC02006 在食管癌组织中呈高表达；与肿瘤的淋巴结转移和 TNM 分期相关；可通过 miR-214-3p 参与食管癌的增殖和侵袭；有望成为检测食管癌转移的标志物。

206. Diagnostic and prognostic value of preoperative systemic inflammatory markers in anaplastic thyroid cancer

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Background: Easily accessible, generalized, and inexpensive methods are expected to differentiate anaplastic thyroid carcinoma (ATC) from advanced differentiated thyroid cancer (aDTC). We aimed to explore potential diagnostic and prognostic value of systematic inflammatory markers (SIMs) in ATC and aDTC.

Methods: About 22 ATC, 101 aDTC, and 100 matched early DTC patients were analyzed retrospectively. SIMs included the comprehensive index, neutrophilmonocyte-platelet-to-lymphocyte ratio (NMPLR) and the previously reported ones. Receiver operating characteristic, Kaplan-Meier, and COX regression analyses were mainly conducted.

Results: NMPLR exhibited the highest area under the curve value 0.806 (P < .0001) to diagnose ATC

from aDTC. NMPLR was identified as an independent risk factor for overall survival (OS) (hazard ratio [HR]: 47.821, 95% confidence interval [CI], 2.863-798.765, P = .007) in ATC, as well as for OS (HR: 7.360, 95% CI, 1.620-33.430, P = .010) and recurrence-free survival (HR: 4.172, 95% CI, 1.139-15.286, P = .031) in aDTC. Taken both refractory types (ATC and aDTC) together, NMPLR could independently predict OS (HR: 6.470; 95% CI, 2.134-19.616; P = .001).

Conclusion: NMPLR is a generalized index. It showed excellent potential in differential diagnosis and survival prediction in refractory thyroid cancer. However, it needs to be validated in larger cohort and clinical practice.

207. Histone demethylase JMJD2D promotes the stemness of liver cancer stem cells through enhancing EpCAM and Sox9 expression via Wnt and Notch signaling pathways

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Cancer stem cells (CSCs) contribute to high rate of tumor heterogeneity, metastasis, therapeutic resistance, and recurrence. Histone demethylase JMJD2D is highly expressed in colon and liver tumors to promote cancer progression. However, the role of JMJD2D in cancer stem cells remains unclear. Here, we showed that JMJD2D expression was increased in liver cancer stem cells (LCSCs); Downregulation of JMJD2D inhibited the proliferation of LCSCs in vitro and in vivo; Downregulation of JMJD2D reduced the survival and the early lung seeding of circulating LCSCs, and inhibited the lung metastasis of LCSCs. Mechanistically, JMJD2D promoted the stemness of LCSCs through enhancing the expression of stem cell markers EpCAM and Sox9 via interacting with β-catenin/TCF4 and Notch1 intracellular domain (NICD1) to reduce the H3K9me3 levels on the promoters of EpCAM and Sox9, respectively. Restoration of EpCAM and Sox9 expression in JMJD2D-knockdown liver cancer cells rescued the stemness of LCSCs. Pharmacological inhibition of JMJD2D using 5-c-8HQ reduced the stemness of LCSCs and liver cancer progression. Collectively, our findings suggest that JMJD2D is essential for the stemness maintenance of LCSCs and JMJD2D is a potential therapeutic target for liver cancer.

208.非吸烟与吸烟肺腺癌患者是否存在肿瘤基因表达和微环境的差异

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目的：肺腺癌（LUAD）中非吸烟患者占有较大的比例。本研究分析了吸烟和不吸烟 LUAD 患者的基因表达和微环境差异，以阐明非吸烟相关 LUAD 发生发展的潜在分子机制，并在将来可用于临床肿瘤标志物的筛选。

方法：通过各种生物信息学手段分析癌症基因组图谱（TCGA）和基因表达综合数据库（GEO）中吸烟与非吸烟 LUAD 患者体细胞突变，RNA、microRNA（miRNA）表达，免疫浸润和干细胞性指数的差异。并用 R 语言进行 GO，KEGG 和 GSVA 分析，构建蛋白质相互作用网络及 mRNA-miRNA 关联网络。 并在本科室 20 对非吸烟与吸烟患者的肿瘤样本中用 qRT-PCR 验证 4 个表达差异最明显的 mRNA 和 2 个 miRNA。

结果：在 TCGA 数据库中共获得 501 例 LUAD 患者，其中非吸烟组 209 例，吸烟组 292 例。共发现 174 个表达显着改变的体细胞突变，包括肿瘤蛋白 p53 和表皮生长因子受体，这些突变在非吸烟 LUAD 中下调。在 RNA 水平上，获得了 231 个差异表达的基因。其中非吸烟组中有 124 个显著上调，107 个显著下调。 GSVA 分析显示这些差异表达的基因富集在 42 个方面，包括受体活性调节和受体结合等。在非吸烟和吸烟 LUAD 患者间还发现了肿瘤微环境的差异，包括免疫浸润和干细胞性指数的差异。在发现差异表达的 mRNA 与 miRNA 之间存在 79 对相互作用对，其中 miR-335-5p 和 miR-34a-5p 位于中心位置。而在分别用尼古丁和 DMSO 培养的 A549 细胞中，发现包括玻连蛋白，神经降压素和神经素在内的 21 个基因均差异表达。并在我们自己的样品中证实了神经降压素，神经素，三叶因子家族 2，再生家族成员 4，miR-377-5p，miR-34a 同样存在相同趋势的显著表达差异。

结论：与吸烟者相比，不吸烟的 LUAD 患者在体细胞突变，mRNA，miRNA 表达和肿瘤微环境方面具有不同的特征，这表明非吸烟 LUAD 可能存在独特的致癌机制，及其特有的肿瘤标志物。

关键词：肺腺癌，非吸烟，基因组，肿瘤微环境

209. Circ-RNF13 Promotes Paclitaxel Resistance in Nasopharyngeal Carcinoma by Mediating Ubiquitination of p53

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Increasing evidence suggests that abnormal expression of circular RNA (circRNA) plays important roles in the occurrence, development, and chemoresistance of malignant tumors. Here, we confirm that hsa_circ_0067717 (termed it as circ-RNF13) is significantly upregulated in nasopharyngeal carcinoma (NPC) cell lines and tissues and is associated with paclitaxel resistance in NPC. Mechanistic studies show that circ-RNF13 can directly bind to TRIM41 and p53. Moreover, NPC cells with high expression of circ-RNF13 recruit more TRIM41 proteins than those with low expression of circ-RNF13, promoting TRIM41-induced p53 degradation via ubiquitination and resulting in reduced p53 protein levels, which conferred paclitaxel chemoresistance to NPC cells. Oligo blocking assay further confirms the circ-RNF13-TRIM41-p53 interaction and blocking of either p53 or TRIM41 promotes p53 stability, restoring the sensitivity of NPC cells to paclitaxel. We conclude that circ-RNF13 can increase paclitaxel chemoresistance in NPC by promoting TRIM41-induced p53 degradation through ubiquitination.

210. ingle-cell Multiomics Sequencing Reveals Tumor Heterogeneity and Prevalent Genomic Alterations in Stromal Cells of Human Colorectal Cancer

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Although genomic instability, epigenetic abnormality, and gene expression dysregulation are hallmarks of colorectal cancer (CRC) cells, these features have not been simultaneously analyzed at single-cell resolution. Additionally, to what extent the stromal cells in tumor microenvironment (TME) are transformed by CRC cells is largely unexplored. For cancer cells, we performed single-cell multiomics sequencing together with multi-regional sampling of the primary tumor, lymphatic and distant metastases, and provide insights beyond intratumoral heterogeneity. Genome-wide DNA methylation levels were relatively consistent within a single genetic sub-lineage. The genome-wide DNA demethylation patterns of cancer cells were consistent in all 10 sequenced patients. The cancer cells' DNA demethylation degrees clearly correlated with the densities of the heterochromatin-

associated histone modification H3K9me3 of normal tissue, and those of repetitive element Long Interspersed Nuclear Element 1. To dissect the alterations of the non-malignant cells in TME, we performed single-cell multiomics sequencing of 21 patients with microsatellite-stable CRC and 6 cancer-free, elderly individuals. Surprisingly, somatic copy number alterations (SCNAs) are prevalent in immune cells, fibroblasts and endothelial cells in both TME and normal tissues of each individual. Moreover, the proportions of fibroblasts with SCNAs in tumors (11.1-47.7%) are much higher than those in adjacent normal tissues (1.1-11.5%), with gain of chromosome 7 strongly enriched in TME, clearly indicating clonal expansion. Furthermore, five genes (BGN, RCN3, TAGLN, MYL9 and TPM2) are identified as fibroblast-specific biomarkers of poorer prognosis of CRC. In summary, our work demonstrates the feasibility of tracing epigenomic and transcriptomic dynamics of cancer cells, and provides evidence and functional relevance of pervasive genomic alterations in the stromal cells of TME in CRC.

211. The Dual Role of Exojuice as Both Cushion and Gradient Enables One Step Large Scale Purification of Exosome from Medium, Serum, Milk and Saliva

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Exosomes are nano-scale extracellular vesicles secreted by most cell types. They play important roles for intercellular communication by exchanging their contents. The current challenges in exosome preparation are the yield and purity. Traditional ultracentrifugation methods for exosome isolation have led to contamination, impurities, deformation of the exosome, or difficulty removing gradient matrix reagents. Here we report the development of Exojuice for purer exosome isolation by one-step ultracentrifugation. We compared the purity of exosomes purified using Exojuice with those purified using other methods, such as 60% iodixanol via ultracentrifugation, by their purity, analyzing their size distribution and examining their surface markers. We found that Exojuice can serve as both the cushion and gradient in exosome purification. When Exojuice was used as a cushion, a density gradient was formed within a one-hour spin after adding the exosome solution. Exojuice can be used to purify exosomes from cell culture medium, plasma/serum, urine, saliva, milk and other biofluids. Exosomes from bodily fluids such as plasma and saliva and bovine milk were isolated. Stronger expression of the exosome biomarkers CD9, CD63, CD81 and TSG101 were observed in plasma and saliva samples. Exojuice displayed a low osmotic pressure, thus intact exosomes were isolated without shape deformation. Cell assay indicted that Exojuice was not cell toxic, which is expected since Exojuice was a component of several FDA approved clinical medicines.

212. 2010-2015 年内蒙古胃癌发病与死亡现状及趋势分析

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目的：描述和分析 2015 年内蒙古肿瘤登记地区胃癌发病与死亡现状，评估内蒙古年胃癌发病和死亡情况，对 2010-2015 年胃癌发病和死亡趋势进行分析，为内蒙古肿瘤防治工作提供参考依据。**方法：**按照全国肿瘤登记中心制定的审核方法和评价标准，对内蒙古符合要求的 10 个肿瘤登记处上报的胃癌发病、死亡和人口数据进行汇总分析。按城乡、性别、年龄别分层分析胃癌发病与死亡粗率、标化率、累计率（0-74）及顺位和构成等指标，计算早死概率，并结合内蒙古 2015 年户籍人口资料，估算全区胃癌发病（死亡）数。应用 Joinpoint 统计软件分析 2010-2015 年内蒙古胃癌发病和死亡趋势，估算总体年度变化百分比（annual percentage change，APC）。人口标准化率计算以全国 2000 年人口普查的人口结构和 Segi's 世界人口结构为标准。**结果：**2015 年内蒙古自治区估计胃癌新发病例 6036 例（男性 4379 例，女性 1657 例），估计胃癌死亡 3877 例（男性 2882 例，女性 996 例）。内蒙古肿瘤登记地区胃癌发病率粗为 23.43/10 万，中标率为 17.67/10 万，世标率为 17.71/10 万，0-74 岁累积发病率为 2.16%，占全部恶性肿瘤发病的 9.21%，位居恶性肿瘤发病顺位第 5 位；胃癌粗死亡率为 16.03/10 万，中标率为 12.04/10 万，世标率为 12.11/10 万，0-74 岁累积死亡率为 1.43%，早死概率为 0.95%，占全部恶性肿瘤的 10.45%，位居恶性肿瘤死亡顺位第 3 位。其中，胃癌发病率和死亡率城市均高于农村，男性高于女性；发病率在 75-岁前随年龄增长而上升，之后开始下降，而死亡率则随年龄增长总体呈上升趋势。2010-2015 年内蒙古肿瘤登记地区发病中标率 APC 为 0.22%，胃癌死亡中标率 APC 为-2.81%，但都无统计学意义。其中，农村男性死亡中标率 APC 为-4.54（P=0.015），变化趋势有统计学意义。从年龄别趋势来看，45-59 年龄组在 2010-1015 年发病中标率（APC=-4.83）和死亡中标率（APC=-8.16）均总体呈下降趋势，且差异有统计学意义。**结论：**中老年人群为胃癌防治的重点人群，加强胃癌防控知识的宣传教育，降低高危人群暴露于危险因素的概率，探索先进的胃癌筛查手段，扩大筛查范围，是提高胃癌患者生存率的关键。

[关键词]：胃癌;发病率;死亡率;趋势;内蒙古

213. Trends in incidence and mortality of esophageal cancer in Inner Mongolia, 2010–2015

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Background: Esophageal cancer is among the leading cancer types in Inner Mongolia. This study aimed to investigate the incidence and mortality rates of esophageal cancer in 2015 and the trends in these rates in the 2010–2015 period in this region.

Methods: National Colorectal Cancer Roundtable (NCCR) screening methods and criteria were used to extract data from 10 cancer registries stratified by area (urban/rural), sex, and age group. The Chinese standard population in 2000 and Segi's world population were used to calculate age-standardized rates. The annual percentage change (APC) in these rates was calculated using the Joinpoint Regression Program.

Results: In 2015, Inner Mongolia had 4 324 new cases (4 027 male vs. 297 female patients) and 3 559 deaths (3 300 male vs. 259 female patients) by esophageal cancer. The crude incidence, age-standardized incidence by Chinese population, age-standardized incidence by world population, and cumulative incidence were 13.45/100 000, 9.92/100 000, 10.18/100 000, and 1.30%, respectively. The corresponding figures for mortality were 11.32/100 000, 8.35/100 000, 8.53/100 000, and 1.04%. The incidence and mortality increased with age between 40 and 80 years. The rates in rural dwellers, especially men, showed negative APC (-13.25% vs. -11.08%; $p < 0.05$).

Conclusions: The incidence and mortality rates of esophageal cancer in Inner Mongolia increased between 2010 and 2015. The rates were high in rural men and middle-aged and old individuals. Prevention and control programs focused on these groups, in addition to early diagnosis and treatment of esophageal cancer, are needed to reduce these rates.

214. DNA methylation markers for monitoring minimal residual disease identified from genome-wide screening of acute lymphoblastic leukemia-discordant twins that achieve post-chemotherapy complete remission

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The cure rate of acute lymphoblastic leukemia (ALL) has improved because of the risk-directed treatment and breakthrough in therapy of certain types of ALL in the last 40 years. However, at least one-third of patients following complete remission (CR) will undergo relapse, for which minimal residual disease (MRD) is a major course. Assessment of MRD is used to monitor the prognostic states of ALL and predict relapse at an early stage. Besides, treatments decision guided by MRD can improve the outcome of ALL patients.Currently, flowcytometry and polymerase chain reaction (PCR) analysis are two broadly applicable techniques to measure MRD. However, conventional flowcytometry is not sensitive enough, whereas current PCR analyses mainly focus on the most identified genomic mutations that can only cover limited types of patients. Therefore, more sensitive methods are urgently needed to monitor MRD.We hypothesize that a number of genomic regions of ALL patients that achieve CR may still maintain DNA methylation aberrancy, which can be a promising epigenetic biomarker of early diagnosis of relapse and monitoring MRD. To test it, four genetically identical but B-ALL-discordant monozygotic (MZ) twin pairs and one B-ALL-discordant dizygotic (DZ) twin pair were used as models. All these 5 ALL-twins achieved CR after chemotherapy, and relapsed and deceased later in their lives. We applied whole-genome sequencing and whole-methylome sequencing on peripheral blood samples of these twin pairs that achieved CR. We validated SNPs and indels through Sanger sequencing and Illumina MiSeq sequencer, and amplified suspected copy number variations (CNVs) through quantitative PCR. No evidence showed that any genomic mutations were maintained in the genomes of these ALL-twins. However, 26 recurrent differential methylated regions (DMRs) which targeted 19 genes were commonly identified across these ALL-twins, while more prevalent individual-specific DNA methylation aberrancy were found.

To further validate these candidate regions of DNA methylation aberrancy in ALL population, we applied high-throughput MiSeq amplicon sequencing on libraries constructed by a bisulfite

sequencing PCR (BSP)-based procedure. Samples of 153 B-ALL patients are in different statues (including 36 CR samples) with representative molecular background and 135 healthy siblings of patients as control. We successfully amplified 21 DMRs, 10 of them targeted 10 genes were with at least 10 X depth for each CpG site and recurrent in at least 100 samples. We then applied a machine learning model to fit on the DNA methylation level of the 10 genes, acquiring 73.3% specificity, 44.4% sensitivity, and 59.6% accuracy. Although the unevenness of DMR amplification impeded us to get a more accurately predictive model, we show a highly promising gene panel that can be further tested and validated for measuring MRD and diagnosing ALL patients at an early stage.

215. 基于全基因组多组学数据鉴定结肠癌的三个 lncRNAs 预后标志物

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【摘要】 目的 长非编码 RNA（long non-coding RNA，lncRNA）是能够在表观遗传水平上调节基因表达的 RNA 子集，对于众多生物学过程和癌症发展至关重要。因此，这项研究的目的是对公开数据集综合分析，以确定可能在结肠癌（colon cancer ,CC）发生和发展中起关键作用的甲基化驱动的 lncRNA（methylation-driven lncRNA，MDlncRNA），并在此基础上，开发风险预测模型和列线图，以改善 CC 的生存预测。**方法** 从癌症基因组图谱（the Cancer Genome Atlas，TCGA）数据库下载 473 例 CC 组织和 41 例癌旁组织的表达谱数据, 310 例 CC 组织和 37 例癌旁组织的甲基化数据，以及相应的临床数据。同时，基因表达综合数据库(Gene Expression Omnibus，GEO)中 GSE39582 队列被作为外部验证集。通过 edgeR 包筛选差异表达基因、Spearman 秩次相关判断表达谱数据和甲基化数据的相关性。Cox 回归模型被用于构建风险预测模型和列线图。**结果：**通过对 TCGA 和 GEO 数据库联合分析，鉴定出 20 个 MDlncRNAs。单因素 Cox 分析鉴定了 4 个 MDlncRNAs (LINC00675，LINC01082，LINC01207 和 RP1-170O19.14)与 CC 患者的总生存期（overall survival，OS）相关。基于多因素 Cox 回归分析构建风险预测模型，风险评分=（-0.10747*LINC01082 的表达值）+（-0.11029*LINC01207 的表达值）+（-0.08597*RP1-170O19.14 的表达值）。列线图的 1 年，3 年和 5 年 OS 预测的 AUC 分别为 0.802、0.763 和 0.736；TNM 分期的 1 年，3 年和 5 年 OS 预测的 AUC 分别为 0.762、0.760 和 0.678。列线图的一致性指数（concordance indexe, C-index）为 0.768（95%CI：0.714~0.822），而 TNM 分期的 C-index 为 0.732（95%CI：0.676~0.788）。**结论** 本项研究对公共数据库的全面分析，开发了 CC 患者的风险预测模型，并结合年龄、TNM 分期和风险评分建立了列线图，可以促进 CC 患者 OS 的个体化预测。

216. Combined analysis of PIK3C3 and other hub genes in Pancreatic adenocarcinoma

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Purpose: This study is to study the roles of PIK3C3 in pancreatic adenocarcinoma. **Methods**: Bioinformatics-related methods were used to analyze the expression of PIK3C3 with SMAD4 selected from other hub genes in pancreatic adenocarcinoma and their roles in the tumor prognosis, and then immunohistochemistry and survival analysis were used to analyze the related proteins in cancer tissues and tumor prognosis. **Results**: mRNA expression of PIK3C3 or SMAD4 alone did not change in pancreatic adenocarcinoma and does not affect the prognosis of patients. However, their protein expression levels in the adjacent tissues were significantly higher. When the protein of either PIK3C3 or SMAD4 was highly expressed, the prognosis of pancreatic adenocarcinoma patients was better. **Conclusions**: PIK3C3 may become a new pancreatic adenocarcinoma predictor.

217. Indoleamine 2, 3-dioxygenase 1 (IDO1) and CD8 expression profiling revealed an immunological subtype of colon cancer with a poor prognosis

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Background: Colon cancer is characterized by extreme heterogeneity due to histopathological differences, molecular characteristics, genomic instability, and expression signature of immune genes. The Immunoscore method, based on the distribution of the quantification of cytotoxic and memory T cells, provides an indicator of tumor recurrence for colon cancer. However, recent evidence has suggested that immune checkpoint expression represents a surrogate measure of tumor-infiltrating T cell exhaustion, and therefore may serve as a more accurate prognostic biomarker for colon cancer. Indoleamine 2, 3-dioxygenase 1 (IDO1), a potent immunosuppressive molecule, has been strongly associated with T-cell infiltration, but it lacks universal prognostic significance among all of the cancer subtypes. Our aim was to elucidate the prognostic significance of the combination of IDO1 and CD8A expression in colon cancer.

methods: Gene expression and clinical survival data were analyzed using The Cancer Genome Atlas (TCGA) data set and validated using NCBI Gene Expression Omnibus (NCBI-GEO) cohort. The batch effect was corrected by the Combat method and visualized by the PCA plot. The expression values of genes with the highest log-rank test score in survival analysis were considered as cut-off to stratify patients into distinct subgroups. Hierarchical clustering, functional enrichment analyses, and

immune infiltration analysis were applied to evaluate the distinctive immune statuses in colon cancer risk subgroups stratified by IDO1 and CD8A expression. Moreover, Multivariate Cox regression analysis and Receiver Operating Characteristic (ROC) analyses were conducted to determine the prognostic value of IDO1/CD8A stratification. The IDO1/CD8A classifier may be suitable for use in the prediction of cancer development. It was validated via an in vivo murine model.

Results: A bimodal distribution of log-rank test scores for IDO1 expression was shown and different survival patterns based on the double peaks were observed, which indicate a unique role of IDO1 in the survival of colon cancer patients, furthermore, the opposite IDO1 prognostic outcomes are dependent on CD8A gene expression levels when subdividing patients. The strongly correlation between the expression of IDO1 and CD8A in colon cancer was also validated by multiple platforms and methods. The stratification analysis demonstrated that the colon cancer subtype with the $CD8A^{high}IDO1^{high}$* tumor resulted in the worst survival despite high levels of CD8 infiltrates. Its poor prognosis was associated with high levels of immune response, checkpoint genes, and Th1/IFN-γ gene signatures, regardless of CMS classification. Moreover, the IDO1/CD8A stratification was identified as an independent prognostic factor of overall survival (OS) and a useful predictive biomarker in colon cancer. In vivo data revealed the $CD8A^{high}IDO1^{high}$ group showed strong correlations with late-stage metastasis of colon carcinoma cells and upregulation of immune checkpoints.

Conclusions: The findings indicate that the proposed IDO1/CD8A stratification has exact and independent prognostic implications beyond CD8 T cell alone and CMS classification. The distinct immune patterns among the IDO1/CD8A stratified groups illustrated the extent of heterogeneity of colon cancer with respect to immunity. As a result, it may represent a promising tool for risk stratification in colon cancer and improve the development of immunotherapies for patients with colon cancer in the future.

218. Rasal2 高甲基化与宫颈鳞癌放化疗敏感性的关联分析

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阐明 RASAL2 基因甲基化水平与宫颈鳞癌放化疗敏感性的关系。**方法**本研究系统分析了 60 例宫颈鳞癌活检样本和 10 例正常宫颈组织中 RASAL2 基因启动子区甲基化状态和 mRNA 表达水平。RASAL2 的甲基化和表达水平与临床病理参数的关联性采用 Mann-Whitney U 检验进行评估。P<0.05 认定为具有统计学意义。**结果**相较于正常组织，RASAL2 基因异常甲基化和表达缺失普遍存在于肿瘤组织中。RASAL2 基因甲基化程度与肿瘤细胞分化程度呈显著相关性，且异常高甲基化可作为患者同步放化疗不良应答的标志物。**结论**启动子区异常甲基化导致 RASAL2 在宫颈癌细胞中表达缺失，且高甲基化状态与肿瘤细胞分化及患者的临床应答密切相关。

219. Identification of an Immune-related Signature for Predicting Prognosis in Patients with Pancreatic Ductal Adenocarcinoma

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Purpose: Pancreatic ductal adenocarcinoma (PDAC) is one of the highest fatality rate cancers with poor survival rates. The tumor microenvironment (TME) is vital for tumor immune responses , leading to resistance to chemotherapy and poor prognosis of PDAC patients. This study aimed to provide a comprehensive evaluation of the immune genes and microenvironment in PDAC that might help in predicting prognosis and guiding clinical treatments. **Methods:** We developed a prognosis-associated immune signature (i.e., PAIS) based on immune-associated genes to predict the overall survival of patients with PDAC. The clinical significance and immune landscapes of the signature were comprehensively analyzed. **Results:** Owing to gene expression profiles from TCGA database, functional enrichment analysis revealed a significant difference in the immune response between PDAC and normal pancreas. Using transcriptome data analysis of a training set, we identified an immune signature represented by 5 genes (ESR2, IDO1, IL20RB, PPP3CA, and PLAU) related to the overall survival of patients with PDAC, significantly. This training set was well-validated in a test set. Our results indicated a clear association between a high-risk score and a very poor prognosis. Stratification analysis and multivariate Cox regression analysis revealed that PAIS was an important prognostic factor. We also found that the risk score was positively correlated with the inflammatory response, antigen-presenting process, and expression level of some immunosuppressive checkpoint molecules (e.g., CD73, PD-L1, CD80, and B7-H3). These results suggested that high-risk patients had a suppressed immune response. However, they could respond better to chemotherapy. In addition, PAIS was positively correlated with the infiltration of M2 macrophages in PDAC. **Conclusions:** This study highlighted the relationship between the immune response and prognosis in PDAC and developed a clinically feasible signature that might serve as a powerful prognostic tool and help further optimize the cancer therapy paradigm.

220. 以真实世界数据探索肿瘤中抗血管生成药物的全新的机制性生物标志物

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血管生成是肿瘤发展的重要过程，涉及调控的许多因子是药物开发的主要靶点。然而血管生成的调节网络是复杂的，单个信号通路的抑制可能被其他潜在血管生成机制所补偿。虽然 Folkman 教授在 1971 年就提出抑制血管生成可以作为肿瘤治疗的一种策略，目前在 ClinicalTrials.gov 数据库中能检索到超过 3000 个注册的抗血管相关肿瘤临床试验，然而癌症患者对抗血管药物响应的确切作用机制和药物对肿瘤微环境的具体影响仍未完全清楚，这也使得目前没有可靠的生物标志物可以用于预测抗血管药物的响应人群。

不同于其他生信分析选择 GWAS 中的 SNP，我们建立的 DAGM 机器学习框架选择罕见编码变异基因避免分析受到人种的影响，最重要的是 DAGM 不止步在基因组突变，而是进一步将罕见编码突变基因与基因表达关联起来，从中筛选出在不同细胞或组织中会导致几乎相同基因表达变化的全局驱动基因，并映射在信号通路活性上。所以 DAGM 在揭示基因突变与表型关系的同时，也揭示可能导致这种关系的生物学功能信号通路。通过 DAGM 对 TCGA 的真实世界数据分析，发现不同癌种患者的血管生成信号通路激活程度有显著差异，这个结果提示不同适应症患者可能从抗血管生成药物获益的大致比例，可以作为抗血管药物的临床试验设计参考。在患者激活比例高的适应症，抗血管生成可以作为通用药物；如果适应症患者的血管生成信号通路激活比例分布不均，甚至较多为不激活的状态，则应该考虑以伴随诊断识别出可能响应的患者。此时基于实际临床要求，可以从 DAGM 给出的 APSP 评分设定响应与否的阈值,迅速建立相应的伴随诊断方案；或者选定相关信号通路上的细胞因子，以其他实验室常见的检测方法设计伴随诊断方案，这里通过 DAGM 选定的细胞因子就是具体参与响应机制的生物标志物。此外，也能通过 DAGM 分析不响应患者的信号通路活性图谱，排查患者可能的耐药机制，进一步选择适合的治疗方案。目前为止 DAGM 是第一个能对血管生成相关信号通路激活状态做判别，并以此作为肿瘤患者对抗血管生成药物响应预测的方法。本研究中 DAGM 通过 TCGA 的真实世界数据已经获得非常接近临床状况的模型，当具体需要明确特定患者群体对特定药物的响应比例和判定响应的机制性生物标志物时，只需要通过小规模的临床试验，收集若干例实际的临床样本，DAGM 就可以直接进行微调获得该场景的实际模型，能有效并经济地加速伴随诊断建立和治疗方案开发。

221. 萘酰亚胺类 DNA 嵌合剂抗肿瘤构效关系研究进展

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萘酰亚胺类化合物作为细胞探针、DNA 靶向剂和抗肿瘤药物开发是当前药物领域的研究热点之一，先后有氨萘非特、双萘法德等多种衍生物进入了临床试验，但受限于毒性作用，未能进入市场。本文综述了单、双萘酰亚胺的设计开发过程，并对萘酰亚胺的结构与抗肿瘤活性之间的关系进行了分析总结，发现多种结构修饰对提高抗肿瘤活性、减少毒性作用具有意义。

222. The long noncoding RNA KTN1-AS1 promotes bladder cancer tumorigenesis via KTN1 cis-activation and the consequent initiation of Rho GTPase-mediated signaling

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Background: Accumulating evidence supports the hypothesis that long noncoding RNAs (lncRNAs) are involved in several physiological and pathological conditions, including cancer. Here, we investigated the potential role of lncRNAs in bladder cancer.

Methods: We first looked at available datasets retrieved from the TCGA database and discovered that the lncRNA KTN1-AS1 was significantly upregulated, not only in bladder cancer but also in several other tumors. Therefore, we focused our attention on KTN1-AS1. Using both in vitro and in vivo systems that allowed the modulation of KTN1-AS1 and expression of other relevant proteins, we investigated in-depth the role of KTN1-AS1 in bladder cancer (and the mechanism behind). We further investigated the potential KTN1-AS1-interacting proteins using RNA immunoprecipitation, and explored the KTN1-AS1-related epigenetic landscape (with a particular emphasis on acetylation) using chromatin immunoprecipitation assays.

Results: KTN1-AS1 silencing inhibited the proliferation, invasion, and migration of bladder cancer cells, while KTN1-AS1 overexpression had the obvious opposite effects. Mechanistically, KTN1-AS1 promoted the recruitment of EP300, a histone acetyltransferase that enriched H3K27Ac in the KTN1 promoter region. This epigenetic modulation contributed to the upregulation of KTN1, which affected bladder cancer growth and progression via the regulation of Rho GTPase (RAC1, RHOA, and CDC42)-mediated signaling.

Conclusion: Overall, our data support the idea that the lncRNA KTN1-AS1 promotes bladder cancer tumorigenesis via modulation of the KTN1/Rho GTPase axis and is a promising new therapeutic target for the treatment of bladder cancer.

223. 选择性 HADC6 抑制剂增强胃癌的免疫治疗作用研究

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摘要：染色质核小体由组蛋白和 DNA 两部分组成，其中组蛋白的一些修饰对于基因的表达、转录、翻译和细胞周期、细胞代谢、周期等发挥着重要的作用，包括组蛋白的甲基化、乙酰化、泛素化、磷酸化等，其中组蛋白的乙酰化和去乙酰化作用是基因表达过程中重要的调控方式，是转录过程中的关键修饰。HDAC6 作为一种组蛋白去乙酰化酶，主要存在于细胞质中，能够使组蛋白上的赖氨酸去乙酰化，通过致密组蛋白的结构，从而抑制 DNA 的功能，促进肿瘤的发生与发展。另外，在细胞分裂周期中，不恰当的去乙酰化以及从胞质到胞核的重新分布，都可能引起转录抑制，基因表达异常，从而诱发肿瘤。当然，HDAC6 也可以使 α-Tubulin 和 HSP-90 等一些非组蛋白去乙酰化。HDAC6 选择性抑制剂，从 HDAC6 和 HDAC 其他亚型的结构重叠中，识别亚型之间的微小差异，从而为选择性 HDAC6 抑制剂的设计提供了结构上的基础。HDAC6 选择性抑制剂可以通过在癌症微环境中调节免疫应答来抑制肿瘤的生长，在肿瘤免疫应答系统中，HDAC6 选择性抑制剂调控 IL-10 和 PD-L1 的表达，特异性的活化 TH-17 细胞，增强 T 细胞在癌组织中的充分浸润，打破肿瘤环境对免疫系统的封闭，从而增强其免疫功能。而且与泛 HDAC 抑制剂相比，选择性 HDAC6 抑制剂基本不具有毒性。本篇文章将已经得到的先导化合物，设计合成新型高效低毒的选择性 HDAC6 抑制剂，并探讨在胃癌的治疗中，得到的一系列化合物对于抗肿瘤免疫增效方面的活性和效果，并得到可靠有用的 HDAC6 选择性抑制剂。

关键词：选择性 HDAC6 抑制剂；组蛋白；去乙酰化；抗肿瘤；免疫增效

224. 分裂式 G-四链体动态可逆开关的组装和应用

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受 G4 富含鸟嘌呤的序列保守性的限制，严重影响了 G4 对其他外部刺激的相应，因为这些外部刺激与 G-四分体构象不直接相关，例如疾病诊断和生物医学相关的蛋白质和核酸。因此，探究能在外部刺激下发生构象重组的 G4 纳米装置将具有重要意义。因此，我们研究出一种基于分裂式 G4 的可逆 DNA 纳米开关装置。通过将 G4 序列分裂开，我们成功地使 G-四分体结构的形成与外部刺激下解除关联。通过合理的设计，G4（T30695）序列被分成两个相等的部分，并且彼此远离进行固定。由于双螺旋间隔序列的刚性，两个 G4 片段无法相互靠近。MiRNA 可与间隔序列杂交并通过锚点介导的链置换使其构象转换。当间隔序列变为单链时，失去了对两段 G4 对阻隔作用，此时便可以得到完整的 G4 结构。我们选择硫黄素 T（ThT）作

为信号分子来监测此开关的 0FF/ON 状态，因为 ThT 与完整的 G4 结合后可以使荧光增强。我们的工作不仅为基于 G4 的纳米器件设计提供了新思路，还为 DNA 纳米装置用于生物传感和药物递送打下了新的基础。

225. 基于捕获和连接的环介导等温扩增技术（CLIP-LAMP）

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目的 随着生物医学的发展，建立高灵敏度、高特异性且快速简便的核酸检测方法在疾病的早期诊断、病原体的检测和筛查及防治等方面有着重要的作用。这一需求在今年新型冠状病毒的诊断、筛查和防治方面更加凸显。本文中，我们建立了基于探针捕获和连接反应的环介导等温扩增技术（Capture and ligation-based loop-mediated isothermal amplification，CLIP-LAMP），为医学诊断和病原体检测提供新的技术手段。

方法 该方法通过一系列的探针杂交和核酸恒温扩增反应完成，无需核酸提取，也无需进行 RNA 的逆转录。探针包括基于靶标 RNA 序列设计的特异性的捕获探针和具有茎环结构的检测探针。捕获探针包含两部分，一部分与靶标特异性结合，另一部分与固定在 96 孔板的管壁上的核酸序列杂交。全血或干血片等样本直接裂解后，通过捕获探针将靶核酸固定于 96 孔板的管壁上。检测探针基于靶序列进行特异性的连接反应，形成扩增模板，进行荧光定量的环介导等温扩增反应。我们将此方法应用于疟疾的检测中，定量检测疟原虫的 18S rRNA，评估方法的灵敏度、特异性和重复性，并将其应用于实际样本的检测。

结果 此方法具有较高的灵敏度和特异性，可检测到低至 0.01 个/ml 的疟原虫，较传统的镜检和 RDT 灵敏度高，可准确检测到疟原虫的感染样品。此方法可在 4 小时内完成 96 个样本的检测，快速高效。疟疾实际样品检测中，测得 4 个疟疾病例，与标准方法 qPCR 的检测结果一致。

结论 建立了一种免核酸提取，免反转录的基于捕获和连接的等温扩增技术，该方法流程简单，灵敏度高，且具有较高的通量，适用于大规模的疾病筛查。为疾病的分子诊断和基因筛查提供了新的灵敏、高效的方法.

226. miR-125b motivates migration and invasion in colorectal cancer by targeting CFTR and CGN

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Colorectal cancer (CRC) is among one of the most leading causes of cancer-related death in the world, in which metastasis plays a key role. It is well established that approximately 25% of patients with CRC show synchronous metastases, while another 25% develop metastases throughout the course of their disease. Nevertheless, the directly causative factor underlying metastasis is so far unknown, to date, which is tightly regulated by numerous proangiogenic and antiangiogenic factors. It has been proposed that miR-125b plays essential and versatile functions as tumor-promoter in CRC patients, whereas, how exactly miR-125b elicits a metastasis-promoting phenotype in CRC patients remains rather complex and call for further investigation.

Herein, miR-125b expression in human tissues was analyzed by Fluorescence in situ hybridization (FISH) assay firstly, indicating that its expression was deregulated stepwisely in distant metastasis, primary tumors, and adjacent normal tissues. Kaplan–Meier analysis implied that the enriched miR-125b in CRC foreshadowed poor clinical outcome, while corresponding correlation analysis demonstrated that higher miR-125b expression spawned poor tumor invasion, lymph node metastasis, and high American Joint Committee on Cancer (AJCC) stage. In CRC cell lines, the enhanced migration capacity in cells transfected with mimics convincingly proved its metastasis-promotor role in vitro and in vivo for a further step.

Then we were devoted to revealing the mechanism underling this promotive role. It has been universally recognized that miRNAs function by binding to 3’UTR of target genes. Here, we identified Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and cingulin (CGN) as two crucial target genes of miR-125b in the process of enhanced metastasis by database scanning, luciferase reporter assays, and in vitro or in vivo metastasis assays. CFTR, a member of ATP binding cassette (ABC) proteins, mainly functions as an anion channel for Cl- and HCO 3 -, affecting secretion and absorption of anion and water in epithelium tissues, and has been reported as a tumor-suppressor in multiple diseases. CGN is a novel protein component of the cytoplasmic plaque of tight junction, and a dimer composed of two units, each of which containing a globular head, a coiled-coil rod, and a globular tail. Based on that, metastatic assays verified that both CFTR and CGN could remarkably attenuate CRC migration and invasion capacity independently. Mechanistically, we came to the conclusion that CFTR conferred an inhibitory characterization on CRC by restraining the epithelial-mesenehymal transition (EMT) process and the production and secretion of urokinase plasminogen activator (uPA), concurrently, while CGN reduced its invasion capacity by inhibiting the activity of RhoA protein. Subsequently, the expression of miR-125b, CFTR, and CGN was detected in human

specimen by FISH, rt-PCR, and IHC, showing an inverse relationship between miR-125b and CFTR or CGN. Furthermore, it was demonstrated that miR-125b served as a tumor-motivator by orchestrating CFTR and CGN simultaneously.

Taken together, these evidences collectively support a key functional role of miR-125b/CFTR/CGN axis as a novel predictive biomarker and feasible therapeutic target for CRC.

227. miR-125b modulates migration and invasion by targeting CFTR and CGN in colorectal cancer

Xiaohui Zhang

Xijing Hospital of Digestive Diseases， the Air Force Military Medical University

Colorectal cancer (CRC) is among one of the most leading causes of cancer-related death in the world, in which metastasis plays a key role. Nevertheless, the directly causative factor underlying metastasis is so far unknown, to date. It has been proposed that miR-125b plays essential and versatile functions of tumor-promoter in CRC patients, whereas, how exactly miR-125b elicits a metastasis-promoting phenotype in CRC patients remains to be defined. Herein, we identified that miR-125b enhanced metastasis by targeting CFTR and CGN in CRC patients. miR-125b expression in human tissues was analyzed by FISH assay, indicating that its expression was deregulated stepwisely in distant metastasis, primary tumors, and adjacent normal tissues. And the enhanced migration capacity in cells transfected with mimics also proved that for a further step. Then, Cystic Fibrosis transmembrane conductance regulator (CFTR) and the tight junction-associated adaptor, cingulin (CGN) were identified as two putative target genes via scanning of miRNA databases and dual-luciferase reporter assays. Moreover, we came to the conclusion that CFTR conferred an inhibitory characterization on CRC by restraining the epithelial-mesenchymal transition (EMT) process and the production and secretion of uPA, concurrently, while CGN reduced its invasion capacity by inhibiting the activity of RhoA. Furthermore, it was demonstrated that miR-125b exerted a tumor-promoting role by repressing CFTR and CGN simultaneously. Together, these evidences collectively support a key functional role of miR-125b/CFTR/CGN axis as viable biomarkers for the treatment of CRC.

228. 肾透明细胞癌患者铁死亡相关基因的预后作用

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【摘要】 目的 探讨铁死亡相关基因在肾透明细胞癌患者中的表达及其预后价值。 **方法** 通过 TCGA 数据库下载 KIRC 的相关测序数据与检索到的铁死亡相关基因取交集，进行铁死亡相关基因的差异分析。之后利用单变量和多变量 Cox 回归分析，筛选具有预后价值的基因，构建预

测患者生存情况的风险评分模型，并对模型进行验证。对高低风险组进行 GO 与 KEGG 通路富集，探讨风险差异的可能原因；通过 ssGSEA 分析，评估高低风险组间的免疫浸润情况。**结果** 在 KIRC 患者的肿瘤组织和正常组织中，共得到 21 个差异的铁死亡相关基因；通过单因素 Cox 回归分析，获得 28 个与 KIRC 预后相关的基因；之后进行 Lasso 回归与多因素 Cox 回归分析，结果显示有 10 个基因被纳入模型，计算公式为：风险值（risk score）=(0.0245)*ALOX5 表达值+(0.1260)*CBS 表达值+(0.1995)*CD44 表达值+(0.2183)*CHAC1 表达值+(-0.2959)*HMGCR 表达值+(0.0367)*MT1G 表达值+(0.0614)*SLC7A11 表达值+(-0.0807)*FDFT1 表达值+(0.1603)*PEBP1 表达值+(-0.2205)*GOT1 表达值。生存状态图表明，高风险组死亡病例数多于低风险组；ROC 曲线表明风险评分模型具备一定预测能力；K-M 生存分析显示，高风险组总体生存率低于低风险组（P=5.73e-13）。GO 与 KEGG 富集分析提示，高低风险组间免疫情况及 IL-17 信号通路存在显著差异；进一步的 ssGSEA 富集显示，高低风险组间大部分免疫细胞的评分存在显著差异。 **结论** 基于铁死亡相关基因的预后风险评分模型可用于 KIRC 的预后预测，针对铁死亡相关基因设计靶点可能是治疗 KIRC 的一种新选择。

229. RANBP2 activates O-GlcNAcylation through inducing CEBPα-dependent OGA downregulation to promote Hepatocellular carcinoma malignant phenotypes

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O-GlcNAcylation is an important post-translational modifications (PTMs) jointly controlled by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). Hyper-O-GlcNAcylation is reported to account for Hepatocellular carcinoma (HCC) malignancy, but the underlying mechanisms by which OGT/OGA imbalance regulates HCC tumorigenesis remains largely unknown. Here we reported that RAN binding protein 2 (RANBP2), one of small ubiquitin-like modifier (SUMO) E3 ligases, was associated with malignant phenotypes in HCC. RANBP2 was firstly found to enhance O-GlcNAc level through downregulating OGA while not affecting OGT expression. RANBP2 could facilitate CCAAT/enhancer-binding protein alpha (CEBPα) SUMOylation and degradation by direct interaction with CEBPα. As transcriptional factor, CEBPα was verified to augment OGA transcription, and further experiments demonstrated that its transcriptional inactivity by RANBP2 was indispensable for OGA downregulation. Importantly, we provided in vitro and in vivo evidence of HCC malignant phenotypes that the imbalance of OGT/OGA and subsequent higher O-GlcNAcylation events on oncogenic proteins such as peroxisome proliferative activated receptor, gamma, coactivator 1 alpha (PGC1α) via RANBP2 could be reversed by CEBPα restoration. Together, our results identify novel

molecular mechanism by which RANBP2 regulates its function in CEBPα-dependent OGA downregulation and hyper-O-GlcNAcylation, encouraging further study of their promising HCC therapeutic implications.

230. Tumor Microenvironment Characterization in bladder cancer Identifies Prognostic and Immunotherapeutically Relevant Biomarker

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Background: The tumor microenvironment (TME) has a significant influence on prognosis and immunotherapy. There are no studies on the systematic analysis of bladder cancer TME and its effect on immune checkpoint inhibitor therapy.

Methods: We comprehensively evaluated the TME infiltration pattern of bladder cancer in 1,889 patients and conducted extensive immunogenomic analysis to explore the heterogeneity and prognostic significance of the TME of bladder cancer. The principal component analysis algorithm was used to calculate the immune cell (IC)score to quantify the level of IC infiltration. We used the receiver operating characteristic (ROC) curve, Tumor Immune Dysfunction and Exclusion (TIDE), and Subnetwork Mappings in Alignment of Pathways (SubMAP) algorithms to evaluate whether the ICscore can predict the benefits of immune checkpoint inhibitors in bladder cancer patients.

Results: We identified three different TME phenotypes using unsupervised clustering methods. To explore the potential biological pathways that drive the formation of these microenvironmental phenotypes, we demonstrated the clinical and pathological characteristics, biological signaling pathways, cancer immune circulation, copy number, and somatic mutation differences among the different subtypes. In addition, univariate and multivariate Cox regression analyses showed that the ICscore is a reliable and independent prognostic marker. The ICscore can also predict immune checkpoint inhibitor responsiveness as patients with higher ICscores showed a significant therapeutic advantage in immunotherapy.

Conclusions: This study increases our understanding of the characteristics of TME infiltration in bladder cancer and provides guidance on more effective personalized immunotherapeutic strategies.

231. 基于生物信息学的肺腺癌关键生物标志物识别与鉴定

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郑州大学

摘要：目的：非小细胞肺癌(NSCLC)是世界上发病率和死亡率最高的癌症之一。肺腺癌(LUAD)诊断较晚，治疗选择少，缺乏有效治疗，治疗效果和预后较差。本研究旨在探索与 LUAD 发生、发展、转移和预后相关的新的生物标志物，以期为 LUAD 提供新的靶向生物标志物。方法：从 GEO（Gene Expression Omnibus）数据库中下载 GSE10072、GSE32863、GSE7670 的基因芯片数据集。然后筛选出非小细胞肺癌与正常组织之间的差异表达基因(DEGs)。随后将三个基因芯片的差异基因的交集进行基因本体论(Gene Ontology，GO)分析和 KEGG（Kyoto Encyclopedia of Genes and Genomes）通路富集分析，以确定这些 DEG 的生物学功能。此外，还构建了蛋白质-蛋白质相互作用(PPI)网络，以找出这些基因之间的相互作用，并在 GEPIA 数据库验证 HUB 基因的表达以及不同表达水平对预后的影响。结果：从 GSE7670、GSE10072 和 GSE32863 中获得了 1072、644 和 1269 个差异表达基因。通过对 GSE7670、GSE10072 和 GSE32863 数据集的综合生物信息学分析，共筛选出 300 个差异表达的重叠基因，其中 210 个基因显著上调，90 个基因显著下调。对这些 DEGs 进行 GO 分析，发现这些 DEGs 产物主要富集在细胞粘附、蛋白结合和质膜上。KEGG 分析表明，富集的途径包括 PI3K-Akt 信号通路、焦点粘附、ECM-受体相互作用、蛋白质消化和吸收等途径。从蛋白质-蛋白质相互作用网络来看，CDC20、KIAA0101、CENPF、TOP2A、MCM4、TYMS、ASPM、NUSAP1、MELK 和 UBE2C 的蛋白质-蛋白质相互作用关系最强。GEPIA 在线生存分析工具分析证实有 10 个基因在肺腺癌中表达水平均高于正常组织且均与肺腺癌的预后密切相关，即 Hub 基因表达水平较高的患者总体生存时间较短。结论：CDC20、KIAA0101、CENPF、TOP2A、MCM4、TYMS、ASPM、NUSAP1、MELK 和 UBE2C 可能是 LUAD 关键蛋白的编码基因，其作为 LUAD 潜在的生物标志物和候选治疗靶点的可行性及其诊断、预后价值需要我们进一步研究。

232. Long noncoding RNA RP11-624L4.1 is associated with unfavorable prognosis and promotes proliferation through CDK4/6-CyclinD1-Rb-E2F1 pathway in nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in southern China and southeast Asia. Emerging evidence revealed that long noncoding RNAs (lncRNAs) might play important roles in the development and progression of many cancers, including NPC. The functions and mechanisms of the vast majority of lncRNAs involved in NPC remain unknown. In this study, a novel lncRNA RP11-624L4.1 was identified in NPC tissues using next-generation sequencing. In situ hybridization (ISH) was used to analyze the correlation between RP11-624L4.1 expression and the clinicopathological features or prognosis in NPC patients. RPISeq predictions and RIP assays were used to identify RP11-624L4.1's interactions with CDK4. As a result, we found RP11-624L4.1 is hyper-expressed in NPC tissues, which was associated with unfavorable prognosis and clinicopathological features in NPC. By knocking down and over-expressing RP11-624L4.1, we also found that it promotes the proliferation ability of NPC in vitro and in vivo through CDK4/6-CyclinD1-Rb-E2F1 pathway. Overexpression of CDK4 in knocking down RP11-624L4.1 cells can partially rescue NPC promotion, indicating its role of RP11-624L4.1-CDK4/6-CyclinD1–Rb-E2F1 pathway. Taken together, RP11-624L4.1 is required for NPC unfavorable prognosis and proliferation through CDK4/6-CyclinD1-Rb-E2F1 pathway, which may be a novel target for therapeutic and prognostic in patients with NPC. (Mol Ther Nucleic Acids. 2020 Oct 15. doi: 10.1016/j.omtn.2020.10.017. Epub ahead of print. PMID: 33078086; PMCID: PMC7558227)

233. 抗乳腺癌潜在靶点 CYP4Z1 的发现与研究进展

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化疗在乳腺癌治疗中仍占有重要地位，但化疗耐药是乳腺癌治疗面临的一大难题。研究表明肿瘤干细胞（CSCs）是化疗耐药产生的根本原因。细胞色素 p450（cytochrome p-450, CYP）4 家族是含血红蛋白的一类多基因超家族酶系，参与饱和脂肪酸和不饱和脂肪酸的代谢，在乳腺癌发生发展中起重要作用。研究显示，相比于庞大的 CYP 家族其他成员，CYP4Z1 在乳腺癌组

织中特异性高表达，且 CYP4Z1 的表达与乳腺癌的进展呈正相关。后续研究发现过表达 CYP4Z1 可促进乳腺癌血管生成。本人近年来深入研究了 CYP4Z1 在调控乳腺癌发生发展中的作用，发现 CYP4Z1 在乳腺癌组织及细胞中高表达，在正常乳腺组织及细胞中低表达；敲减 CYP4Z1 基因的表达，对乳腺癌细胞活性没有显著影响，但可显著抑制乳腺癌血管生成能力，增加乳腺癌细胞凋亡水平；且 CYP4Z1 的表达水平在耐药细胞株中较野生型细胞株显著上调，敲低 CYP4Z1 可促进耐药细胞株对他莫昔芬的敏感性；此外，通过干细胞成球实验收集干性较强的 BCSC 微球体，发现 CYP4Z1 的表达水平在 BCSC 微球体中显著上调；进一步通过体内外实验证实了敲减 CYP4Z1 可显著削弱乳腺癌 CSC 样特性、改善乳腺癌多柔比星耐药。同时最近有研究在乳腺癌病人的血清中检测到高滴度的 CYP4Z1 抗体，并提出“CYP4Z1 可能是治愈乳腺癌的关键蛋白”，提示 CYP4Z1 蛋白可能是促进乳腺癌 CSC 样特性的关键驱动基因。因此，我们猜想 CYP4Z1 可能是一个潜在的抗乳腺癌靶点。

234. N6-methyladenosine (m6A) regulates tumor immune microenvironment infiltration and affects the efficacy of anti-PD-L1 immune checkpoint inhibitor therapy in bladder cancer

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Background: N6-methyladenosine (m6A) has emerged as one of the most important modifications of RNA. However, the potential role of m6A in the immune microenvironment and immunotherapy for bladder cancer remains unclear. (2)Methods: Based on the expression of 23 kinds of m6A regulatory factors, we identified three different m6A modification patterns in bladder cancer. The effects of the three kinds of m6A modification modes on the mutation characteristics, clinicopathological characteristics, expression of bladder cancer-related genes, immune cell infiltration level, and gene expression level of immune checkpoint genes were comprehensively analyzed. In addition, the effects of different m6A modification modes on the therapeutic efficacy of anti-PD-L1 (atezolizumab) are also discussed.(3)Results: Our results confirm that m6A methylation plays an important role in the immune cell recruitment process in the tumor microenvironment of bladder cancer, and the difference in m6A modification mode is an important factor leading to the heterogeneity and complexity of the tumor microenvironment, which is influences the efficacy of anti-PD-L1 therapy for bladder cancer. We established a method to quantify the level of m6A modification (m6Ascore), which is an important and powerful prognostic method and predictor for bladder cancer. In addition, we found that the eraser molecule FTO may be involved in the occurrence and development of bladder cancer and affect the

efficacy of anti-PD-L1 immune checkpoint treatment, and have a predictive effect on the immune checkpoint inhibitor response.(4)Conclusions: This study comprehensively analyzed the effect of m6A methylation modification on the cell infiltration characteristics of the immune microenvironment of bladder cancer, and its effect on the anti-PD-L1 treatment of bladder cancer. We provide new insights into the regulatory pathways of the immune microenvironment and the methylation function of m6A in bladder cancer, which will help to design novel diagnostic methods, prognostic tools, and therapeutic targets.

235. 肺癌转移预测因子的研究进展

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肺癌的全球致死率在恶性肿瘤中居首位，其中非小细胞肺癌(Non-small cell lung cancer，NSCLC)占比约为 85%。早期 NSCLC 的治疗方式以手术为主，但术后的高转移发生率是导致死亡的主因，而现有综合治疗体系对转移防控欠佳。目前指南推荐主要基于临床 TNM 分期及病理特征筛选术后需要辅助治疗预防复发转移的患者，但在真实世界中即使分期相同、治疗过程相同的患者，其预后依然相差甚远，表明现有的筛选方法对患者术后复发转移的评估缺乏精准化与个体化。随着现代医学在液态活检、分子病理分型、各种组学等领域的快速发展，促使针对肺癌转移及复发的预测方面取得了一定的成果。因此本文对 NSCLC 转移及复发的生物预测因子研究进展进行总结，以期为预测 NSCLC 转移提供更广阔的思路，进而提高临床中转移防治效率。

236. Se@Albumin nanoparticles ameliorate intestinal mucositis caused by cisplantin through the gut microbiota targeted regulation

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Chemotherapy associated intestinal mucositis is still one of major challenge on the first-line clinical cancer treatment. Selenium element has been shown its health benefit on enteritis in trace uptake, however, which was limited because of its narrow safety. Here, a new form of Se@Albumin complex nanoparticles (Se@Albumin NPs) were developed by self-assembly of denatured human serum albumin and selenite salt. the Se@Albumin NPs significantly improves intestinal mucositis of mouse model with cisplantin（CDDP） induced through attenuating the level of intestinal oxidative stress, reducing intestinal permeability and relieving gastric dysmotility. Very interesting, the restoration of

anti-inflammatory bacteria (Bacteroidetes, Firmicutes) and reduced abundance of proinflammatory bacteria (Escherichia) contributed to the Se@Albumin NPs reduce intestinal mucositis of mouse. And, the fecal microbiota transplantation (FMT) with material from Se@Albumin NPs-treated mice significantly protected pseudoaseptic mice from CDDP induced intestinal mucositis, compared with Se NPs-treated mice. In conclusion, our findings showed that Se@Albumin NPs can significantly improve CDDP-induced intestinal mucositis, and the benefit of Se@Albumin NPs on CDDP-induced intestinal mucositis may be directly mediated by the gut microbiota regulation, which will provide new helpful information for clinical treatment.

237. Analysis of autophagy-related signatures identified two distinct subtypes for evaluating the tumor immune microenvironment and predicting prognosis in ovarian cancer

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Ovarian cancer is the gynecologic malignant tumor with the highest mortality rate. The interaction between autophagy and the tumor immune microenvironment has clinical importance. Hence, it is necessary to explore reliable biomarkers associated with autophagy-related genes (ARGs) for risk stratification in OC. Here, we obtained ARGs from the MSigDB database and downloaded the expression profile of OC from TCGA database. The k-means unsupervised clustering method was used for clustering, and two subclasses of OC (cluster A and cluster B) were identified. SsGSEA method was used to quantify the levels of infiltration of 24 subtypes of immune cells. Metascape and GSEA were performed to reveal the differential gene enrichment in signaling pathways and cellular processes of the subtypes. We found that patients in cluster A were significantly associated with higher immune infiltration and immune-associated signaling pathways. Then, we established a risk model by LASSO Cox regression. ROC analysis and Kaplan-Meier analysis were applied for evaluating the efficiency of the risk signature, patients with low-risk got better outcomes than those with high-risk in overall survival. Finally, ULK2 and GABARAPL1 expression was further validated in clinical samples. In conclusion, Our study constructed an autophagy-related prognostic indicator, and identified two promising targets in OC.

238. Analysis of Clinicopathologic Features of Glycogen-rich Clear Cell Carcinoma (GRCC) of the Breast

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Objectives: To explore the clinicopathological features of glycogen-rich clear cell carcinoma (GRCC) of the breast in order to further deepen the understanding of the disease and improve the diagnostic level.

Methods: Six patients with pathologically diagnosed GRCC of the breast from January 2015 to December 2019 were collected, and their pathomorphological features, clinical pathological features, and immunophenotypic features were analyzed.

Results: All 6 patients were female, and the age of onset was 46-57 years old, most common among middle-aged women. All 6 cases underwent pathological examination and found that triple negative breast cancer accounted for 50%, which indicates that the malignancy of GRCC is relatively high and the prognosis is poor.

Conclusions:GRCC of the breast is a rare type of breast cancer. Pathology is an important means of diagnosis. It depends not only on the morphological characteristics of the tumor tissue, but also on the expression of its specific immunohistochemical indicator period acid-Schiff (PAS). Differentiate other diseases to achieve the purpose of early diagnosis and early treatment.

239. Lipid-rich carcinoma of the breast with clinicopathologic characteristics analysis

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Lipid rich carcinoma is a rare variant of breast cancer, WHO defines it as breast cancer with 90% tumor cells rich in neutrophils, accounting for <1%-6% of all breast malignant tumors. We retrospectively analyzed the clinicopathologic characteristics of lipid-rich carcinomas of the breast. We observed the histopathological features of the tumor under the light microscope. A panel of estrogen receptor, progesterone receptor, human epidermalgrowth factor receptor-2 (HER-2), cytokeratin (CK) 5/6, P63 and PAS was prepared for detection of lipid-rich carcinoma.Cytokeratin(CK)5/6, P63 and PAS were negative. Estrogen receptor(6/11),Progesterone receptor(5/11), and HER-2 (8/11) were positive. Lipid rich breast carcinoma is highly malignant and with poor prognosis.It is very important to be familiar with its pathological and molecular characteristics, to improve the vigilance and consciousness of the disease and to avoid misdiagnosis。

240. Artificial intelligence-assisted interpretation of Ki-67 expression and repeatability in breast cancer

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Objective: Ki-67 Label Index (Ki-67LI) is a breast cancer（BC） predictive and prognostic factor. The lack of standardization and reproducibility of evaluation methods limits its use in routine work. In this study, Ki-67 standard comparison card (SRC) and artificial intelligence (AI) software were used to evaluate breast cancer Ki-67LI. We established training and validation sets and studied the repeatability inter-observers.

Methods: A total of 300 invasive breast cancer specimens were randomly divided into training and verification sets, with each set including 150 cases. Breast cancer Ki-67 standard comparison cards ranging from 5% to 90% were created. The training set was interpreted by nine pathologists of different ages through microscopic visual assessment (VA), SRC, microscopic manual counting (MC), and AI. The validation set was interpreted by three randomly selected pathologists using SRC and AI. Friedman M was used to analyze the difference. The intra-group correlation coefficient (ICC) and Bland-Altman scatter plot were used for consistency analysis.

Results: Ki-67LI interpreted by the four methods in the training set did not obey a normal distribution ($P<0.05$). Friedman M test showed that the difference between pathologists using the same method was statistically significant ($P<0.05$). After Bonferroni correction, Ki-67LI interpreted using SRC and AI showed that the difference between each pathologist and the gold standard was statistically significant ($P<0.05$), and the difference between pathologists was not statistically significant ($P>0.05$)， Ki-67LI interpreted using VA and MC showed that the difference between each pathologist and the gold standard and the difference between pathologists were statistically significant ($P<0.05$). The intra-group correlation coefficient（ICC） obtained by nine pathologists in the training set that used SRC (ICC=0.918) and AI (ICC=0.972) to interpret Ki-67LI, was significantly higher than when VA (ICC=0.757) and MC (ICC=0.803) were used. Through SRC, the initial and intermediate pathologists in the training set had an increased ICC. In the homogeneous group of the training set, the agreement on observers of VA, MC, SRC, and AI among observes was very good, with all ICC values above 0.80. In the heterogeneous group, SRC and AI showed a good agreement among observers (ICC= 0.877 and 0.959, respectively). In the homogeneous and heterogeneous groups of validation sets, the consistency among the pathologists that used SRC and AI was very good, with an ICC of＞0.9. In the verification set, using SRC and AI, three pathologists obtained results that were very consistent with the gold standard, having an ICC above 0.95, and the inter-observer agreement was also very good, with an ICC of＞0.9.Conclusion: AI has satisfactory inter-observer repeatability, and the true value was closer to the gold standard, which is the preferred method for Ki-67LI

reproducibility; While AI software has not been popularized, SRC may be interpreted as breast cancer Ki-67LI's standard candidate method.

241. 乳腺癌肿瘤浸润淋巴细胞的异质性及其预后意义

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背景：乳腺癌中的肿瘤浸润淋巴细胞 TILs 可提供预后和预测信息。 这项研究旨在评估乳腺癌中肿瘤浸润淋巴细胞的时空异质性及其与免疫细胞亚型的关系。

方法：免疫组织化学确定的免疫细胞亚型； 在一系列侵袭性乳腺癌（n = 846）中评估了 T 细胞标志物（CD3，CD8 和 FOXP3），B 细胞标志物（CD20）和组织细胞标志物（CD68）。判读全苏木和曙红（H＆E）染色的玻片，以检查原发肿瘤和相应的局部复发癌中肿瘤浸润淋巴细胞的异质性，以报告肿瘤浸润淋巴细胞的时空异质性。对代表不同肿瘤的多个肿瘤块（每例 3-4 个块）的 H＆E 染色切片进行了评估，以评估肿瘤浸润淋巴细胞切片间异质性以及切片内异质性。 评估了基质肿瘤浸润淋巴细胞平均值（AV-TILs）和热点值（HS-TILs）。

结果：AV-TILs 显示与所有免疫细胞亚型相关。 主要成分是 CD3 +细胞（平均数= 62），而 CD20 +细胞组成最少（平均数= 17）。 在同一病例的肿瘤块之间，TIL 之间无统计学差异（AV-TIL 为 p = 0.362，HS TIL 为 p = 0.184）。 与其他乳腺癌亚型相比，三阴性乳腺癌显示更高的 TIL（p <0.001）。 高 AV-TIL，CD3 +，CD8 +和 CD20 +细胞与三阴性乳腺癌中的更长生存期相关（p <0.04）。 复发性肿瘤中较高的 AV-TILs 与较短的复发后存活率显着相关（p = 0.003）。

结论：尽管免疫细胞类型成分具有异质性，但一个 H＆E 染色切片中的平均肿瘤浸润淋巴细胞仍能可靠地代表整个肿瘤肿瘤浸润淋巴细胞。 TILs 与三阴乳腺癌的结局相关，并在复发性肿瘤中提供预后意义。

242. HER2-Residual cancer burden system can well predict the prognosis of patients after neoadjuvant therapy in breast cancer

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Objective: Residual cancer burden (RCB) classification can effectively predict the long-term prognosis of patients after neoadjuvant therapy. However, a limitation of the RCB classification is that it takes into account only the presence of residual tumors in the pathological specimen after therapy but not the preoperative factors. Therefore, this study analyzed the related factors affecting the RCB

grading of breast cancer patients after neoadjuvant therapy, and modified the traditional RCB system according to the expression of HER2 before neoadjuvant therapy. At the same time, we also analyzed the predictive effect of the modified RCB system on breast cancer patients with different molecular types. **Methods:** 1274 patients were retrospectively analyzed who were diagnosed with invasive carcinoma of the breast by preoperative hollow needle aspiration pathology from January 2009 to December 2017, and who underwent surgical resection after neoadjuvant therapy. And 1,186 patients were followed up successfully. From 2009 to 2016, 837 patients were randomly assigned to the training set, and combined with HER2 expression before neoadjuvant therapy for revised residual cancer burden system (HER2-RCB). In 2017, 349 patients formed a verification set, which was used to verify the effectiveness of the analytical model. **Results:** All patients in this study were female, with an average age of 50+8.7 years (24-86 years). Spearman correlation analysis showed that RCB classification was positively correlated with ER, PR expression, clinical stage, and age before neoadjuvant therapy ($P<0.05$), and negatively correlated with KI67, HER2 expression before neoadjuvant therapy, postoperative vascular tumor thrombus and lymph node metastasis ($P<0.05$). In the training set and validation set groups, the HER2-RCB classification has a good and consistent calibration between the predicted value of the patient's overall survival (OS) and disease-free survival (DFS) risk and the actual observed value. Sexuality is high ($P>0.05$), and the prognostic risk stratification of patients is higher than RCB classification (AUC=0.782, 0.699; 0.819, 0.719). According to the molecular types of breast cancer, and compared with other molecular typing, the differences that the RCB classification predicts the OS of patients with HER2 over-expression and Luminal B HER2 positive breast cancer were statistically significant ($P<0.05$), but there was no statistically significant difference in DFS ($P>0.05$), while the differences that the HER2-RCB classification predicts OS and DFS in patients with HER2 over-expression, and Luminal B HER2-positive breast cancer were statistically significant ($P<0.05$). **Conclusions:** HER2-RCB classification is more accurate than RCB classification in predicting prognosis, and the prediction of recurrence and metastasis risk in patients with HER2 over-expression and Luminal B HER2 positive breast cancer is better than RCB classification. It is suggested that HER2-RCB classification has better clinical applicability.

243.肝细胞癌双胞胎基因组重测序检测 LFNG 缺失可通过 NOTCH 信号通路促进肝癌形成

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背景：原发性肝细胞癌(HCC)是世界四大高发癌症之一，中国新病例占全球 55%。破解肝癌发病机制对提高肝癌患者生存率意义重大。研究表明 O-岩藻糖肽 3-β-N-乙酰氨基葡萄糖氨基转移酶(LFNG)在胰腺癌、结直肠癌、乳腺癌及前列腺癌中发挥抑制作用。但在肝癌中未见报道。方法与结果:本研究通过人类基因组重测序技术，鉴定了一对双胞胎兄弟(肝癌患者)的肿瘤组织样本及其父(正常)，其母(正常)的外周血样本的基因组序列，通过比较基因组分析发现共有 5 个突变基因:1) LFNG (类型:frameshift Indel GATG hg19 chr7:2552882;基因型: 纯合子;父母: 杂合子)。 2) HERC2 (类型:SNV G/A hg19 chr15: 28475625; 结果: Thr1566Met; 基因型:纯合子; 父母:杂合子)。3) MLC1 (Type: SNV T/C hg19 chr22 50502491; Consequence: Ala1031Gly, 基因型: 纯合子; 父母:杂合子); 4) ARHGAP4 (类型:SNV T/C hg19 chrX 153175826;结果: Asp692Gly;基因型:纯合子;父母: 父正常,母杂合子)。5) HOXA4 (类型:SNP C/T chr7 27170350;结果: 起始密码子缺失; 基因型:杂合子;父母:父杂合子,母正常)。基于 LFNG 在孩子中纯合移码突变导致基因功能丧失这一个可能早期致癌的假设，通过 NCBI 分析发现，LFNG 突变(插入/缺失)序列 del(GATG)3 的基因组突变频率为 0.3036（ALFA Project），该变异导致 LFNG 获得丧失。HCCDB 分析发现，LFNG 在 HCC 中的表达量低于癌旁（log2HCC/allAdiacent =-1.90）。GOProcess 和 GoFunction 分析，LFNG 主要参与 Notch 信号通路,且调节 LFNG 酶活性。String 分析发现 LFNG 主要互作蛋白为 DLL1，NOTCH1，NOTCH2 和 JAG1。KEGG 和 Reactome 分析表明 LFNG 缺失通过修饰特定 EGF 样结构域上的 O-岩藻糖残基，从而导致 JAG1 对 NOTCH1 抑制减少来调节 NOTCH1 活性。进一步，我们利用 50 例人肝癌样本进行免疫组化检测，发现与对照相比肝癌样本的 LFNG 的表达量显著下调。综上所述，这些数据揭示了 LFNG 表达缺失可能通过 Notch 信号通路促进肝癌的形成。

244. Comparison of the detection of Helicobacter pylori infection status by 13C-urea breath test, recombinant immunoblot and sequencing of the microbial 16S ribosomal RNA gene

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Objective: Helicobacter pylori (H. pylori) is one of the most common human infections in the world. And it is known as the strongest risk factor for gastric cancer (GC). Recently, numerous detection methods for the presence of the H. pylori have been developed. The aim of this study was to compare the infection status of H. pylori by 3 diffenert methods, ^{13}C-urea breath test (^{13}C-UBT), recombinant immunoblot, a serological method, and sequencing of the microbial 16S ribosomal RNA gene and to explore the reason for the different results.

Materials and Methods: 3 different methods, ^{13}C-UBT, recombinant immunoblot, a serological method, and sequencing of the microbial 16S ribosomal RNA gene were used to detect the infection status among the 153 subjects in Linqu County, Shandong province, a high-risk area of GC in Northern China with an exceptionally high prevalence of H.pylori infection. The cut-off point of ^{13}C-UBT was set at 4.0 (DOB≥4.0 for positive). Recombinant Immunoblot (recomLine) was applied to detect H.pylori-specific antibodies such as CagA, VacA, GroEL, FliD, HpaA and so on. The test result was determined by adding the point values according to point evaluation of the antigens. The infection status was determined by the sum of points (points≤2 for negative, points=3 for inconclusive, points≥4 for positive). Gastric mucosal biopsies were taken from subjects for deep sequencing of the microbial 16S ribosomal RNA gene. The cutoff value of H. pylori sequence percentage for H. pylori colonization by sequencing of the microbial 16S ribosomal RNA gene was set at approximately 1%.

Results: The presence of H. pylori sequences was detected in all H. pylori-positive samples and in 55% of H. pylori-negative samples among the 150 subjects by ^{13}CUBT. Sensitivity and specificity is 100% and 45% respectively. The kappa value is 0.547 ($p<0.05$) between the method of ^{13}C-UBT and sequencing of the microbial 16S ribosomal RNA gene. Also, the presence of H. pylori sequences was detected in 92% H. pylori-positive samples and in 35% of H. pylori-negative samples among the 144 subjects by recomLine. Sensitivity and specificity is 92% and 65% respectively. The kappa value is 0.516 ($p<0.05$) between the method of recombinant immunoblot and sequencing of the microbial 16S ribosomal RNA gene. And the presence of H. pylori specific antibodies were detected in 97% H. pylori-positive samples and in 50% of H. pylori-negative samples among the 147 subjects by ^{13}C-UBT. Sensitivity and specificity is 97% and 50% respectively. The kappa value is 0.548 ($p<0.05$) between

the method of recombinant immunoblot and ^{13}C-UBT.

Conclusion: These results suggest that different methods maybe detect various status of H.pylori Sequencing of the microbial 16S ribosomal RNA gene enable to detect low abundance gastric H. pylori sequences even in subjects that were negative with the method of ^{13}C-UBT. To some extent, the result of recombinant immunoblot reflects the state of the organism.

245. Circulating serum exosomal long non-coding RNAs FOXD2-AS1, NRIR, and XLOC_009459 as diagnostic biomarkers for colorectal cancer

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Background: Long non-coding RNAs (lncRNAs) can modulate tumor growth and metastasis and can be used as a diagnostic and prognostic biomarkers for cancer detection. The aim of this study was to identify a few circulating serum exosomal lncRNAs for the diagnosis of colorectal cancer (CRC).

Materials and Methods: Exosomes were isolated from the serum of all participants by ultracentrifugation, after which they were verified by transmission electron microscope (TEM), qNano and immunoblotting. The exosomes isolated from 4 CRC patients and 2 healthy donors were subjected to RNA isolation and lncRNA sequencing. QRT-PCR was performed to screen and evaluate the expressions of candidate exosomal lncRNAs in 203 primary CRC patients and 201 healthy donors. The receiver operating characteristic curve (ROC) was used to assess the diagnostic efficiency of serum exosomal lncRNAs.

Results: Sixteen candidate lncRNAs were screened according to the results of lncRNA sequencing and gene expression. Only serum exosomal FOXD2-AS1 and NRIR and XLOC_009459 (TCONS_00020073) levels were significantly upregulated in 203 CRC patients and 80 early-stage CRC patients compared to 201 healthy donors and 20 benign diseases; the area under the curve (AUC) was 0.736 and 0.758, respectively. The expression levels of exosomal FOXD2-AS1, NRIR, and XLOC_009459 were significantly decreased postoperatively compared to the baseline levels determined before surgery.

Conclusions: Exosomal lncRNAs FOXD2-AS1, NRIR, and XLOC_009459 may be used as potential non-invasive, sensitive, and specific biomarkers for diagnosis of CRC patients and early-stage CRC patients.

246. PD-1/PD-L1 抑制剂免疫联合治疗晚期 NSCLC 的临床研究进展

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据 2020 年美国癌症数据统计，肺癌是发病率第二、死亡率第一的恶性肿瘤。在肺癌的组织学分型中，绝大部分是非小细胞肺癌，其中非小细胞肺癌（NSCLC）占肺癌组织学类型的 80%-85%。目前，非小细胞肺癌的传统治疗方法主要包括手术、化疗、放射治疗和靶向治疗。然而这些治疗方法都各有缺点。由美国“国家癌症研究中心”最新数据统计，在 2009-2015 年期间，肺癌的 5 年生存率不足 20%。近年来，随着肿瘤免疫研究的深入，免疫治疗在癌症治疗方面取得了突破性进展。特别是程序性细胞死亡蛋白-1/程序性细胞死亡配-1(PD-1/PD-L1)抑制剂的发展，使治疗进入了一个新的阶段。美国 FDA 批准的用于治疗晚期 NSCLC 中有 5 种单克隆抗 PD-1/PD-L1 抗体：纳武单抗、帕博利珠单抗（pembrolizumab）、阿特珠单抗（atezolizumab）、德瓦鲁单抗（durvalumab）和阿维单抗（avelumab）。尽管免疫检查点抑制剂（ICIs）在临床治疗方面取得了成功，但并非所有患者长期有反应，不同患者的反应也各不相同。考虑到不可逆的自身免疫毒性，选择合适该治疗方法的病人变得更加关键。因此，迫切需要找到可靠的生物标志物，以帮助确定哪些患者将受益于 ICI。目前，预测 PD-1/PD-L1 抑制剂治疗的反应及其局限性最常见的 3 种生物标志物：免疫组化 PD-L1 的表达、肿瘤突变负荷(TMB)和微卫星不稳定性(MSI)。

在 ICIs 临床治疗中，只有小于 30%的患者可能受益于免疫检查点单药治疗。因此，这一现象导致临床医生和研究人员优先考虑更有效的免疫联合治疗。为了扩大受益人群，联合治疗是目前一大趋势。不同治疗方式的组合不仅可以产生较大的抗肿瘤协同作用，而且可以减少每种治疗药物的剂量，避免耐药性的出现[5]。本综述主要介绍 3 种生物标志物——免疫组化 PD-L1 的表达、肿瘤突变负荷(TMB)和微卫星不稳定性(MSI)在预测 PD-1/PD-L1 抑制剂治疗的反应及其局限性方面的研究进展，分别阐述 PD-1/PDL-1 抑制剂联合化疗、放疗、靶向治疗、其他免疫治疗的策略和相关临床研究进展，有助于全面了解 PD-1/PDL-1 抑制剂免疫联合治疗晚期 NSCLC 的临床有效性和安全性。

壁报交流

247. 利用血清 CA242 鉴别诊断 CA19-9 检测结果的假阳性

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目的：糖类抗原 CA19-9 是临床上常用的消化道肿瘤标志物之一，但是 CA19-9 易受良性肝胆、胰腺疾病（如胰腺炎、肝硬化、胆汁淤积等）等因素影响而产生较高的假阳性概率。而 CA242 受上述因素影响较小，可用于鉴别诊断 CA19-9 检测结果的假阳性，从而大大提高了血清学肿瘤标志物检测结果的准确性。

方法：对 129 例不同良恶性疾病患者的血清 CA19-9 和 CA242 检测结果进行统计分析，统计不同疾病患者 CA19-9 和 CA242 的阳性率，并结合临床诊断，比较两种消化道肿瘤标志物的特异性与灵敏度。判断 CA242 能否用于鉴别诊断 CA19-9 检测结果的假阳性，从而提高血清学肿瘤标志物检测结果的准确性。

结果：对于消化道恶性病，如胰腺癌、胃癌、结直肠癌、十二指肠肿瘤，血清 CA19-9 和 CA242 的检测结果均为阳性，与临床诊断一致。然而，对于消化道良性病，如胰腺炎、肝硬化、胆结石、黄疸、急慢性胆囊炎等，CA19-9 存在 29% ～62%的假阳性概率，而 CA242 的假阳性概率仅为 1.6～7.5%，相比之下，CA242 的特异性显著高于 CA19-9。对于良性并患者，可以利用血清 CA242 鉴别诊断 CA19-9 检测结果的假阳性。

结论：消化道肿瘤标志物 CA242 的特异性显著高于 CA19-9，血清学检测 CA242 可以用于鉴别诊断 CA19-9 的假阳性检测结果，从而大大提高了血清学肿瘤标志物检测结果的准确性。

关键词：肿瘤标志物；CA242；CA19-9；假阳性；

248. 生物信息学方法在肿瘤标志物研究的应用

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生命科学和计算机科学的发展为这两种学科的交互融合带来了理论基础，生物信息学应运而生，这是一种通过计算机工具对生物信息进行存储、分析的科学，可以在数以万计的生物数据中来获取有用的信息。乳腺癌作为现在关注度最高的癌症之一，生物信息学方法在乳腺癌标志物的挖掘中扮演着重要的角色：利用 R（及其插件）等软件进行差异分析从而发现标志物在肿瘤和正常组织中表达的差异；或者运用共表达分析和富集分析构建出表达网并探究其所涉及的生物学活动；同时利用各种开放式的生物信息学工具（如 Oncomine、LncATLAS、STRING 等），也可以更便捷的挖掘各类数据库的信息，从而在寻找信号通路，靶点的过程中节约时间和精力；或者对于开发新的药物，优化实验流程，寻找更适宜的治疗方案有着指导作用。

249. 糖尿病患者内脏脂肪面积与血清 CA199 等的相关性研究

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[摘要] 目的：测定内脏脂肪面积，探讨血清 CA199 与内脏脂肪面积（VFA）的相关性。方法：选取我院 2 型糖尿病患者（T2DM）313 例，分为 CA199≤30 U/ml 组（n=238）CA199 > 30 U/ml 组（n=75），分别统计分析两组性别、年龄、空腹血糖值、舒张压、收缩压、身高、体重、体质指数（BMI）、头围、颈围、腰围、臀围、内脏脂肪面积、皮下脂肪面积、完成度、高血压病史、高脂血症病史、抽烟史、饮酒史、空腹 C 肽、120 分钟 C 肽、糖化血红蛋白、ALT、AST、ALP、γ-GT、BUN、Cr、TG、TC、HDL-c、LDL-c、hsCRP、癌胚抗原测定（CEA）、糖类抗原 CA199 等相关指标。结果：CA199≤30 U/ml 组内脏脂肪面积 87.1（57.2,115.3），CA199 > 30U/ml 组内脏脂肪面积 70.2（33，94.1）。差异有统计学意义（P<0.05）。Spearman 相关分析显示，内脏脂肪面积与年龄、皮下脂肪面积、身高、体重、体质指数（BMI）、头围、颈围、腰围、臀围、高血压病史、高血脂病史、舒张压、收缩压、空腹 C 肽、BUN、UA、TG、CA199 成正相关（r 分别为 0.149、0.612、0.161、0.572、0.619、0.332、0.415、0.663、0.487、0.209、0.149、0.164、0.121、0.033、0.180、0.134、0.018、0.190、0.157、0.005、0.116），与糖化血红蛋白、HDL 成负相关（r 分别为 -0.120、-0.208）Logistic 回归分析显示，内脏脂肪面积是 CA199 升高的独立危险因素（OR=1.256，98%CI:1.172-1.346）。

[关键词] 糖尿病 2 型；内脏脂肪面积;CA199；相关性探讨

250. ZBTB48 对鼻咽癌的 EMT 和转移的作用及相关机制初步研究

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目的: 放化疗后出现复发和远处转移是导致鼻咽癌(NPC)患者治疗失败和死亡的主要原因；上皮-间充质转化(EMT)在肿瘤早期侵袭和转移过程中扮演重要角色。目前，ZBTB48 在肿瘤发生发展中的功能还鲜有报道。

方法: 体外实验探讨 ZBTB48 和靶基因 MGAT5 在 NPC 细胞 EMT 和迁移侵袭中的作用；ChIP-qPCR 和启动子荧光素酶报告基因实验确证 ZBTB48 调控 NPC 细胞 EMT 和迁移侵袭等的作用可否由其靶基因 MGAT5 介导；免疫组化方法揭示 ZBTB48 及其靶基因 MGAT5 等的表达相关性及与生存预后的关系。

结果: qRT-PCR 和免疫组化结果表明 ZBTB48 在 NPC 组织标本中表达显著下调，ZBTB48 表达与肿瘤 T 分期、颈部淋巴结转移、远处转移以及临床分期等呈负相关。Western blot 检测结果显示，在过表达 ZBTB48 的 HONE1-EBV 细胞中，E-cadherin 表达水平显著升高，N-cadherin 和 vimentin 表达水平均显著降低；Transwell 和划痕迁移实验结果显示，ZBTB48 过表达抑制 HONE1-EBV 细胞的体外迁移。Western blot 结果显示，ZBTB48 敲除的 5-8F 细胞中，上皮标志性基因 E-cadherin 和 bβ-catenin 表达水平显著降低，N-cadherin 和 vimentin 表达水平均显著升高；Transwell 和划痕迁移实验结果显示，ZBTB48 敲除极大促进 5-8F 细胞的体外迁移。ChIP-qPCR 和启动子荧光素酶报告基因实验证实 ZBTB48 负向调控 MGAT5 的表达。对 177 例 NPC 组织免疫组化检测发现，ZBTB48 表达和 MGAT5 表达水平呈负相关。qRT-PCR 和 Western blot 检测结果显示，在 MGAT5 敲除的 HONE1-EBV 细胞中，E-cadherin 和β-catenin 表达显著升高，N-cadherin 和 vimentin 表达水平显著降低；Transwell 迁移实验结果显示，MGAT5 敲除明显抑制了 HONE1-EBV 细胞的体外迁移。Boyden 小室侵袭实验结果显示，siMGAT5 可大部分逆转 ZBTB48 敲除所致 5-8F 细胞增强的体外侵袭能力。

结论: 鼻咽癌 ZBTB48 表达下调，将导致其靶基因 MGAT5 表达上调，进而引起 NPC 细胞发生 EMT，从而促进了 NPC 的侵袭转移。

251.2 型糖尿病患者中高三酰甘油腰围表型与 ca199、cea 的关系

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摘要：目的 探讨 2 型糖尿病（T2DM）患者中高三酰甘油（TG）腰围表型与 ca199、cea 的关系。方法 2014 年 7 月至 2019 年 5 月于我院内分泌科就诊的 2 型糖尿病患者，选取泸州地区 1459 名 18 岁及以上人群为研究对象。问卷均由通过统一培训的调查员面对面询问填写,包括人口学基本特征、吸烟状况、饮酒频率、业余时间体育锻炼情况、睡眠总时长以及既往疾病史等信息,进行身高、体重、腰围等体格检查和血脂、血糖等生化指标测定。以血 TG≥1.7 mmol/L、男性腰围≥90 cm 或女性腰围≥80 cm 为切点，分为 TG 和腰围正常组（103 例）、单纯高三酰甘油血症组（67 例）、单纯腹型肥胖组（87 例）、高三酰甘油血症-腰围表型（HTWC）组（116 例），比较比较各组间 ca199、cea 升高的情况。结果：TG 和腰围正常组、单纯高三酰甘油血症组、单纯腹型肥胖组、HTWC 组 ca199 升高的概率分别为 20.3%（27/103）、20.9%（14/67）、33.3%（29/87）、34.7%（25/72），TG 和腰围正常组、单纯高三酰甘油血症组、单纯腹型肥胖组、HTWC 组 cea 升高的概率分别为 26.2%（27/103）、20.8%

（14/67）、33.3%（29/87）、41.6%（30/72）。在调整了年龄、性别、空腹血糖、餐后 2 h 血糖、收缩压、糖化血红蛋白 后，多分类无序 Logistic 回归分析结果显示，糖尿病中 HTGW 表型人群的 cea、ca199 较 TG 和腰围正常组升高，其 OR （95%CI）分别为 2.704（1.274～5.739）与 3.073（1.499～6.301）。结论 糖尿病中 HTWC 表型是 cea、ca199 升高的危险因素，可作为筛选预测肿瘤的简便指标。

关键词：甘油三酯类；糖尿病；2 型；流行病学研究；高三酰甘油腰围表型；肿瘤标志物

252. Hypoxia-inducible USP13 contributes to tumor growth and metastasis via enhancing the TLR4/MyD88/NF-κB pathway in hepatocellular carcinoma

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Abstract

Aim: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death worldwide. It has been shown that activation of the toll-like receptor 4 /myeloid differentiation primary response gene 88/nuclear factor-κB (TLR4/MyD88/NF-κB) pathway contributes to the development and progression of human HCC. Ubiquitin-Specific Protease 13 (USP13), which belongs to the deubiquitinating enzymes superfamily, is implicated in the occurrence and progression of human cancer via promoting deubiquitination and stabilization of substrate proteins, including MCL1, PTEN, MITF, Myc, USP10 and RAP80. A recent study presents that USP13 silencing represses HCC growth possibly by decreasing Myc expression. However, whether the deubiquitinase USP13 stabilizes TLR4 and regulates the TLR4/MyD88/NF-κB pathway in HCC remains unclear.

Methods: Real-time PCR and immunohistochemical staining were used to detect the expression of USP13 in HCC tissues. Western blotting was performed to measure USP13, TLR4, MyD88, HIF-1α, Ub, P-NF-κB p65, and epithelial-mesenchymal transition (EMT) markers, including E-cadherin, N-cadherin, and Vimentin in HCC cells. The CCK-8, EdU, and transwell assays were employed to determine the proliferation, migration, and invasion of HCC cells. Nude mice were used to detect the tumorigenesis and metastasis ability of HCC cells in vivo. An immunoprecipitation assay was carried out to confirm the interaction between USP13 and TLR4 in HCC cells.

Results: Our data and TCGA data consistently revealed that USP13 mRNA expression in HCC tissues was higher than in nontumor liver tissues. Immunohistochemical staining further indicated a higher level of USP13 protein in HCC samples. Moreover, the elevated expression of USP13 was detected in HCC cells (SK-HEP-1, HepG2, Huh7, and Hep3B) compared to LO2 cells. Interestingly, the positive expression of USP13 was closely correlated tumor size ≥ 5 cm and advanced tumor stage (III+IV) and

conferred to significantly lower survival of HCC patients. Next, we demonstrated that USP13 knockdown prominently reduced the proliferation, migration, invasion, and EMT of Hep3B and Huh7 cells. The silencing of USP13 significantly restrained tumor growth and reduced the lung metastasis of HCC in nude mice. Conversely, USP13 overexpression significantly enhanced the proliferation, migration, invasion, and EMT of HepG2 and LO2 cells. Mechanistically, the depletion of USP13 markedly inhibited the TLR4/MyD88/NF-κB pathway in HCC cells. USP13 inhibited the ubiquitination-mediated proteolysis of TLR4 and accordingly enhanced its protein stability. Herein, TLR4 was recognized as a novel targeting substrate for USP13 in HCC. Significantly, TLR4 re-expression remarkably reversed the effects of USP13 knockdown on HCC cell proliferation, migration, and invasion. The expression of USP13 was markedly upregulated in HCC cells under hypoxia conditions. Notably, USP13 knockdown repressed hypoxia-induced activation of the TLR4/MyD88/NF-κB pathway in HCC cells.

Conclusions: Our findings elucidated that the upregulated expression of USP13 in HCC tissues conferred to poor clinical outcome. We provided evidence to support that USP13, induced by hypoxia, promoted HCC progression by maintaining the TLR4/MyD88/NF-κB pathway. These data might provide novel insights into the pathogenesis of HCC.

253. BRD8, which is negatively regulated by miR-876-3p, promotes the proliferation and apoptosis resistance of hepatocellular carcinoma cells via KAT5

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Abstract

Aim: Bromodomain-containing 8 (BRD8) belongs to the histone acetyltransferase (HAT) complex, which includes p400 and Tip60. Previous studies have reported the biological roles of BRD8 in colorectal cancer (CRC). BRD8 is highly expressed in advanced CRC and contributes to tumor growth and resistance to Taxol. BRD8 is recognized as a crucial downstream target of MRG-binding protein (MRGBP) and mediates the effect of MRGBP on CRC cell proliferation. Furthermore, BRD8 depletion results in apoptosis in a p53-dependent manner and induces a DNA damage response (DDR) in HCT116 cells. However, the role of BRD8 and its related regulatory mechanisms in hepatocellular carcinoma (HCC) remain unexplored.

Methods: Real-time PCR and immunohistochemistry were used to detect BRD8 and miR-876-3p in HCC tissues. Western blotting was carried out to determine BRD8 and KAT5 levels in HCC cells. The proliferation and apoptosis of HCC cells were measured using CCK-8, EdU, and flow cytometry assays after alliterating BRD8, KAT5, and miR-876-3p level. A luciferase reporter assay confirmed

the interaction between miR-876-3p and BRD8.

Results: We found that the level of BRD8 mRNA in HCC was prominently higher than that in nontumor tissues. Furthermore, immunohistochemistry analysis indicated that BRD8 protein expression was upregulated in HCC compared to noncancerous tissues. The positive expression of BRD8 was closely associated with HBV infection, a tumor size ≥5 cm, and an advanced TNM stage. Moreover, HCC patients with elevated expression of BRD8 had an obvious poorer survival rate. Functionally, the BRD8 knockdown markedly reduced the proliferation of Hep3B and Huh7 cells. The depletion of BRD8 obviously induced the apoptosis of HCC cells. Conversely, BRD8 overexpression promoted the proliferation and apoptosis resistance of Huh7 cells. Lysine acetyltransferase 5 (KAT5) expression was significantly upregulated in HCC tissues. In addition, BRD8 knockdown obviously reduced the level of KAT5 protein and the mRNA expression of KAT5-induced genes in both Hep3B and Huh7 cells. KAT5 knockdown showed similar effects as BRD8 silencing on HCC cell proliferation and apoptosis. The expression of miR-876-3p was downregulated and inversely correlated with the BRD8 mRNA level in HCC tissues. The expression of BRD8 protein in HCC cells was reduced by the overexpression of miR-876-3p and enhanced by the knockdown of miR-876-3p. A luciferase reporter assay demonstrated that BRD8 was a direct target of miR-876-3p. Notably, in HCC cells, the ectopic expression of miR-876-3p inhibited proliferation and induced apoptosis.

Conclusions: Our results revealed the overexpression of BRD8 and the underexpression of miR-876-3p in HCC. Furthermore, we confirmed the essential roles of miR-876-3p, BRD8, and KAT5 in HCC cell growth and apoptosis. BRD8, a direct target of miR-876-3p, positively regulated KAT5 abundance in HCC cells. Future work is needed to uncover the role of BRD8 in the development and progression of HCC in vivo.

254. Piwi 蛋白互作 RNA piR-015026 在大肠癌组织中表达的研究

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目的：检测 piR-015026 在大肠癌组织和癌旁正常组织中的表达水平，分析 piR-015026 的表达水平与患者临床病理特征之间的相关性。方法：纳入 2017 年 1 月至 2019 年 12 月于内蒙古自治区肿瘤医院胃肠外科接受大肠癌根治术治疗的患者 51 例，采用实时荧光定量 PCR 检测 piR-015026 在大肠癌组织及对应癌旁正常组织中的表达水平，比较两组间表达水平的差异，分析大肠癌组织中 piR-015026 的表达水平与患者临床病理特征的相关性。结果：piR-015026 在大肠癌组织中的相对表达量显著高于癌旁正常组织 （P =0.013）。不同组织分化程度和淋巴结转移情况的患者间，癌组织中 piR-015026 的表达水平无显著差异（P > 0.05）；男性患者较之女性

患者（P =0.034），≥ 60 岁患者较之 < 60 岁患者（P =0.006），直肠癌患者较之结肠癌患者（P =0.045），肿瘤直径 ≥ 3 cm 的患者较之肿瘤直径 < 3 cm 的患者（P =0.030），TNM Ⅲ期和Ⅱ期患者较之Ⅰ期患者、Dukes C 期和 B 期患者较之 A 期患者显示出更高的 piR-015026 表达水平。结论：piR-015026 在大肠癌组织中表达上调，可能作为促癌因子参与了大肠恶性肿瘤的生长与浸润。

255. Integrated Bioinformatics Analysis of the Functions and Prognostic Values of RNA Binding Proteins in Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most commoncancer in the world, which has a high mortality rate. RNA binding proteins (RBPs) show effect on almost every step ofthe expression of tumor-related genes,, and the abnormal expression level of RBPs exert effect on the development and prognosis of a variety of tumors. Nonetheless, the functions of RBPs in HCC is still lack of clearity. In this study, we obtained gene expression data and the corresponding clinical information about HCC from The Cancer Genome Atlas (TCGA) database, and identified differently expressed RBPs between the HCC and the non-cancer tissues. Then, we performedbioinformatics analyses to explore the prognostic value of these RBPs. There were totally 356 RBPs met our criteria, which contains 228 upregulated and 128 downregulated RBPs. Gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes database (KEGG) pathway analyses showed that the differently expressed RBPs were mainly enriched in RNA metabolic and splicing process, RNA degradation, RNA transport pathway, Ribosome biogenesis, Spliceosome, Hepatitis C and Influenza A. Next, five genes (TCOF1, DHX58, EIF2AK4, CSTF2 and MRPS31), resulting from the univariate and multivariate Cox regression analyses, were used to construct a prognostic model. Further internal validation in the HCC cohort demonstrated that our model has preferable performance on prognosis predication in HCC. Our results contributed to find a new prognostic indicator and a new sight of precise prognosis in HCC.

256. 胃癌预后预测生物标志物和治疗靶点的筛选与研究

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目的 挖掘有前景的生物标志物准确地预测胃癌患者的总生存，寻找新的胃癌治疗靶点改善患者预后。

方法 通过 NCBI-GEO 数据库中包含胃癌组织和正常组织基因表达谱的芯片，筛选出胃癌组织中相比正常胃组织高表达的差异基因。再借助 GEPIA 数据库验证这基因的表达。通过 Kaplan－Meier plotter 数据库分析基因表达的高低与患者预后的相关性。最后借助 HCMBD 数据库分析基因的功能。

结果 筛选出 26 个在胃癌组织中高表达的基因，进一步通过 GEPIA 数据库证明其中 25 个基因在胃癌中高表达，还有 22 个基因的表达随着胃癌疾病进展表达逐渐升高。这 25 个高表达的基因在胃癌患者中进行生存分析显示有 23 个基因的表达与胃癌患者总生存期显著负相关。结合这些基因的具体功能，最终选出 7 个基因有希望成为胃癌预后预测生物标志物和潜在的治疗靶点。

结论 我们筛选出了与胃癌发展及预后高度相关的关键基因，有助于进一步了解胃癌的分子基础，指导临床胃癌患者复查频率和开发新的靶向治疗。

257. Trajectory and Functional analysis of PD-1high CD4+CD8+ T cells in Hepatocellular Carcinoma by Single-Cell Cytometry and Transcriptome Sequencing

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The spatial heterogeneity of immune microenvironment in hepatocellular carcinoma(HCC) remains elusive. Here, a single-cell study involving 17,432,600 immune cells of 39 matched HCC(T), non-tumor(N) and leading-edge(L) specimens by mass-cytometry is conducted. The tumor-associated CD4/CD8 double-positive T(DPT) cells are found enriched in L regions with synergetic expression of PD-1/HLA-DR/ICOS/CD45RO, and exhibit higher level of IFN-γ, TNF-α and PD-1 upon stimulation. Single-cell RNA-seq further characterizes the molecular features of DPT cells and uncovers 11 clusters with different cytotoxicity, exhaustion and activation scores. TCR-based trajectory analysis reveals that tumor-associated DPT clusters share separated ancestries with local CD4+ or CD8+SPT cells rather than CD3+PBMC cells. TCR clones with frequency above 10 are mainly found coexisting in DPT and CD8+SPT cells. Specifically, PD-1highDPT cluster(TDPT_10) shares the same ancestry with exhausted CD8+SPT cluster(TCD8T_2) and shows higher expression

similarity and closer pathological location to PD-1+CD8+ than PD-1+CD4+T cells.

258. The identification and functional analysis of CD8+PD-1+CD161+ T cells in hepatocellular carcinoma

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Immunotherapy is a powerful therapeutic strategy for end-stage hepatocellular carcinoma (HCC). It is well known that T cells, including CD8+PD-1+ T cells play important roles involving tumor development. However, their underlying phenotypic and functional differences of T cell subsets remain unclear. We constructed single-cell immune contexture involving approximate 20,000,000 immune cells from 15 pairs of HCC tumor and non-tumor adjacent tissues and 10 blood samples (including 5 of HCCs and 5 of healthy controls) by mass cytometry. scRNA-seq and functional analysis were applied to explore the function of cells. Multi-color fluorescence staining and tissue micro-arrays were used to identify the pathological distribution of CD8+PD-1+CD161+/- T cells and their potential clinical implication. The differential distribution of CD8+ T cells subgroups was identified in tumor and non-tumor adjacent tissues. The proportion of CD8+PD1+CD161+ T cells was significantly decreased in tumor tissues, whereas the ratio of CD8+PD1+CD161- T cells was much lower in non-tumor adjacent tissues. Diffusion analysis revealed the distinct evolutionary trajectory of CD8+PD1+CD161+ and CD8+PD1+CD161- T cells. scRNA-seq and functional study further revealed the stronger immune activity of CD8+PD1+CD161+ T cells independent of MHC class II molecules expression. Interestingly, similar change in the ratio of CD8+CD161+/ CD8+CD161- T cells was also found in peripheral blood samples collected from HCC cases, indicating their potential usage clinically. We here identified different distribution, function and trajectory of CD8+PD-1+CD161+ and CD8+PD-1+CD161- T cells in tumor lesions, which provided new insights for the heterogeneity of immune environment in HCCs and also shed light on the potential target for immunotherapy.

259. The efficacy of CAN017, a novel anti-HER3 antibody, and the significance of NRG1 as a biomarker in mouse avatars of esophageal squamous cell carcinoma

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Background: CAN017 (AV-203), a novel anti-HER3 antibody, exerts very promising anti-tumor activities in multiple human tumor models with NRG1 as a predictive biomarker, which will be further investigated in esophageal squamous cell carcinoma (ESCC) with Chinese characteristics in this study.

Methods: Two separate cohorts of ESCC patient-derived xenografts (PDX) models including 24 (cohort 1 as training models, from Crown Bioscience Inc.) and 22 (cohort 2 as validating models, from Peking University Cancer Hospital) models, respectively, were used to study the efficacy and safety of CAN017, as well as the correlation of NRG1 expression to the response of CAN017.

Results: In cohort 1, all PDX models showed good tolerance to CAN017 and 8 out of 24 (33.3%) PDX models responded to CAN017 with tumor growth inhibition (TGI) ≥ 70% compared to controls. Furthermore, the efficacy of CAN017 was positively correlated with NRG1 expression and the response rates in cohort 1 were 73% (8/11) versus 0% (0/13) in NRG1 high and low expression models, respectively. These results were also validated in PDX models of cohort 2 indicated as the powerful anti-tumor activity of CAN017 in PDX models with NRG1 high expression.

Conclusion: HER3-targeting therapy was first demonstrated to have potency in ESCC, and NRG1 served as a predictive biomarker to screen patients in future clinical trials

KEYWORDS: ESCC; anti-HER3 therapy; CAN017; NRG1

260. 基于全基因组甲基化分析的结直肠癌预后标志物研究

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目的：结直肠癌是在全球危害最严重的恶性肿瘤之一。DNA 甲基化是重要的表观遗传方式，其变化涉及发育、繁衍、衰老等多个生物进程，甲基化水平的不同可影响相应基因的表达，高甲基化常常抑制基因转录，而去甲基化则可使基因被重新激活；局部高甲基化和全基因组低甲

基化，常常与疾病的发生和预后相关。癌症是遗传和表观遗传障碍共同引起的结果，目前癌症的甲基化研究已广泛开展，有研究发现甲基化水平可用于区分癌组织和癌旁组织，且某些基因的甲基化水平与患者的预后相关。甲基化预后标志物可帮助预测患者的生存状况，进而采取恰当的医疗措施。本研究从 TCGA 公共数据库下载数据，进行全基因组甲基化分析，探索结直肠癌甲基化预后标志物。

方法：从 TCGA 数据库下载甲基化 450k 芯片数据，预处理后共保留 395 例结直肠癌组织和 45 例癌旁组织的样本资料。筛选差异甲基化位点和差异甲基化区域，绘制热图对两者分布情况进行描述。根据 Illumina 提供的注释文件，统计差异甲基化区域在基因组的分布位置。对差异甲基化区域所在基因进行 GO 注释和 KEGG 富集分析。根据每个差异化甲基化区域的平均甲基化水平，将患者分为高甲基化组与低甲基化组，进行 Kaplan－Meier 生存分析评估差异甲基化区域的甲基化水平与结直肠癌患者预后的关系，并对所得预后标志物的甲基化水平与所在基因表达水平进行相关性分析。

结果：共鉴定出 15252 个差异甲基化位点与 959 个差异甲基化区域，结直肠癌组织的甲基化水平比癌旁组织更高。这些差异甲基化区域主要位于转录起始点、1stExon 和 Body 区域；多半处于 CpG 岛、其余主要在 CpG 岛岸。功能富集分析显示，差异甲基化区域的相关基因在一些重要的癌症信号通路富集。所有的差异甲基化区域中，共有 5 个与结直肠癌患者的预后显著相关，高甲基化者预后更差；3 个与其基因表达水平有显著关联，高甲基化者基因表达受到抑制，可作为结直肠癌预后标记物。

结论：本研究通过比较 395 个结直肠癌组织和 45 个癌旁组织的甲基化状况，揭示了结直肠癌甲基化模式的特征，其涉及一些在其他癌症中已知的可疑基因与信号通路。另外，依靠公共注释数据集，对差异甲基化区域进行定位，描述了其分布特征，并最终鉴定了 3 个结直肠癌差异甲基化功能区域作为预后标志物。为探讨异常甲基化在结直肠癌患者生存预后的应用提供依据

关键词：结直肠癌；甲基化；TGCA

261. HPSE is a key regulator in the tumor microenvironment of colorectal cancer

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Background: Immune checkpoint inhibitors (ICIs) have dramatically reformed the therapeutic strategy for CRC patients harboring microsatellite instability-high (MSI-H). Nonetheless, the benefit of ICIs in CRC is limited for the vast majority of patients with microsatellite instability low (MSI-L) or microsatellite stable (MSS). The immunosuppressive tumor microenvironment (TME) is mainly

responsible for the frustrating efficacy of ICIs in MSI-L or MSS CRC. Heparanase (HPSE) is a multifunctional molecule mediating tumor-host crosstalk in cancer progression. However, the function of HPSE in TME of CRC is not yet clear.

Methods: Transcriptome and clinical data of CRC tissue samples were downloaded from The Cancer Genome Atlas (TCGA) data portal and Gene Expression Omnibus (GSE39582). We evaluated the impact of clinical features on HPSE expression by multiple linear regression. Spearman ́s correlation was applied to all correlation analyses. Immune infiltration levels of immune cells were computed by CIBERSORTx and xCell. Gene set enrichment analysis (GSEA) was performed to figure out the biological pathways that differ between high and low HPSE expression groups. Survival analysis was conducted by the Kaplan-Meier survival curve and the Cox proportional hazard model. All analyses were completed in R (version 3.6.3).

Results:

In total, 967 samples from TCGA (n = 457) and GSE39582 (n = 510) were included. Multivariate analysis revealed that BRAF mutation status, MSS/MSI type, and CMS type were independently predictive factors of HPSE expression. HPSE expression had a significant positive association with the transcriptional expression level of PD-L1 (R^2 = 0.45, p = < 0.001 in TCGA; R^2 = 0.49, p = < 0.001 in GSE39582) and tumor mutation burden (TMB) (R^2 = 0.22, p = < 0.001). Activated NK cells, Macrophages M1, and Neutrophils, as well as the microenvironment score, presented a positive correlation. PD-L1 expression, TMB, and peritumoral immune infiltration are potential predictors of tumors response to ICIs. Therefore, these results suggested that patients with high HPSE level might be more likely to respond to ICIs therapy.

Immune-related pathways were remarkably enriched in HPSE high-expression group, such as ‘positive regulation of defense response’ and ‘adaptive immune response’ terms in GO, and ‘cytokines and cytokine receptors interaction’ pathway in KEGG. Furtherly, we focused on some essential components of the immunosuppressive TME. Results indicated that high transcriptional levels of many of these genes accompanied by a high HPSE level. HPSE could promote tumor escape by regulating their expression.

Interestingly, the high HPSE level presented a poor prognosis in MSS subgroup for disease-free survival (HR = 1.57, 95% CI 1.11 ~ 2.22, p = 0.01) in GSE39582. Multivariate survival analysis also confirmed the prognostic role of HPSE in MSS CRC.

Conclusion: The multifunctional molecule, HPSE, contributes to the formation of TME with increasing immune infiltration but promoting tumor escape in CRC. Its overexpression conveys an earlier relapse or progression among MSS CRC, which provides the potential basis for combining HPSE inhibition with immunotherapy to improve the survival of patients with MSS CRC.

Key words: HPSE; Colorectal cancer; Tumor microenvironment; Immunotherapy; Microsatellite stable

262. MRGPRF promotes NSCLC progression by regulating JAK2-STAT3-PD-L1 signaling axis

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Lung cancer is the leading incidence and predominant cause of cancer related deaths in China，which seriously threaten people's lives and health. It is very important to uncover the mechanism of lung progression and explore new molecular markers and treatment targets. MRGPRF, a candidate tumor-related genes screened by a new transcriptome analysis method-CVAA, is consistently down-regulated in pan-cancers including lung cancer. Over-expression of MRGPRF in NSCLC cell lines can inhibit cancer cells’ progression, such as proliferation and migration. Mechanistically, we found MRGPRF overexpression decreased expression level of PD-L1 at mRNA and protein level and even reduced pJAK and pSTAT3 level, which is confirmed by GSEA results and prompting that MRGPRF plays a significant role in NSCLC progression and immune evasion through regulating JAK2-STAT3-PD-L1 signaling axis, which may provide a new target for clinical diagnosis and treatment of NSCLC in the future.

263. ROS1-mutant cancer and immune checkpoint inhibitors: A large database analysis

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Introduction: ROS1 is a receptor tyrosine kinase belongs to the insulin receptor family. Chromosomal rearrangements of ROS1 gene can induce the formation of oncogenic receptor tyrosine kinase. ROS1 rearrangements were originally identified in glioblastoma, and subsequently described in various human tumors including non-small-cell lung cancer (NSCLC), gastric cancer and so on[4]. Approximately 1–2% of NSCLC patients have ROS1 mutations and this distinct molecular subset of NSCLC was sensitivity to ROS1-tyrosine kinase inhibitors (TKIs). However, acquired resistance to TKIs is inevitable. Despite a large number of studies on ROS1 in NSCLC, the efficacy of immune checkpoint inhibitors (ICIs) in patients with ROS1 mutations has never been reported. Mathods: we analyzed the tumor mutational burden (TMB) and immunotherapy database to find the association between ROS1 and the responses of patients who received ICIs treatment. Genomic and survival data from 1661 patients sequencing by Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets assay were included in this database.\

Results: The prevalence of ROS1 mutations was 7% (120/1661) in the entire group and 4% (15/350) in the NSCLC subgroup. At first, we performed a TMB analysis in patients either in the entire group

or NSCLC subgroup. We found the TMB was significantly higher in patients harboring ROS1 mutation in the entire cohort ($p < 0.001$) but not in the NSCLC subgroup ($p = 0.573$). To evaluate the efficacy of ICIs in patients with ROS1 mutation, we analyzed the over survival in both ROS1 mutation and wild type subsets. Corresponding to the TMB results, we found patients who harbored ROS1 mutations had longer overall survival in the entire group ($p < 0.001$) but not in the NSCLC subgroup ($p = 0.604$).

Conclusion: Our results suggested ROS1 mutation was associated with higher TMB and could serve as a favorable prognostic biomarker in various human cancers received ICIs treatment. As the far as we known, this is the first study to investigate the role of ROS1 mutation in patients with ICIs treatment. Unfortunately, our results did not show the benefit from ICIs corresponding ROS1 mutation in the NSCLC patients. Considering the limited samples, only 15 patients harboring ROS1 mutations in the NSCLC subgroup, further studies will be necessary to elucidate the relationship between ROS1 mutation and the efficacy of ICIs in NSCLC.

264. Identification of an Immune Signature Predicting Prognosis Risk and Lymphocyte Infiltration in Colon Cancer

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Increasing studies have highlighted the effects of the tumor immune micro-environment (TIM) on colon cancer (CC) tumorigenesis, prognosis, and metastasis. However, there is no reliable molecular marker that can effectively estimate the immune infiltration and predict the CC relapse risk. Here, we leveraged the gene expression profile and clinical characteristics from 1430 samples, including four gene expression omnibus database (GEO) databases and the cancer genome atlas (TCGA) database, to construct an immune risk signature that could be used as a predictor of survival outcome and immune activity. A risk model consisting of 10 immune-related genes were screened out in the Lasso-Cox model and were then aggregated to generate the immune risk signature based on the regression coefficients. The signature demonstrated robust prognostic ability in discovery and validation datasets, and this association remained significant in the multivariate analysis after controlling for age, gender, clinical stage, or microsatellite instability status. Leukocyte subpopulation analysis indicated that the low-risk signature was enriched with cytotoxic cells (activated CD4/CD8+ T cell and NK cell) and depleted of myeloid-derived suppressor cells (MDSC) and regulatory T cells. Further analysis indicated patients with a low-risk signature harbored higher tumor mutation loads and lower mutational frequencies in significantly mutated genes of APC and FBXW7. Together, our constructed signature could predict prognosis and represent the TIM of CC, which promotes individualized

treatment and provides a promising novel molecular marker for immunotherapy.

265. Association of LRP1B Mutation With Tumor Mutation Burden and Outcomes in Melanoma and Non-small Cell Lung Cancer Patients Treated With Immune Check-Point Blockades

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Background: Tumor mutation burden (TMB) have been served as the most prevalent biomarkers to predict immunotherapy response. LRP1B (low-density lipoprotein receptor-related protein 1B) is frequently mutated in melanoma, non-small cell lung cancer (NSCLC) and other tumors; however, its association with TMB and survival in patients with immunotherapy remains unknown. Methods: We curated somatic mutation data and clinicopathologic information from 332 melanoma immunotherapy samples for discovery and 113 NSCLC samples for further corroboration. Bayesian variants non-negative matrix factorization was used to extract tumor mutational signatures. Multivariate Cox and logistic regression models were applied to adjust confounding factors. The CIBERSORT and GSEA algorithm were separately used to infer leukocyte relative abundance and significantly enriched pathways. Results: Patients with LRP1B mutation were identified to be associated with prolonged survival in both immunotherapy cohort. Higher tumor mutation burden was found in LRP1B mutated patients, and the association remained significant after controlling for age, gender, stage, mutations in TP53 and ATR, and mutational signatures. Immune response and cell cycle regulation circuits were among the top enriched pathways in samples with LRP1B mutations. Conclusion: Our studies suggested sequencing even a single, frequently mutated gene may provide insight into genome-wide mutational burden, and may serve as a biomarker to predict immune response.

266. The immune response‐related mutational signatures and driver genes in non‐small‐cell lung cancer

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Immune checkpoint blockade (ICB) therapy has achieved remarkable clinical ben- efit in non-small-cell lung cancer (NSCLC), but our understanding of biomarkers that predict the response to ICB remain obscure. Here we integrated somatic mutational profile and clinicopathologic information from 113 NSCLC patients treated by ICB (CTLA-4/PD-1). High tumor mutation burden (TMB) and neoantigen burden were identified significantly associated with improved efficacy in NSCLC

immunotherapy. Furthermore, we identified apolipoprotein B mRNA editing enzyme, catalytic poly-peptide-like (APOBEC) mutational signature was markedly associated with respond- ing of ICB therapy (log-rank test, P = .001; odds ratio (OR), 0.18 [95% CI, 0.06-0.50], P < .001). The association with progression-free survival remained statistically sig- nificant after controlling for age, sex, histological type, smoking, PD-L1 expression, hypermutation, smoking signature and mismatch repair (MMR) (HR, 0.30 [95% CI, 0.12-0.75], P = .010). Combined high TMB with APOBEC signature preferably predict immunotherapy responders in NSCLC cohort. The CIBERSORT algorithm revealed that high APOBEC mutational activity samples were associated with increased in- filtration of CD4 memory activated T cells, CD8+ T cells and natural killer (NK) cells, but reduced infiltration of regulatory T cells. Besides, individual genes mutation of IFNGR1 or VTCN1 were only found in responders; however, the PTEN mutation was only found in non-responders (Fisher's exact test, all P < .05). These findings may be applicable for guiding immunotherapy for patients with NSCLC.

267. AC007255.1 可能是一个与食管癌预后相关的免疫相关性增强子 RNA

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目的：本研究旨在探索食管癌中活性增强子区域中的关键长非编码 RNA（lncRNA），称为增强子 RNA（eRNA）。方法：利用 PreSTIGE 算法对从活性增强子区域转录的 lncRNA 进行分析，然后预测其目的基因。基于 TANRIC 数据库中的食管癌 RNA-seq 数据，确定了与总存活率相关的 eRNAs。计算 AC007255.1 表达与食管癌各项临床特征的相关性。根据其共表达基因进行了功能富集分析。基于 TIMER 数据库，我们分析了 AC007255.1 的表达与免疫浸润水平的相关性。QRT-PCR 检测 AC007255.1 和 PRR15 在食管鳞癌和正常组织中的表达。结果：从活性增强子区域转录出 2695 个 LncRNAs 中与总存活率显著相关的有 33 个。AC007255.1 是一个关键的 eRNA。PRR15 是 AC007255.1 的靶基因(相关系数 r=0.936)。AC007255.1 高表达的患者总生存率较低。AC007255.1 的表达与肿瘤状态、肿瘤位置、患者反流史、grade 分级和 N 分期等临床特征显著相关。AC007255.1 与免疫应答中的紧密连接和中性粒细胞活化密切相关。AC007255.1 的表达与 B 细胞、树突状细胞和中性粒细胞的浸润程度有关。QRT-PCR 结果证实 AC007255.1 和 PRR15 在食管癌组织中均表达上调，且两者呈正相关。结论：我们的发现为食管癌提供了一个新型免疫相关性 eRNA，即 AC007255.1，它可能是食管癌的一个有价值的预后因素。

268. 复杂畸胎瘤标志物诊断

于先强

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畸胎瘤是常见的生殖细胞肿瘤，多数病例通过影像学检查可以诊断，并且血 AFP 往往显著增高。然而有极少数病例难以通过影像学检查与寄生胎进行鉴别，易造成误诊。畸胎瘤是临床常见的生殖细胞来源肿瘤，多见于年轻女性性腺。典型的畸胎瘤 CT 表现为囊实性不规则混杂密度占位 。目前通过手术彻底切除肿物是畸胎瘤最佳的治疗方式。畸胎瘤是一种真性肿瘤，来源于原始性腺的生殖细胞，具有肿瘤性生长的特点，没有完整的胎儿形态和器官系统。另外，畸胎瘤通常不具备发育完好的器官，如内脏器官和完整的脊柱、肋骨等。然而临床常有不典型的畸胎瘤，通过常规的影像学检查难以诊断，我们探索利用大数据基因筛查以确定能够提高畸胎瘤鉴别诊断的标志物。

269. Transcriptional Expressions of CXCL9/10/12/13 as Prognosis Factors in Breast Cancer

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CXCLs play critical roles in antitumor immunity by activating tumor-specific immune responses and stimulating tumor proliferation, thus affecting patient outcomes. However, the expression and prognostic values of CXCLs in breast cancer have not been well clarified. The aim of this study was to investigate the impact of CXCLs transcriptional expression on breast cancer patients. Oncomine database, GEPIA (Gene Expression Profiling Interactive Analysis), UALCAN, Kaplan-Meier Plotter, TIMER (Tumor Immune Estimation Resource) and DAVID were used in our study. The transcriptional levels of CXCL9/10/11/13 in breast cancer tissues were significantly elevated while the transcriptional levels of CXCL1/2/3/12 were decreased based on intersections of Oncomine database and GEPIA. Among them, breast cancer patients with high transcriptional levels of CXCL2/9/10/12/13 and low transcriptional level of CXCL3 were associated with a better prognosis. We also found most of CXCLs expressions are significantly correlated with known prognostic factors, such as patient's age, major subclasses, individual cancer stages and nodal metastasis status. In addition, the expression of CXCL9/10/12/13 were also indicated to be correlated with the infiltration of six types of immune cells (B cells, $CD8^+$ T cells, $CD4^+$T cells, macrophages, neutrophils, and dendritic cells). The functions of differentially expressed CXCLs are primarily related to the immune response and cytokine–cytokine receptor interactions. Our results may provide novel

evidence of new prognostic or predictive biomarkers for breast cancer patients.

270. Biomarkers of the Response to Immune Checkpoint Inhibitors in Metastatic Urothelial Carcinoma

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Background: The mechanisms underlying the resistance to immune checkpoint inhibitors (ICIs) therapy in metastatic urothelial carcinoma (mUC) patients are not clear. It is of great significance to discern mUC patients who could benefit from ICI therapy in clinical practice.

Methods: The clinicopathological and processed gene expression data of 348 mUC patients in IMvigor210 were retrieved from IMvigor210CoreBiologies. In this study, we performed machine learning method to select prognostic genes for constructing the immunotherapy response nomogram for mUC patients. Calibration with bootstrapping and receiver operating characteristic were conducted to verify the performance of the prognostic nomogram. CIBERSORT was also performed for immune infiltrates and potential mechanism analysis.

Results: By using machine learning method, we selected 10 prognostic genes for the construction of the immunotherapy response nomogram for mUC patients. The calibration plot suggested that the nomogram had optimal agreement with actual observations when predicting the 1- and 1.5-year survival probabilities. The prognostic nomogram had favorable discrimination of overall survival of mUC patients with area under curve values of 0.815, 0.752 and 0.805 for ICI response (ICIR) prediction in the training cohort, testing cohort and combined cohort, respectively. Further decision curve analysis showed that the prognostic nomogram was superior to either mutation burden or neoantigen burden for overall survival prediction when the threshold probability was greater than 0.35. Immune infiltrate analysis indicated that low ICIR-Score values in mUC patients were significantly related to $CD8^+$ T-cell infiltration and immune checkpoint-associated signatures. We also identified differentially mutated genes, which could act as driver genes and regulate the response to ICI therapy.

Conclusion: We developed and validated an immunotherapy responsive nomogram for mUC patients, which could be conveniently used for the estimate of ICI response and the prediction the overall survival probability for mUC patients.

271. Identification of potential diagnostic and prognostic values of P4HA1 expression in lung cancer, breast cancer and head and neck cancer

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To investigate the expression of prolyl-4-hydroxylase subunit alpha-1 (P4HA1) and its relationship with the clinicopathological features in lung cancer (LC), breast cancer (BC) and head and neck cancer (HNSC). Discussing the possibility of P4HA1 to be a potential diagnostic and prognostic biomarker. RNA expression profile, protein expression profile and relevant clinical information were downloaded from The Cancer Genome Atlas (TCGA) and the Human Protein Atlas databases. The relationship between P4HA1 mRNA expression and clinicopathological features was evaluated. Survival analysis were performed to assess the overall survival (OS) and relapse-free survival (RFS). Multivariate cox regression model was employed to analyze the independent prognostic factors. Finally, the protein-protein interaction networks was constructed and enrichment analysis was performed to identify the latent P4HA1-related terms and pathways. This study showed P4HA1 was up-regulated in three types of tumor tissues ($P<0.05$) and high-P4HA1 was significantly relevant to the clinical features of patients with LC, BC or HNSC. Survival analysis indicated that patients with high-P4HA1 had unfavorable clinical outcomes. Multivariate analysis showed that the high-P4HA1 expression was independent prognostic factor for poor OS and RFS in LC and HNSC patients. Bioinformatic analysis were performed to predict P4HA1-interacted proteins and further evaluate possible signal pathways. In the current study, the rising P4HA1 was identified in LC, BC and HNSC and significantly correlated with the clinicalpathological features of patients. High-P4HA1, suggesting poor clinical outcomes, could be used as an early diagnostic and prognostic biomarker for patients with aforementioned tumors.

272. The prognostic value of HGF-c-MET signaling pathway in gastric cancer: a study based on TCGA and GEO databases

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Gastric cancer is a heterogeneous tumor that underlying molecular mechanisms are largely unclear. This study aimed to elucidate the expression level of HGF-c-MET in gastric cancer patients and to investigate the prognostic and diagnostic value of HGF-c-MET. In silico analysis of the TCGA and GEO database found that HGF and c-MET mRNA expression are significantly higher in gastric cancer tissues than those in peritumor tissues. Both higher mRNA expression of HGF and c-MET were associated with a poorer prognosis. c-MET expression was modulated by methylation in the promoter regions. HGF was positively correlated with CD8+ T cell, CD4+ T cell, macrophage, neutrophil and dendritic cell. Furthermore, functional enrichment analysis and protein-protein interaction networks further shown that HGF-c-MET and related proteins mainly participated in growth factor receptor binding, protein tyrosine kinase activity and signaling receptor binding. Finally, outcome of GSEA analysis shown 13 shared KEGG pathways enriched in high expressed group of HGF and c-MET.

Key words: HGF; c-MET; gastric cancer; TCGA; prognosis; GEO;

273. HER2 copy number quantification in primary tumor and cell-free DNA provides additional prognostic information in HER2 positive early breast cancer

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Objective The quantitative relationship between HER2 copy number and prognosis in HER2 positive adjuvant setting remain controversial due to the administration of anti-HER2 therapy, and few studies focus on adjuvant setting to illustrate the potential clinical relevance of HER2 in cfDNA. Our study was aim to develop a novel method in HER2 quantification and explore the relationship between HER2 copy number in primary tumor or cfDNA and prognosis in HER2 positive early breast cancer. Methods Two hundred and two patients with early breast cancer were included in a study where primary cancer tissue, matching non-cancer breast tissue, and corresponding plasma were collected, and subjected to CNVplex for HER2 detection. Cox proportional hazard analysis was employed to determine the prognostic value of HER2 gene copy number in tissue and cfDNA. Tissue

based nomograms and time-dependent decision curve analysis were used to evaluate the practicality of HER2 copy number stratification. Results HER2 amplification defined by CNVplex demonstrated a robust concordance with results from FISH (concordance,89.2%). A three-tiered system of tissue and a two-tiered system of cfDNA classification were shown to be independent prognostic factors. A tissue copy number-based nomogram was fitted and further evaluation revealed a good performance in discrimination (c statistic, 0.801) and calibration. Conclusions We first report CNVplex as a viable alternative for HER2 detection. Quantitative evaluation of HER2 presents tremendous potential for use in risk stratification. We also uncovered the potential of HER2 copy number in cfDNA to function as a biomarker for prognosis in HER2 positive adjuvant setting.

274. HER2 copy number quantification in primary tumor and circulating free DNA provides additional prognostic information in HER2 positive early breast cancer

Xiaobin Chen1,Yuxiang Lin1,Zhengwen Jiang2,Yan Li1,Tigua Zhang3,Ying Wang2,Feng Yu2,Wenhui Guo1,Lili Chen1,Minyan Chen1,Wenzhe Zhang1,Chuan Wang1,Fangmeng Fu1

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Objective The quantitative relationship between HER2 copy number and prognosis in HER2 positive adjuvant setting remain controversial due to the administration of anti-HER2 therapy, and few studies focus on adjuvant setting to illustrate the potential clinical relevance of HER2 in cfDNA. Our study was aim to develop a novel method in HER2 quantification and explore the relationship between HER2 copy number in primary tumor or cfDNA and prognosis in HER2 positive early breast cancer. Methods Two hundred and two patients with early breast cancer were included in a study where primary cancer tissue, matching non-cancer breast tissue, and corresponding plasma were collected, and subjected to CNVplex for HER2 detection. Cox proportional hazard analysis was employed to determine the prognostic value of HER2 gene copy number in tissue and cfDNA. Tissue based nomograms and time-dependent decision curve analysis were used to evaluate the practicality of HER2 copy number stratification. Results HER2 amplification defined by CNVplex demonstrated a robust concordance with results from FISH (concordance,89.2%). A three-tiered system of tissue and a two-tiered system of cfDNA classification were shown to be independent prognostic factors. A tissue copy number-based nomogram was fitted and further evaluation revealed a good performance in discrimination (c statistic, 0.801) and calibration. Conclusions We first report CNVplex as a viable alternative for HER2 detection. Quantitative evaluation of HER2 presents tremendous potential for use in risk stratification. We also uncovered the potential of HER2 copy number in cfDNA to function as a biomarker for prognosis in HER2 positive adjuvant setting.

275. Glutamine-fructose-6-phosphate transaminase 2 (GFPT2) promotes the EMT of serous ovarian cancer by activating the hexosamine biosynthetic pathway to increase the nuclear location of β-catenin

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The hexosamine biosynthetic pathway (HBP), a branch of glucose metabolism, provides a substrate for glycosylation modifification, which has a wide-ranging effffect on cellular functions. Glutamine-fructose-6-phosphate transaminase 2 (GFPT2) has been reported to regulate the HBP as the fifirst and rate-limiting enzyme. Given the inverse association between GFPT2 expression and survival of patients with serous ovarian cancer (SOC) observed in The Cancer Genome Atlas(TCGA) database, we attempted to investigate the role of GFPT2 and its related mechanisms in SOC. The results showed that GFPT2 was over-expressed in SOC tissues, and positive correlations with advanced stage (FIGO III/IV), suboptimal removal rate and poor survival were observed in 90 SOC patients. Cell migration and invasion were also inhibited in GFPT2 knockdown SKOV3 and HEY cells. The levels of O-linked β-N-acetylglucosamine (O-GlcNAc) and intranuclear β-catenin were evaluated and the observed increase in O-GlcNAcylation induced by GFPT2 may contribute to epithelial-mesenchymal transition (EMT). These data provide novel insights into the function of GFPT2 and O-GlcNAcylation in the EMT and thus the invasiveness SOC.

276. 观察血清异常糖链糖蛋白表达和细胞免疫功能对肺癌预后的影响

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目的：观察血清异常糖链糖蛋白（TAP）表达和细胞免疫功能对肺癌患者预后的影响。方法：选取 2016 年 1 月—2017 年 5 月陕西中医药大学附属医院收治的 49 例肺癌患者的临床资料，依据治疗方式不同分为观察组（肺癌根治术加术后辅助化疗，n=28）和对照组（化疗，n=21)。分别于治疗前及治疗后 1、3 个月检测两组患者血清 TAP 表达和细胞免疫功能指标，卡氏（Karnofsky，KPS）功能状态评分。结果：两组患者治疗前 TAP 表达阳性率比较，差异无统计学意义（ x 2=1.647，P>0.05）；观察组治疗后 TAP 表达阳性率较治疗前显著下降，差异有统计学意义（比较治疗后 1 个月与治疗前， x 2=4.2486，P=0.0393；比较治疗后 3 个月与治疗

前， χ2=31.2391，P=0.0000，P<0.05）；对照组治疗后 TAP 表达阳性率较治疗前无明显变化（比较治疗后 1 个月与治疗前， χ2=0.8281，P=0.3628；比较治疗后 3 个月与治疗前， χ2=2.4846，P=0.1150，P>0.05）；两组间治疗后 1、3 个月 TAP 表达对比存在差异（治疗后 1 个月， χ2=9.819，P=0.007；治疗后 3 个月， χ2=6.716，P=0.035，P<0.05）。观察组治疗后 CD4+/CD8+比值较治疗前升高（比较治疗后 1 个月与治疗前，t=-9.6353，P=0.0000；比较治疗后 3 个月与治疗前，t=-6.7035，P=0.0000，P<0.05），对照组治疗后 CD4+/CD8+比值较治疗前下降（比较治疗后 1 个月与治疗前，t=-1.6487，P=0.1050；比较治疗后 3 个月与治疗前，t=2.1757，P=0.0340，P>0.05）；治疗后 1、3 个月，观察组 CD4+/CD8+比值均显著高于对照组，差异有统计学意义（P<0.01）。治疗后 3 个月生活质量评分（KPS 评分），观察组有效率 57.14%，对照组有效率 38.09%，治疗后观察组生活质量评分较对照组明显升高，有统计学意义（ χ2=7.2746，P=0.0070，P<0.05）。 结论：血清 TAP 和细胞免疫功能可作为评估肺癌预后疗效、复发的指标，有临床应用价值。

关键词：肺癌；异常糖链糖蛋白；细胞免疫功能；预后

277. Identification of a potentially functional regulatory network for investigating pathogenesis and providing possible biomarkers of Hepatocellular carcinoma

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Background: Hepatocellular carcinoma is a common public health problem in the world. Due to its high invasion and metastasis, hepatocellular carcinoma is prone to recurrence after operation and the 5-year survival rate is low. As it is known,Epithelial-mesenchymal transition (EMT) is a critical step in the acquisition of metastatic and invasive power for tumor cells. Circular RNAs (circRNAs), a novel class of noncoding RNAs, have recently drawn lots of attention in the pathogenesis of human cancers. However, the role of circRNAs in HCC cells epithelial–mesenchymal transition (EMT) remains unclear. In this study, we aimed to identify novel circRNAs that regulate HCC cells' EMT and explored their regulatory mechanisms and clinical significance in HCC.

Methonds: The RNA-seq assay was used to screen the circRNA expression profiles associated with invasion and metastasis in cell lines. Then we studied the clinical significance of an upregulated circRNA, Has-circ-0091578, in a large cohort of patients with HCC. We further investigated the functions and underlying mechanisms of Has-circ-0091578 in HCC cells' EMT. Moreover, we evaluated the regulation effect of Has-circ-0091578 on miR-941, and its target genes, Twist1 and Vim, in two independent cohorts from our institute and The Cancer Genome Atlas(TCGA).

\Results: The upregulated expression of Has-circ-0091578 was positively associated with advanced clinical stage and worse survival in patients with HCC. We further revealed that Has-circ-0091578 promoted HCC cell's EMT via sponging miR-941. Clinical analysis from two independent HCC cohorts showed that the Has-circ-0091578/miR-941/Twist1/Vim pathway was essential in supporting HCC invasion and metastasis.

Conclusions: Has-circ-0091578 exerts critical roles in promoting HCC cells' EMT and/or invasion and metastasis,and is a prognostic biomarker of the disease, suggesting that Has-circ-0091578 may serve as an exploitable therapeutic target for patients with HCC.

Keywords: HCC; has-circ-0091578; miR-941; EMT; Biomarker

278. Targeting Enhancer Reprogramming to Mitigate MEK Inhibitor Resistance in Advanced Ovarian Cancer

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Ovarian cancer is characterized by aberrant activation of the mitogen-activated protein kinase (MAPK), highlighting the importance of targeting the MAPK pathway as an attractive therapeutic strategy. However, the clinical efficacy of MEK inhibitors is limited due to intrinsic or acquired drug resistance. Here, we established patient-derived ovarian cancer models resistant to MEK inhibitors and demonstrated that resistance to the clinically-approved MEK inhibitor trametinib was associated with chromatin remodeling. We also showed that enhancer decommissioning induced the downregulation of negative regulators of the MAPK pathway, leading to constitutive ERK activation

and acquired resistance to trametinib. Epigenetic compound screening uncovered that HDAC inhibitors could alter the enhancer remodeling and upregulate the expression of MAPK negative regulators, resulting in sustained MAPK inhibition and reversal of trametinib resistance. Consequently, a combination of HDAC inhibitor and trametinib demonstrated a synergistic anti-tumor effect in vitro and in vivo, including patient-derived xenograft mouse models. These findings demonstrated that chromatin remodeling of the MAPK regulatory pathway could serve as a new mechanism underlying MAPK inhibitor resistance and concurrent targeting of epigenetic pathways and MAPK signaling could provide a potentially effective treatment strategy for advanced ovarian cancer.

279. YEATS2 在肝细胞癌中的表达及临床意义

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目的 探讨 YEATS2 在肝细胞癌（hepatocellular carcinoma，HCC）中的表达及其与预后的关系。方法 收集我院 2010 年 1 月至 2014 年 1 月 112 例手术切除的 HCC 癌组织和癌旁组织石蜡标本，采用 Real-time PCR 检测 HCC 癌组织及癌旁组织中 YEATS2 mRNA 的表达，Western blot 和免疫组化染色检测 YEATS2 蛋白水平，免疫荧光染色检测 YEATS2 在 HCC 癌组织中的表达定位，并分析 YEATS2 与 HCC 患者临床病理特征和预后的关系，同时采用 TCGA 数据库数据验证。结果 Real-time PCR 结果显示，YEATS2 mRNA 在 HCC 癌组织中的表达较癌旁组织上调（P<0.001）；Western blot 检测结果显示，YEATS2 在约 66.67%（12/18）的 HCC 癌组织中表达升高；免疫组化染色分析发现，约 71.43%（80/112）的 HCC 患者中 YEATS2 表达上调，其表达与 TNM 分期明显相关（P<0.001）；YEATS2 主要在 HCC 癌组织细胞核中表达；多因素分析结果显示 YEATS2 高表达是患者不良预后的独立危险因素（HR=2.204，95%CI：1.388~3.500， P=0.001）。TCGA 数据库中 HCC 队列分析也表明 YEATS2 高表达的患者 OS 更差（HR=1.751，95%CI:1.107~2.770， P=0.017）。 结论 YEATS2 在 HCC 组织中高表达，且与患者不良预后相关。

280. Diagnostic performance of exosomes in non-invasive or minimally invasive detection of bladder cancer:A systematic review and meta-analysis

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northweat university

Object: To evaluate overall diagnostic value of exosomes methods in detecting bladder cancer(BC).

Materials and Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) guidelines, involved studies were comprehensively searched in PubMed,Embase,Web of Science,and Cochrane databases up to Apirl 9,2020.The quality of included studies assessed by The Quality Assessment of Diagnostic Accuracy Studies 2(QUADAS-2).The statistical software:Review Manager5.2 ,Stata15.1,and Meta-DiSc1.4 were used to analyze raw data.

Results: A total of 281 studies were explored by databases search.We finally enrolled 11 studies with including 1414 individuals in this meta-analysis after methodological quality assessment.The total sensitivity,specificity, positive likelihood ratio (PLR), negative likelihood ratio(NLR), diagnostic odds ratio (DOR) and the area under curve(AUC) of summarized receiver operating characteristic(SROC) curve for total exosomes in detecting BC are 0.73[95% confidence interval (CI) 0.70-0.76], 0.79(95%CI 0.75-0.82), 3.34(95%CI 2.80-4.00), 0.31(95%CI 0.23-0.42) , 11.87 (95%CI 7.42-18.99) and 0.8507 respectively.The merged sensitivity for urine-derived and blood-derived exosomes in detecting BC are 0.72(95%CI 0.68-0.76) and 0.78(95%CI 0.73-0.82) respectively.The pooled specificity are 0.79(95%CI 0.73-0.85) and 0.79(95%CI 0.74-0.83) respectively. The pooled PLR are 3.26(95%CI 2.26-4.72) and 3.46(95%CI 2.82-4.24) respectively. The pooled NLR are 0.29(95%CI 0.17-0.49) and 0.28 (95%CI 0.22-0.37) respectively. The pooled DOR are13.29 (95%CI 5.36-32.94) and 12.24 (95%CI 8.42-17.78) respectively. The pooled AUC estimates for urine-derived and blood-derived exosomes in detecting BC are 0.8635 and 0.8449 respectively.

Conclusion:The meta-analysis results confirmed that both urine-derived and blood-derived exosomes act a good diagnostic performance for detecting BC.

281. Genetic susceptibility genes of Familial/Hereditary Breast Cancer Families in China

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Objective: For Chinese women, Breast cancer has become the most common malignant tumor and the fifth common cause of cancer death, of which about 5%~10% presents familial aggregation. The main purpose of this study is to explore the susceptibility genes, and the relationship between mutation genes and clinicopathological characteristics in familial/hereditary breast cancer families in China

Methods: This study collected a total of 116 samples from 27 family clusters of breast cancer.Ion Torrent S5™ second-generation sequencing platform was used to screen out germline mutation sites in the family, and the correlation between the mutation and clinical pathology of breast cancer patients was statistically analyzed.

Results: There were 88 germline mutations on 27 genes identified in 96 samples. 81.5% of mutation genes were related to DNA damage repair. Of 27 families enrolled, 22 (81.5%) breast cancer families were caused by mutations in known genetic susceptibility genes. In families with known genetic susceptibility genes, only 36.4% (8/22) were caused by BRCA gene mutation, while 66.7% (14/22) were caused by non-BRCA gene mutation. Among 116 samples, 96 (82.8%) samples were found to carry gene mutations. Among the mutation carriers, 47.9% (46/96) of them were BRCA mutations carriers and 52.1% (50/96) were found to only carry non-BRCA mutations. The mutation frequency of BRCA2 gene was 1.3 times (56.5%/43.5%) higher than that of BRCA1 gene among Chinese familial breast cancer families. The BRCA mutation group had higher rate of axillary lymph node metastasis (ALNM) than the negative group (81.82% vs. 28.57%, P=0.049). Compared with the negative group, the non-BRCA mutation group had a higher proportion of breast benign disease history and the difference was statistically significant (72.22% vs. 14.29%, P=0.021).

Conclution: RCA1 and BRCA2 genes play a very important role in the genetic risk of breast cancer, but the impact of other genes should not be ignored. It is necessary to detect other breast cancer susceptibility genes in suitable population. At the same time, large-scale studies are still needed in the future to comprehensively evaluate the impact of the above breast cancer susceptibility genes on the risk of breast cancer.

282. 乳腺癌患者术前血清载脂蛋白 B 与载脂蛋白 A-I 比值的预后价值

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背景:在妇女中，乳腺癌是大多数国家女性癌症死亡的主要原因。载脂蛋白 A-I (ApoA-I)是高密度脂蛋白(HDL)的主要蛋白质成分,能将多余的胆固醇从外周组织转运至肝脏，具有抗炎、抗凋亡和抗氧化作用。ApoA-I 水平在其他肿瘤中与预后相关，但在乳腺癌中的预后价值尚不清楚。载脂蛋白 B (ApoB)是一种重要的血液载脂蛋白，与心脏代谢紊乱有关。目前，ApoAI，ApoB 分别被认为是动脉粥样硬化的保护因素和危险因素。最近的前瞻性研究表明，ApoB/ApoA-I 比值可能是心血管疾病死亡率的有用预测指标，而且这个比值甚至可能比脂质生物标记物更能预测心血管疾病的死亡风险。乳腺癌的发生、发展被考虑与脂类代谢有关。我们的研究旨在评估载脂蛋白 B (ApoB)与载脂蛋白 A-I (ApoA-I)比值(ApoB/ApoA-I)在乳腺癌患者

中的预后价值。

方法:我们收集了 416 例 2012 年 1 月至 2016 年 12 月在中山大学附属第三医院行乳腺癌根治术的患者的术前基线数据，并进行了电话随访，最后回顾性分析了这些乳腺患者的血脂水平。在我们的研究中，我们采用 ROC 分析来确定血脂的最佳截断值，采用单因素和多因素 Cox 回归分析来研究血脂的预后价值。我们根据受试者工作特征(ROC)曲线，对患者术前血清胆固醇、甘油三酯、HDL-c、GGT、LDL-c、LDL-c / HDL-c 比值、ApoA-I 和 ApoB、ApoB/ ApoA-I 比值的截断值进行分层。为了消除 ApoB/ApoA-I 组水平基线特征的不平衡，我们还进行了倾向性评分匹配(PSM)分析，平衡了淋巴结转移、术后化疗、分子组化类型的差异。结果:我们利用我们的数据分析无病生存(DFS)时间，发现 ApoB/ApoA-I 水平较低(<0.829)组的 DFS 明显高于 ApoB/ApoA-I 水平较高(≥0.829)组（HR, 1.786 and 1.859;P = 0.019 and 0.014,PSM:P=0.015 and 0.008）。

结论:术前血清 ApoB/ApoA-I 升高是乳腺患者预后不良的独立预后因素。如果进一步的证据支持我们的发现，载脂蛋白 B (ApoB)与载脂蛋白 A-I (ApoA-I)比值的测量可以作为肿瘤标志物预估乳腺癌患者的生存预后。

283. LCP2 may be a new biomarker of TME remodeling in cutaneous melanoma

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To explore the mechanisms involving in tumor microenvironment (TME) remodeling as a prognostic factor and strategy to facilitate cutaneous melanoma (CM) therapy. Methods. 472 CM samples' data was downloaded from The Cancer Genome Atlas (TCGA) database, the content of immune and stromal cells and the proportion of tumor immune infiltrating cells (TICs) in the samples of CM patients were calculated respectively by using ESTIMATE and CIBERSORT. The differentially expressed gene (DEGs) was analyzed by constructing protein-protein interaction (PPI) network, combined with univariate COX regression analysis. Results. Lymphocyte cytosolic protein 2 (LCP2) was found to be a prognostic related gene of CM, and negatively correlated with the T stage and grade, positively correlated with the survival time. Gene Set Enrichment Analysis (GSEA) showed that the genes in the high-LCP2 group were mainly enriched in immune-related active function gene sets. CIBERSORT analysis showed that T cells and Macrophages M1 were positively correlated with LCP2, while Macrophages M2 were negative correlation, suggesting that LCP2 may be closely related to active anti-tumor immunity in TME. Conclusion. This study suggests that LCP2 may be helpful to judge the prognosis of patients with CM and provide a new direction for the immunotherapy of CM.

284. Study on exosome mediated miR-1229 as metastasis markers of colorectal cancer and its mechanism

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Background: Existing evidence has shown that miRNAs are involved in carcinogenesis and cancer progression through regulating the expression of their target genes, and that exosome-mediated miRNAs play an important role in cancer progression and metastasis, suggesting that miRNAs in exosomes may be potential biomarker in cancer.

Methods: To elucidate the role of miR-1229 in exosomes in CRC, we performed quantitative real-time PCR(qRT-PCR), western blot and immunohistochemical(IHC) assays, FISH, Transwell migration/invasion (with Matrigel) assays, in vitro scratch assay, luciferase reporter assay, Western blot and RT-qPCR analysis in vitro. In vivo, LoVo tumor-bearing mice and liver metastasis mice model were applied.

Results: Preliminary studies of our group observed that miR-1229 in exosomes was significantly downregulated in serum and tissue samples of colorectal cancer (CRC) with metastasis. As target genes of miR-1229, IGF2 and IGF2BP3 were markedly overexpressed in tissue samples of CRC metastasis, and promoted the proliferation, invasion and metastasis of cancer cells, indicating that exosome-mediated miR-1229 has a potential clinical value as a biomarker to predict CRC metastasis.

In this research project, serum and tissue samples of CRC with or without metastasis is collected to investigate the value of exosome-mediated miR-1229, in the early diagnosis and prognosis of CRC metastasis; the regulation of IGF2/IGF2BP3 and downstream signaling pathway is investigated to determine the role of signaling pathway in vascular permeability, proliferation, invasion and metastasis of cancer cells in vivo and in vitro; and the mechanisms underlying CRC metastasis is explored as well.

Conclusions: This study will provide clinicians with new insights on clinical diagnosis and the molecular pathogenesis of CRC metastasis.

285. lncRNA MFI2-AS1 regulates TGF β 1 expression by sponging miR-485-5p and miR-331-3p in colorectal cancer

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Background: Abnormal expression of long non-coding RNAs (lncRNAs) has been found in almost all human tumors, providing numerous potential diagnostic biomarkers, prognostic biomarkers, and therapeutic targets.

Methods: We analyzed RNA sequencing data to explore abnormally expressed lncRNAs in colorectal cancer (CRC). The functions of melanotransferrin antisense RNA 1 (MFI2-AS1) were investigated through in vitro and in vivo assays (CCK-8 assay, colony formation assay, flow cytometry assay, EdU assay, wound healing assay, transwell assay, and xenograft model). The mechanism of action of MFI2-AS1 was explored through bioinformatics, RNA fluorescence in situ hybridization, luciferase reporter assay, RNA pull-down assay, chromatin immunoprecipitation assay, and RNA immunoprecipitation assay.

Results: We identified aberrantly expressed lncRNAs in CRC. We found that elevated MFI2-AS1 expression was associated with poor prognosis and CRC progression. Functional studies showed that MFI2-AS1 promoted CRC cell growth, migration and invasion both in vitro and in vivo. Mechanistically, we found that MFI2-AS1 expressed predominantly in the cytoplasm. MFI2-AS1 could interact with miR-485-5p and miR-331-3p and regulate their common target TGF β 1.

Conclusions: Our study elucidated that MFI2-AS1 acted as an oncogene in CRC, which might serve as a novel target for CRC diagnosis and therapy.

286. H3K4me3-activated miR-1290 promotes the progression of CRC through KLF9/p53/MMP9 pathways

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Background:

Colorectal cancer (CRC) ranks third in incidence and second in mortality among cancers worldwide. Emerging researches showed that microRNAs (miRNAs) play an important role in CRC progression. Here, we aimed to investigate the expression and regulatory mechanism of miR-1290 in CRC.

Materials and methods

All clinical samples were collected from Nanjing First Hosptial. RNA-sequencing, quantitative real-time PCR (qRT-PCR) and western blot were used to test gene expression. The effects of miR-1290 on CRC cell proliferation, migration, invasion, and apoptosis were measured by colony formation, EdU, wound healing assay, Transwell assays, flow cytometry, and animal experiments. The target of miR-1290 was identified through algorithm prediction and dual-luciferase reporter assay. Chromatin immunoprecipitation (ChIP) assay was implemented to validate the H3K4me3 level of miR-1290 promoter in CRC.

Results

miR-1290 is significantly overexpressed in CRC primary tissues and metastatic tissues compared to that in normal tissues, and up-regulated miR-1290 is correlated with poor overall survival (OS) of CRC patients. Functional experiments showed that miR-1290 can promote the proliferation, migration,

invasion and inhibit apoptosis of CRC cells. Mechanistically, miR-1290 directly targets KLF9 and promotes the malignancy progression of CRC cells through regulating MMP9 and p53 expression, subsequently. In addition, high H3K4me3 levels in miR-1290 promoter region activate its transcription in CRC.

Conclusions

In summary, our study demonstrated the expression and regulatory mechanism of miR-1290 in CRC which supports the notion that therapeutic targeting of miR-1290 may be a promising treatment approach for CRC patients.

287. 晚期膀胱癌免疫检查点抑制剂治疗分子标志物研究进展

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摘要：膀胱癌是泌尿生殖系统中常见的恶性肿瘤,目前主要治疗方式为手术治疗和联合化疗,但其疗效不尽如人意，近年来免疫检查点抑制剂的研发促使晚期膀胱癌的系统治疗有了划时代的突破，改变了晚期膀胱癌的治疗方案，提升了患者长期生存期。尽管免疫检查点抑制剂目前已批准用于临床上治疗晚期膀胱癌，但选择有适应征患者是临床上的一大难题。这就需要我们不断优化免疫治疗分子标志物，筛选免疫治疗的优势人群，实现膀胱癌的精准免疫治疗进而使膀胱癌患者在免疫治疗中获益。本文就近年来国内外探索膀胱癌免疫检查点抑制剂治疗的分子标志物作一阐述，展望免疫检查点抑制剂治疗分子标志物在临床上的应用。

关键词：膀胱癌，免疫检查点抑制剂，分子标志物

288. Construction of immune-related genes risk model for breast cancer

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Abstract

Background

In tumor immunology, there hasn't investigation to find an immune-related model to predict the survival outcome of breast cancer patients. This study aimed to establish a risk model based on immune-related genes (IRGs) that can predict breast cancer patients’ survival outcomes.

Methods

A total of 2498 IRGs were obtained from The Immunology Database and Analysis Portal (ImmPort) database. The gene expression data of breast cancer patients were downloaded from The Cancer

Genome Atlas database and The Gene Expression Omnibus database. Those data were used for the generation and validation of the risk score model. The Lasso regression and Cox regression analyses were used to find the best prognostic gene and construct the risk model. To assess the independent prognostic ability of the risk model, the Kaplan–Meier survival and receiver operator characteristic (ROC) analysis were performed. Besides, the nomogram was constructed to further improve the prediction performance. The Immucell AI was used to evaluate the abundance of tumor-infiltrating immune cells.

Results

We analyzed the expression of immune-related genes and found 482 differentially expressed genes in breast cancer compared with normal tissues. Using univariate Cox analysis, we found 50 immune-related genes that could predict prognosis and used 13 highly correlated immune-related genes to construct a prognostic risk model with effective predictive power. The risk model demonstrated robust prognostic ability in both the training set and testing set, and could independently predict the survival outcome of breast cancer patients. Patients with high-immune risk were found to be correlated with advanced stage. The gene set enrichment analysis (GSEA) results showing an intensive connection of our model with immune pathways.

Conclusions

This risk model accurately stratified patients with different survival outcomes, and reflected the tumor immune microenvironment, which can promote individualized treatment and provide potential novel targets for immunotherapy.

Keywords

Bioinformatics analysis, Breast cancer, Immune-related genes, Risk model, Prognosis

289. 长链非编码 RNA CASC7 是一种有前景的肝细胞癌血清生物标志物

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目的: 长链非编码 RNA (long non-coding RNAs, lncRNAs)被认为参与了许多疾病的过程。目前，大量研究发现 lncRNAs 在肝细胞癌的生物学过程中发挥着重要作用，主要参与了肝癌的发生、侵袭、转移和复发。lncRNA 癌症易感性候选基因 7 (CASC7)在肝细胞癌中的作用尚未被研究。本研究的目的是探讨 CASC7 的表达及其与临床特征的相关性，并进一步分析其在肝细胞癌中的诊断价值。

方法: 收集 80 例肝细胞癌患者、80 例慢性乙型肝炎患者和 80 例健康人血清样本。采用数字滴式 PCR 检测血清 CASC7 表达水平。分析 CASC7 表达与肝细胞癌患者临床病理特征的关系，

判断 CASC7 是否参与了肝细胞癌的发展。通过受试者工作特征曲线(ROC)评估诊断价值。数据采用 SPSS 20.0 和 GraphPad Prism 8.0.2 进行处理。

结果: 肝细胞癌患者血清中 CASC7 的表达明显高于慢性乙肝患者(中位数:8.8 vs 2.2 copies/μl，$p < 0.001$; 与健康对照组相比(中位数:8.8 和 3.8 copies/μl，$p < 0.001$)。血清 CASC7 高表达与肿瘤数量($p = 0.005$)、肝内转移($p < 0.001$)、肿瘤大小($p = 0.007$)和 TNM 分期($p = 0.008$)显著相关。CASC7 区分肝癌与慢性乙肝患者及健康对照患者的曲线下面积(AUC)为 0.808 (95% CI: 0.742-0.874)，cut-off 值为 7.24 copies/μl，敏感性为 63.8%，特异性为 95.2%。CASC7 是一个独立危险因素，血清 CASC7 水平高的患者发生肝细胞癌的风险是低血清水平患者的 1.358 倍。

结论: 本研究提示 CASC7 在肝细胞癌患者血清中显著上调，并与肿瘤数量、肝内转移、肿瘤大小和 TNM 分期密切相关，可能是一种有前景的诊断生物标志物。然而 CASC7 在肝细胞癌发病机制中的具体作用机制尚需进一步研究。

290. Long non-coding RNA Linc00485 possesses tumor-suppressive property in colorectal cancer by regulating miR-581/EDEM1 axis

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Background: Long non-coding RNAs (lncRNA) play a vital role in colorectal cancer (CRC) progression. Here, the purpose of this study is to elucidate the role of long intergenic non-coding RNA Linc00485 in CRC.

Methods: Cell viability was measured by Cell counting kit-8 (CCK8) assay. Cell proliferation was monitored by colony formation assay. CRC cell migration and invasion were evaluated by transwell migration and invasion assays. The interactions between lncRNA and microRNA, microRNA and mRNA were validated by dual-luciferase reporter analysis. Gene expression was detected by RT-qPCR and Western blot analysis. In vivo, tumor-bearing mice model and liver metastasis mice model were established.

Results: We found that Linc00485 was significantly upregulated in CRC tissues and cancer cells (LoVo, SW480, HCT8) compared with in paired normal samples and human normal colonic epithelial cells (FHC, NCM460, CCD-18co). And linc00485 knockdown promoted the proliferation and migration of FHC cells, while Linc00485 overexpression weakened the proliferative and migratory abilities of LoVo cells. We then predicted the binding sites for linc00485 via bioinformatics analysis and found that microRNA-581 (miR-581) is the downstream target of linc00485. Dual-luciferase

reporter analysis confirmed that Linc00485 directly binds to miR-581. miR-581 was downregulated in CRC samples and cancer cells compared to normal tissues and normal colonic epithelial cells. miR-581 overexpression induced proliferation, migration, and invasion of normal colonic epithelial FHC cells, but miR-581 antagomir treatment produced opposite results. Furthermore, we found that miR-581 directly targeted the 3' untranslated region (3'UTR) of ER-degradation-enhancing alpha-mannosidase-like protein-1 (EDEM1), resulting in the inhibition of EDEM1 expression and epithelial-mesenchymal transition (EMT) process of colorectal cancer. In the mouse model, Linc00485 knockdown or down-expressed miR-581 not only significantly repressed CRC cell growth, causing the decrease of tumor volume, but also prevented CRC liver metastasis.

Conclusions: Overall, these findings suggested that Linc00485 was implicated in the tumorigenesis and progression of colorectal cancer via targeting the miR-581/EDEM1 axis. Linc00485 may be a potential therapeutic target for colorectal cancer.

Keywords: Linc00485, microRNA-581, EDEM1, colorectal cancer

291. IGF2 loss of imprinting enhances colorectal cancer stem cells pluripotency by promoting tumor autophagy

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Background: IGF2 was found to play an important role in regulating CSCs pluripotency. We performed this study to deep explore the role of IGF2 epigenetic regulation in CRC stem cells pluripotency.

Methods: IGF2 imprint status was detected by PCR-RFLP and bisulfite sequencing. Flow cytometry analysis, Immunofluorescence(IF) and sphere-formation assay were performed to investigate the correlation between IGF2 LOI and CSC. IF and mRFP-eGFP-LC3 fluorescence assay were further used to confirm IGF2 regulation in CSC autophagy. Finally, RNA interference and CO-Immunoprecipitation were conducted in vivo and vitro and the related factors involved were detected by western-blot or real-time PCR.

Results: IGF2 LOI CRC cells usually had a higher CD133 expression and sphere forming efficiency than maintenance of imprint (MOI) cells. Through mRFP-eGFP-LC3fluorescence and IF assay, we found IGF2 LOI CSCs had a higher autophagy than MOI CSCs which might further affect CSCs sphere forming efficiency. Moreover, IGF2/IR-A signal might play a more important role in CRC stem cells sphere formation and autophagy than IGF2/IGF1R. At last, with the help of miRNA-195 mimics, we fortunately found the up-regulated IR-A expression might be due to the degradation of miRNA-195 in CRC.

Conclusion: Our results suggested IGF2 LOI promoted CRC stem cells pluripotency by promoting

CSCs autophagy. For the degradation of miRNA-195, IGF2 showed a higher ability in interacting with overexpressed IR-A rather than IGF1R which would further modulate CSCs autophagy. All these findings might provide a novel mechanistic insight into the CRC diagnosis and treatment.

Keywords: IGF2 LOI, CRC, CSCs pluripotency, autophagy

292. YTHDF1 facilitates the progression of hepatocellular carcinoma by promoting FZD5 mRNA translation in an m6A-dependent manner

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Purpose: Hepatocellular carcinoma (HCC), one of the most aggressive malignancies, ranks as the fourth leading cause of cancer-related deaths worldwide. Emerging evidence indicates that RNA N6-methyladenosine (m6A) plays a critical role in tumor progression. YTHDF1 is a critical m6A binding protein, its biological function in HCC remains unclear.

Methods: YTHDF1 expression was identified by quantitative real-time PCR (RT-qPCR), western blotting, and immunohistochemistry (IHC). Clinical samples were used to evaluate the associations between YTHDF1 expression and the clinicopathological characteristics and prognosis of HCC patients. A chromatin immunoprecipitation (ChIP) assay was conducted to validate the specific binding of transcriptional factors (TFs) in the Ythdf1 promoter. The effects of the gain- and loss-of-function of YTHDF1 were investigated in vitro and in vivo. Photoactivatable ribonucleoside cross-linking and immunoprecipitation and high-throughput sequencing (PAR-CLIP-seq), RNA immunoprecipitation and high-throughput sequencing (RIP-seq), ribosome profiling, m6A RNA immunoprecipitation and qRT-PCR (MeRIP-qPCR), and RIP-qPCR were used to screen the targets of YTHDF1 and to elucidate the underlying molecular mechanisms.

Results: We found that YTHDF1 expression was strikingly elevated in HCC tissues and cell lines, and significantly associated with the prognosis of HCC patients. Moreover, YTHDF1 expression was transcriptionally regulated by USF1 and c-MYC in HCC. Functional studies showed that YTHDF1 can promote HCC cell proliferation and metastasis both in vitro and in vivo. Multi-omics analysis revealed that YTHDF1 can accelerate the translational output of FZD5 mRNA in an m6A-dependent manner and function as an oncogene through the WNT/β-catenin pathway.

Discussion: Our study revealed an essential role of YTHDF1 in the progression of HCC cells, which indicated that targeting YTHDF1 may be a potential therapeutic strategy in HCC.

293. Free fatty acid-to-high density lipoprotein cholesterol ratio predicts clinical outcomes in patients with breast cancer

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Objectives: Correlation of free fatty acid (FFA) -to-high density lipoprotein cholesterol (HDL-C) ratio (FFA/HDL-C) and survival of breast cancer (BC) remains unclear. The purpose of this study is to evaluate the precise effects of FFA/HDL-C on clinical outcomes in breast cancer patients.

Methods: Patients with BC were enrolled from 2009 to 2015. A total of 832 individuals from a single center were divided into prospective training and retrospective test cohorts. Optimal cutoff value of FFA/HDL-C was determined using X-tile software to separate the training cohort into low and high survival groups survival groups according to FFA/HDL-C levels. Survival analyses were performed using Kaplan-Meier curves and a Cox proportional hazards regression model. Preoperative FFA/HDL-C and clinical outcomes were obtained to determine the prognostic significance of serum lipids in the training and test cohorts.

Results: We observed that high FFA and FFA/HDL-C were significantly correlated with poor outcome in BC patients, and high FFA/HDL-C harbored the highest areas under curve to independently predict 5-year overall survival in two cohorts. Furthermore, c-index of the prognostic nomogram including FFA/HDL-C was significantly higher than that without it.

Conclusions: Preoperative serum levels of FFA/HDL-C may be i an efficient and independent factor to predict outcome in breast cancer patient.

Keywords: Breast cancer; free fatty acid; high density lipoprotein cholesterol; Prognosis.

294. MicroRNA-193a-5p as a Potential Biomarker for Triple-Negative Breast Cancer

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Background: MicroRNAs (miRNAs) have been considered to be potential noninvasive diagnostic biomarkers for cancers, containing breast cancer (BC), the first mortality cancer for female. This study aimed to evaluate the diagnostic value of circulating miRNAs for BC detection.

Methods：RT-qPCR was used to evaluate level of miR-193 cluster in cells and serum. Receivers operating characteristic (ROC) curve analysis were manipulated to investigate their diagnostic roles in BC carcinogenesis.

esults: First, we identified miR-193 cluster as candidate diagnostic biomarker referring to previous studies and bioinformatics analysis. In the screening phase, the significant decreased expressions of miR-193 cluster members (miR-193a-3p, miR-193a-5p, miR-193b-3p and miR-193b-5p) were

observed in serum of BC patients compared with healthy controls except miR-193b-3p. The levels of miR-193 cluster members were also detected in BC cell lines compared with normal breast cell. Due to the level of expression and abundance in serum, miR-193a-5p and miR-193b-5p were selected to be further explored. The AUC of miR-193a-5p and miR-193b-5p were 0.888 (95% CI: 0.808-0.969) with sensitivity of 99.17% and specificity of 77.14%, and 0.954 (95% CI: 0.902-1.000) with sensitivity of 94.17% and specificity of 91.43%, respectively. It is noted that the combined AUC of these two miRNAs was 0.982 (95% CI: 0.966-0.999), suggesting higher diagnostic value than single miRNA. Conclusion: In conclusion, our study reported that the miR-193a-5p and miR-193b-5p were significantly down-regulated in BC patients' serum, and that serum miR-193a-5p might serve as a potential biomarker for TNBC.

295. A Heterotrimeric SMARCB1-SMARCC2 Subcomplex is Required for the Assembly and Tumor Suppression Function of the BAF Chromatin-remodeling Complex

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The multi-subunit ATP-dependent chromatin remodeling complex BAF ('mammalian SWI/SNF complex') regulates DNA accessibility during cell fate transitions and functions as a context-dependent tumor suppressor. Through structural and functional studies, we show that the SMARCB1-SMARCC2 subcomplex assembles into an heterotrimer, which is essential for the association of the SMARCA4 ATPase with the SMARCB1-SMARCC1/2 subcomplex. We demonstrate that a subset of cancer-associated mutations impair the association of SMARCB1 and SMARCC1/2 and the assembly of the subcomplex. Reconstitution of SMARCB1-deficient malignant rhabdoid tumor cells with SMARCB1 mutants partially defective in subcomplex assembly fail to inhibit their ability to proliferate in vitro and to form tumors in immunocompromised mice to some degree. These findings indicated that the SMARCB1-SMARCC2 heterotrimer is important for the association of SMARCA4 with the SMARCB1-SMARCC1/2 subcomplex and tumor suppression function of SMARCB1.

296. Lin28A promotes the amplification and cancer stemness of lung cancer cells via activating MAPK pathway dependent on let7 functions

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Lung cancer is one of the most life threatening diseases with high incidence and mortality worldwide. Metastasis and relapse of lung cancer is the main cause of disease-related death. It's reported that tumor metastasis originated from cancer stem cells (CSCs) which possess more potential in proliferation and invasion. However, routine two-dimensional culture system (2D-culture) hardly mimics the growth and functions of lung cancer stem cells (LCSCs) in vivo and therefore significantly decreases the stemness activity of LCSCs. In our previous studies, we applied FGF1 and IGF1 to establish the conditional BME-based three-dimensional culture system (3D-culture) to amplify LCSCs in human lung adenocarcinoma cell line A549 cells in vitro. We found 3D-culture promoted the amplification and cancer stemness of LCSCs in A549 cells displaying higher proliferation potential and invasion activity, but lower apoptosis. Further results indicated that the expression levels of the key genes in the Lin28/let7 loop were abnormal and the MAPK signaling pathway was activated in LCSCs. Lin28 is an important reprogramming factor for human somatic cells. Lin28 and let7 form a double negative feedback regulatory pathway (i.e., the Lin28/let7 loop), which promotes tumorigenesis and tumor progression. In this study, we found Lin28A was highly expressed both in LCSCs from BME-based 3D culture system and LCSCs from lung cancer tissue samples. Besides that, Lin28A was critical for the maintenance of LCSC properties via MAPK signaling pathway, while let7 inhibited the maintenance of LCSC properties via disrupting MAPK signaling pathway. We also observed that let7 inhibitor had the potential to promote LCSC expansion in vitro and in vivo. Our study focused on the interaction between the Lin28/let7 loop and the MAPK signaling pathway, combining them into a "Lin28/let7/MAPK" cascade signaling pathway, and explored the functions and mechanisms of the cascade signaling pathway in promoting the enrichment and amplification of LCSCs in vivo and in vitro, which might be a potential therapeutic target for lung cancer therapy by reducing LCSC expansion. This study will further supplement the regulatory network of cancer stem cells and screen the potential therapeutic targets for lung cancer treatment, as well as provide the solid experimental evidences for the further researches and clinical applications in this field.

297. Vasohibin 2 Promotes Lymphangiogenesis of Lung Squamous Cell Carcinoma through Snail-Dependent VEGF-D Signaling Pathway

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Tumor metastasis is a process in which tumor cells enter the lymphatic vessels and blood vessels and then spread to the secondary site where they form secondary tumors. In vascular biology, angiogenesis and anti-angiogenesis therapy have been extensively studied, however, the molecular mechanism involved in lymphangiogenesis and lymphatic metastasis remains unclear. We analyzed mRNA expression profiles of 1375 primary lung squamous cell carcinoma (LUSC) samples from The Cancer Genome Atlas (TCGA) to explore the genes related to the poor prognosis of LUSC patients, and filtered out Vasohibin 2 (VASH2) as a significant predictive factor, which has been identified to promote angiogenesis in multiple kinds of tumors. Wedemonstrated that high level of VASH2 was associated with poor prognosis and high potential of lymphatic metastasis in an independent Chinese LUSC cohort. Forced over-expression of VASH2 promoted cell proliferation and invasion via up-regulation of Snail. Furthermore, VASH2 facilitated lymphangiogenesis and angiogenesis via up-regulation of Snail-dependent vascular endothelial growth factor-D (VEGF-D) in LUSC cells both in vitroand invivo. Importantly, inhibition of VASH2 dramatically inhibited tumor growth in mice by interfering proliferation of cancer cells and lymphangiogenesis in tumor tissues. In conclusion, VASH2 might serve as a novel biomarker for early diagnosis and prognosis prediction, as well as a potential therapeutic target in LUSC.

298. A novel lncRNA LOC101927811 functions as a ceRNA to promote colorectal cancer growth through regulating focal adhesion signaling

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Background: Long non-coding RNAs (lncRNAs) play critical roles in tumorigenesis and progression of colorectal cancer (CRC). However, functions of most lncRNAs in CRC and their molecular

mechanisms remain uncharacterized. This study aims to identify a specific lncRNA that promotes CRC growth and could be a potential therapeutic target.

Methods: LncRNA expression profiles in matched CRC and adjacent normal tissues were compared using transcriptomic analysis. The biological functions of an identified novel lncRNA, namely LOC101927811 (Focal adhesion-related lncRNA, LncFAR), were assessed in CRC cell lines and in vivo xenografts. Functions of LncFAR in focal adhesion were screened by RNA-seq and validated by Western blot. ceRNA network of LncFAR/miRNAs/integrins were confirmed using real-time PCR, dual luciferase reporter assay and AGO2 RNA immunoprecipitation (AGO2-RIP) assay.

Results: Knockdown of LncFAR inhibited cell proliferation, colony formation and tumor growth in CRC, suggesting oncogenic roles of LncFAR in CRC. Revealed by transcriptomic sequencing, focal adhesion signaling was the most significant enriched pathway positively regulated by LncFAR. Consistently, knockdown of LncFAR inhibited phosphorylation of SRC and ERK. These data indicated requirement of LncFAR on focal adhesion. Mechanistic investigations unveiled that predominantly located in cytoplasm, LncFAR could sponge miR-33b-5p and let-7c-5p/let-7d-5p to regulate gene expression of integrin family genes ITGA3 and ITGB3, respectively. Moreover, targeting LncFAR using antisense oligonucleotide remarkedly reduced cell proliferation and tumor growth in CRC, indicating that upregulated LncFAR might serve as a potential therapeutic target against CRC. In addition, LncFAR was highly expressed in CRC tissues and plasmas. Plasma level of LncFAR was significantly positively correlated with differentiation and TNM stage, as well as plasma levels of ITGA3 and ITGB3.

Conclusion: ceRNA network of LncFAR/miRNAs/Integrins is involved cell proliferation and tumor growth of CRC via regulating focal adhesion. Thus, LncFAR upregulated in CRC tissues and plasma can serve as a potential therapeutic target and predictive biomarker for CRC.

Keywords: colorectal cancer, long non-coding RNA, ceRNA, focal adhesion, integrin

299. Activation-induced cytidine deaminase expression facilitates the malignant phenotype and epithelial to mesenchymal transition in clear cell renal cell carcinoma

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Although advances have been made in the development of anti-angiogenesis targeted therapy and surgery, metastatic clear cell renal cell carcinoma (ccRCC) is still incurable. Activation-induced cytidine deaminase (AID) is mainly expressed in a variety of germ and somatic cells and induces

somatic hypermutation and class-switch recombination, playing a vital role in antibody diversification. We confirmed that AID was expressed at a higher level in ccRCC tissues than in corresponding non-tumor renal tissues. We explored the impact of AID on ccRCC proliferation, invasion, and migration. In 769-p and 786-0 cells, expression of an AID-specific short hairpin RNA significantly reduced AID expression, which markedly inhibited tumor cell invasion, proliferation, and migration. Previous studies showed that AID is associated with Wnt ligand secretion mediator (WLS/GPR177), cyclin-dependent kinase 4 (CDK4), and stromal cell-derived factor-1 (SDF-1/CXCL12) regulation, which was further confirmed in human ccRCC tissues. Therefore, we studied the relationship between AID and these three molecules, and the impact of AID on epithelial to mesenchymal transition (EMT) in ccRCC. WLS/GPR177, SDF-1/CXCL12, and CDK4 were sensitive to 5-Azacytidine (a DNA demethylation agent), which reverted the inhibition of carcinogenesis caused by AID repression. In summary, AID is an oncogene that might induce tumorigenesis through DNA demethylation. Targeting AID may represent a novel therapeutic approach to treat metastatic ccRCC.

300. 基于 4DCT 影像的肺内不同部位肿瘤运动分析

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目的： 个体化的准确测量肿瘤的呼吸移动度是确定胸部肿瘤内边界的前提。本研究利用 4DCT 对肺内不同部位的病灶分别建立三维模型，分析研究肺部不同部位病灶在整个呼吸过程中的运动规律。方法： 精选 10 例肺癌患者，患者均具有不同部位的单个或数个病灶，且分别在近锥体侧、近肋骨侧和近右主支气管末端具有光滑的边界。行 4DCT 扫描，得出重建后的十个呼吸时相的 DICOM 格式图像文件。将十个时相的图像依次导入 mimics10.01 软件中，采用阈值分割、区域生长的方法提取出肿瘤区域，得出三个肿瘤的三维模型。记录患者肺内三个肿瘤的位置，分析十个时相得出的三维模型，得出肺部三个肿瘤的位置变化曲线。结果：三个肿瘤的边界变化范围为近锥体侧：左右（1.95mm，1.74mm ），头脚（11.99mm，12mm），前后（3.5mm,2.03mm）。近肋骨侧：左右（2.16mm，1.01mm ），头脚（12.01mm，15.01mm），前后（2.36mm,2.1mm）。右主支气管末端：左右（4.72mm ，1.19mm），头脚（14.98mm，14.98mm），前后（2.98mm,2.99mm）。右主支气管末端的肿瘤在三个方向上变化范围均接近最大，近肋骨侧肿瘤在 X 方向上远离肋骨的方向变化大于近端，近椎体侧肿瘤在 Z 方向上远离椎体的方向变化小于近端。三个肿瘤均在 Y 方向上有最大的变化范围，同时具体变化范围各不相同，符合肺部肿瘤的运动规律。结论： 利用 4DCT 的十个呼吸时相重建得出的三维模型可以方便的计算出肺部不同病灶在各个时相的运动范围，这将为医师确定肺部不同部位肿瘤的外放边界提供有价值的参考。

301. A three-factor prognostic risk score model for advanced lung cancer

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Background: This study aimed to construct a prognostic risk score model to achieve a more accurate evaluation of prognosis for patients with advanced lung cancer. Methods: This study involved 72 patients with advanced lung cancer at Beijing Hospital. These patients were treated according to the guidelines. Peripheral blood leukocytes obtained before (baseline) and after first few treatment cycles were collected for RNA extraction and for performing paired circulating T cell receptor β chain (TCRB) sequencing. Based on a ratio of 3:1, all the patients were divided into a training dataset (N=52) and a testing dataset (N=17) by stratified sampling based on pathological assessments. The Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression method and leave-one-out cross-validation were used to filter effective factors with the R package “glmnet”. Among the factors, the change percentage of the systemic immune-inflammation index (SII, platelet count × neutrophil count/lymphocyte count) was calculated using the following formula: (posttreatment SII - pretreatment SII)/pretreatment SII×100%. Regression coefficients (β) were used to calculate a weighted sum of the effective factors, which was used as the prognostic risk score. Results: We constructed a three-factor prognostic risk score model to achieve a more accurate evaluation of prognosis. Using the LASSO Cox regression model and leave-one-out cross-validation, three factors were identified as being associated with PFS in the training dataset: smoke status, posttreatment circulating TCRB diversity and change percentage of SII. The risk score was obtained according to the following formula: Risk score= (0.9617 ×value of smoke status) + (-2.9831×value of posttreatment circulating TCRB diversity) + (-1.6088×value of change percentage of SII). We divided the patients into a high-risk group and a low-risk group according to the median value of the risk score. Kaplan–Meier survival curves obtained using the training dataset illustrate that patients in the low-risk group have longer progression-free survival (PFS) compared with those in the high-risk group (log-rank analysis, p<0 0001). The same results were obtained with the testing dataset (log-rank analysis, p=0.03) and the entire dataset (log-rank analysis, p=0.0003). The predictive accuracy of the three-factor prognostic risk score model was assessed by the C-indexes obtained for the training, testing and entire datasets: 0.726, 0.694, and 0.675, respectively. In addition, we constructed a nomogram based on the LASSO Cox regression model that would help clinicians predict the 3-month, 6-month, 1-year and 3-year PFS probabilities for patients with advanced lung cancer. Conclusions: This study established a reliable three-factor prognostic risk score model based on smoke status, posttreatment circulating TCRB diversity and SII, which can predict the PFS of advanced lung cancer. This model can be used as an auxiliary prediction tool in clinical practice.

Keywords:Advanced lung cancer; Prognostic mode; Nomogram; Circulating TCRB diversity; Progression-free survival.

302. PLC ε regulates metabolism and metastasis signaling via HIF‐1α/MEK/ERK pathway in prostate cancer

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Phospholipase C‐ε (PLC ε) is frequently overexpressed in tumors and plays an important role in the regulation of tumorigenesis. Although great progress has been made in understanding biological roles of PLC ε, the relevant molecular mechanisms underlying its pro‐tumor activity remain largely unclear. Here, we demonstrated that PLC ε knockdown reduced cell metastasis, glucose consumption and lactate production in a manner that depended on hypoxia inducible factor 1α (HIF‐1α) expression in prostate cancer cells. Interestingly, our findings showed that the expression levels of PLC ε were positively associated with those of HIF‐1α in clinical prostate carcinoma samples. Knockdown of PLC ε impaired HIF‐1α levels and transcriptional activity by regulating the extracellular‐signal‐regulated kinase pathway, and blocking HIF‐1α nuclear translocation. Furthermore, PLC ε could interact with the von Hippel–Lindau E3 ligase complex to modulate the stability of HIF‐1α. Collectively, our findings demonstrate that PLC ε could be a crucial positive regulator of HIF‐1α, which would promote PLC ε‐enhanced tumorigenesis.

303. KIF4A as a novel prognostic biomarker in cholangiocarcinoma

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Cholangiocarcinoma (CCA) is one of the most common malignant tumors. Although gene-targeted therapies have significantly improved the outcome of many cancers, the results are still not satisfactory for patients with CCA. Due to the lack of an effective biomarker for guiding clinical treatment and monitoring prognosis in patients with CCA, the purpose of this study was to identify a new biomarker that could help predict the outcome of patients with CCA by using bioinformatics tools. Gene expression data were collected from three publicly available datasets, comprising a total of 263 patients with CCA and 22 healthy controls. Differentially expressed genes were obtained using the limma package (FDR<0.05, |Log2FC|>1), and the respective protein–protein interaction revealed five relevant genes in the STRING dataset (TOP2A, BUB1, RRM2, TYMS, and KIF4A). KIF4A was

the only gene significantly associated with overall patient survival (P=0.035), with higher KIF4A expression being associated with poor survival rates. Moreover, KIF4A was significantly correlated with the infiltration of activated memory T cells (P=0.0198) and activated mast cells (P=0.008) in the tumor microenvironment. With higher KIF4A expression, the infiltration degree of the immune cells was affected, which may be involved in the regulation of immune tolerance by CCA cells. Taken together, these findings suggest that KIF4A represents a new biomarker in CCA with the potential to predict the response of patients to targeted immunotherapies.

304. Four novel BRCA mutations found in Chinese hereditary breast cancer patients by next-generation sequencing

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Background Breast cancer is the most frequent cancer among women worldwide. Patients carrying mutations in breast cancer susceptibility genes like BRCA1 and BRCA2 (BRCA1/2) account for 5%-10% of all breast cancer patients. Therefore, screening for breast cancer susceptibility genes may reduce the incidence of breast cancer and improve prognosis.

Methods To provide evidence for mutation interpretation and targeted drug use in breast cancer patients, gene mutations were screened in 78 women diagnosed with sporadic breast cancer using a next-generation sequencing (NGS) panel, confirmed by Sanger sequencing. Then the pathogenicity of the identified novel mutations was explored using in vitro experiments including western blotting, co-immunoprecipitation and cell-migration assays.

Results Four novel mutations (BRCA2 L1390T, BRCA2 G432F, BRCA1 P659L, and BRCA1 C835F) were identified. BRCA2 G432F decreased the expression of BRCA2 protein, enhanced cell migration and invasion ability, and prevented the protein from interacting with RAD51, resulting in a defect in the homologous recombination pathway.

Conclusions The identification of these four novel BRCA mutations and the confirmation of their pathogenicity have enriched the genetic database of breast cancer, especially in the Chinese population. Moreover, the mutations are the genetic risk factors for hereditary breast cancer. Therefore, BRCA mutation detection and genetic counseling for breast cancer patients are meaningful and important.

305. A novel heterozygous HTRA1 mutation is associated with autosomal dominant hereditary cerebral small vessel disease

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Background: We investigated whether the new heterozygous mutation in the high temperature requirement serine peptidase A1 (HTRA1) gene which we found in a autosomal dominant hereditary cerebral small vessel disease pedigree reduce HTRA1 function, and we also examined whether HTRA1 mutation affected the transforming growth factor β 1 (TGF-β1)/Smads signaling. Methods: The sequence of the whole-exome from the proband and her two sisters was detected by whole-exome enrichment and sequencing (WES). The protein expression of HTRA1 and TGF-β1/Smads was detected by western blot after the wild and mutant HTRA1 genes were transfected into human embryonic kidney (HEK) 293 cells.

Results: We found a new heterozygous mutation (c.614C>G:p.Ser205Cys) of the HTRA1 gene in the trypsin-like serine protease domain, which was predicted to be deleterious by in silico tools. It also demonstrated a lost function effect in vitro activity analysis, reduced the proteolytic activity of HTRA1 protein and increased TGF-β1/Smads expression in protein levels. These results of in vitro activity analysis may reveal the cause of autosomal dominant hereditary cerebral small vessel disease.

Conclusions: The heterozygous mutation HTRA1 S205C is associated with autosomal dominant hereditary cerebral small vessel disease. Our results indicate the relationship between HTRA1 and TGF-β1/Smads signaling.

306. The effects of hepatitis B virus integration into the genomes of hepatocellular carcinoma patients

Zhongling Zhuo,Fei Xiao

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Beijing Hospital

Objective: Liver cancer ranks sixth in cancer incidence, and is the third leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, which arises from hepatocytes and accounts for approximately 70%-85% of cases. Hepatitis B virus (HBV) frequently causes liver inflammation, hepatic damage and subsequent cirrhosis. Viral DNA integration into the host cell genome is a key mechanism of hepatocarcinogenesis. However, the detection of HBV-human DNA integration fragments is limited by the short length read of Next-generation Sequencing. Therefore, we applied nanopore technology with the advantage of long length read to

detect HBV integration sequence, methylation and structural variation in the tumor tissue of HCC patients.

Methods: The MinION Flow Cell (R7.3 chemistry) was run for 72 hours on MinKNOW software (v0.49.3.7), producing hundreds of fastq/fast5 files, each file corresponding to a molecule read by the sequencer. Cloud-based basecalling software (Guppy, Oxford Nanopore) was used to convert electrical event data from MinKNOW into basecalled files. We used KMC to count the k-mers in the FASTQ file, then used a local script to map the HBV genome to kmrs to find the HBV-human DNA integration fragment. Methylation of DNA (including CpG, 5mC and 6mA) was identification by Tombo. After using ngmlr to locate the GRCh38 reference genome, the structural variation was analyzed by Sniffles.

Results: We conducted parallel sequencing of 15 HBV-positive HCCs and adjacent normal tissues. We found that HBV integration is observed more frequently in the tumors (86.4%) than in adjacent liver tissues (30.7%). Methylation level of HBV integration site increased significantly. Structural variations were significantly increased at HBV breakpoint locations where chromosomal instability was likely induced. Approximately 40% of HBV breakpoints within the HBV genome were located within a 1,800-bp region where the viral enhancer, X gene and core gene are located. Conclusions: We have shown the ability and reliability of nanopore sequencing, to detect HBV-human DNA integration fragment, modified nucleotides and structural variations. Our findings show that HBV integrations, modified nucleotides and structural variations might be a useful biomarker to monitor disease progression from hepatitis to HCC. These results provided a good foundation for future studies on the pathogenesis of HCC.

307. Long non-coding RNA ZFAS1 promotes the invasion and proliferation of gastric cancer cells by regulating LIN28 and CAPRIN1 and has the potential value of tumor marker

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Background LncRNA ZNFX1-AS1 (ZFAS1) is a newly discovered long non-coding RNA (LncRNA), but its value in the diagnosis of gastric cancer is unclear. The aim of this study was to investigate the potential role of ZFAS1 in gastric cancer and to evaluate the clinical significance of ZFAS1 as a biomarker for gastric cancer screening.

Methods Quantitative real-time polymerase chain reaction (qRT-PCR) was used to screen for gastric cancer-associated LncRNAs in gastric cancer patients, gastric stromal tumor patients, gastritis or

gastric ulcer patients, and healthy controls. The correlation between ZFAS1 expression and clinicopathological features was analyzed. The biological effects of ZFAS1 on proliferation, migration and invasion of gastric cancer cells were studied by MTT assay, colony formation assay and transwell migration assay. The potential mechanism of ZFAS1 was demonstrated using ELISA and qRT-PCR. The relationship between ZFAS1 and tumorigenesis was demonstrated using in vivo tumor formation assays.

Results The expression of LncRNA ZFAS1 in plasma of preoperative patients with gastric cancer was significantly higher than that of the other 4 groups. Increased expression of ZFAS1 was significantly associated with lymph node metastasis, TNM staging, and poor prognosis. ZFAS1 knockdown inhibited the proliferation, migration and invasion of gastric cancer cells. In contrast, ZFAS1 overexpression promoted proliferation, migration and invasion of gastric cancer cells. LIN28 and CAPRIN1 are key downstream mediators of ZFAS1 in gastric cancer cells. ZFAS1 overexpression promoted the growth of gastric cancer cells in vivo. Meanwhile, ZFAS1 knockdown expression inhibited the growth of gastric cancer cells in vivo.

Conclusion LncRNA ZFAS1 promoted invasion and proliferation of gastric cancer cells by modulating LIN28 and CAPRIN1, suggesting that ZFAS1 can be used as a potential biomarker for the diagnosis and prognosis of gastric cancer.

308. **SITR1 在肾细胞癌干细胞中表达与耐药的研究进展**

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摘要：肾癌肿瘤干细胞标记物较少，缺乏特异性，给肾肿瘤干细胞的研究增加难度，我们需在前人的研究基础上进一步探究肾癌干细胞的作用，SIRT1 在胃癌、肝癌、膀胱癌中有研究，对其在癌症中的信号通路有一定的认识，为相关癌症的治疗提供了新的思路，但目前无 SIRT1 在肾癌干细胞中的表达研究，从肾癌干细胞中探究 SIRT1，可能为解释肾癌对化疗药物的耐药性提供新的研究路线。

关键词：肾癌；干细胞；SITR1

309. Establishment of a direct quantitative method for measurement of microRNA-224 in serum of hepatocellular carcinoma by UHPLC/MS/MS

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MiRNAs are known as potential noninvasive biomarkers for cancer diagnosis. However, current available methods of miRNA detection typically require pre-enrichment, amplification, and mostly they are semi-quantitative. Herein, we developed an isotope dilution mass spectrometry approach to convert the signal of miR-224 into the mass response of a reporter peptide. Specifically, the newly formed DNA-peptide probe was hybridized with miR-224, which was biotinylated and attached to streptavidin agarose in advance. After trypsinization, solid phase extraction and blow drying, it used a UHPLC/MS/MS-based quasi-targeted proteomics assay for miR-224 quantification and determines the peak area or peak height ratio of labeled and non-labeled analytes to which an isotope label was added to estimate the concentration of the analyte in the sample. Moreover, this method showed good linearity, precision, accuracy and recovery in the calibration range. In addition, it also demonstrated good performance in comparison with qRT-PCR. Taken together, this study may offer a novel direct quantitative method for serum miRNA analysis applied in clinical practice.

310. IL-10 诱导 NK/T 细胞淋巴瘤细胞对吉西他滨耐药的作用

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背景：结外 NK/T 细胞淋巴瘤（ENKTL）临床预后较差，而化疗药物耐药是导致其治疗失败的主要原因。白细胞介素-10（IL-10）作为一种重要的炎性因子与 ENKTL 的发生和预后关系密切，而与 ENKTL 耐药的相关性目前尚无研究报道。本课题拟研究 IL-10 参与 ENKTL 多药耐药的作用。方法：ELISA 法检测 ENKTL 患者外周血清中 IL-10 浓度，并分析血清 IL-10 浓度与临床特征的关系。分别用不同浓度的 IL-10 和吉西他滨作用于 YTS 细胞，CCK8 检测细胞增殖，流式细胞仪检测细胞凋亡及周期。结果：ENKTL 患者血清 IL-10 浓度较健康志愿者升高。治疗有效组 ENKTL 患者血清 IL-10 浓度高于治疗无效组。血清 IL-10 浓度和患者的年龄、性别、Ann Arbor 分期及 IPI 评分没有相关性，而与血清 LDH 是否升高、是否有 B 症状、EBV 拷贝数是否大于 5000 有显著相关性。IL-10 对 ENKTL 细胞系 YTS 细胞的有轻度的促进增殖作用。低浓度 IL-10 刺激 YTS 细胞后吉西他滨 IC50 值明显增加。IL-10 刺激下，吉西他滨阻滞细胞周期和促进细胞凋亡的作用均被减弱。结论：ENKTL 患者血清 IL-10 浓度升高，IL-

10 可诱导 YTS 细胞对吉西他滨耐药。

311. 鼻咽癌患者血清外泌体转移相关 lncRNA 差异表达的筛选

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鼻咽癌是我国最常见的头颈部恶性肿瘤之一，我国南方为鼻咽癌高发区。虽然现在鼻咽癌 5 年的局部控制率可达到 80-90%，但仍有一些病人治疗失败，局部复发和远处转移仍是死亡的主要原因，也是鼻咽癌治疗的主要难题，探讨其机制为当前鼻咽癌研究的热点。肿瘤患者血清中含有外泌体，其携载多种信号分子，是研究肿瘤的发生发展机制的又一途径。近来研究发现 lncRNA 是一种重要的生物功能调控因子， 在多种肿瘤中存在异常表达。本研究通过高通量测序并筛选外泌体中 lncRNA 差异表达，为进一步探讨外泌体来源的目标 lncRNA 在鼻咽癌发展、转移机制中的作用提供研究基础。

目的：提取转移和未转移的鼻咽癌患者血清来源的外泌体，对两组外泌体中 lncRNA 进行高通量测序，探究 lncRNA 表达谱，并筛选其差异表达。方法：（1）采集鼻咽癌患者血清，根据临床分期以及是否发生转移分为转移组和非转移组，每组 6 例。采用超速离心法，分离血清来源的外泌体；（2） 采用 Western blotting、 透射电镜对所获得的外泌体进行鉴定；（3）利用高通量测序技术分析两组外泌体 lncRNA 的表达谱；（4）筛选显著差异表达的 lncRNA。结果： （1） Western blotting 结果显示外泌体的标志蛋白 TSG101 呈阳性表达；透射电镜结果显示外泌体为圆形或者扁圆形，直径为 30-150nm 不等；（2）高通量测序及生物信息学分析结果显示，转移组与非转移组比较共有 17 个差异表达的 lncRNA， 其中包括 6 个上调表达，11 个下调表达；（3）差异 lncRNA 靶基因的 GO 功能富集分析结果表明，17 个差异 lncRNA 的靶基因主要参与血管生成、细胞增殖、细胞凋亡、细胞周期、DNA 损伤等生物学过程。结论：来源于转移组和非转移组鼻咽癌患者血清的外泌体 lncRNA 存在差异表达，为进一步探讨外泌体来源的目标 lncRNA 在鼻咽癌发展、转移的机制提供研究基础。

关键词：鼻咽癌 转移 外泌体， lncRNA， 生物信息学分析

312. PIWIL1 和 PIWIL4 在 EBV 相关胃癌中的表达

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胃癌是消化系统中最常见的恶性肿瘤之一，EB 病毒相关性胃癌(EBV-Associated Gastric Cancer，EBVaGC)在全球胃癌病例中占近 10%，为胃癌的特殊亚型. 具有独特的生物学行为,但其机制尚不明确。近年来研究表明，PIWI 亚家族异常表达与多种恶性肿瘤的发生、发展密切相关。本研究旨在通过 qPCR 技术检测 PIWIL1 和 PIWIL4 基因在 EBVaGC 的表达，探讨其与 EBVaGC 发生、发展及预后等临床指标的相关性。

目的 探讨 PIWIL1 和 PIWIL4 表达与 EBVaGC 临床病理学特征及预后的相关性。方法 收集 58 例 EBVaGC 胃癌及癌旁组织，采用 qRT-PCR 检测 EBV 相关胃癌细胞株（AGS-BX1）及 EBVaGC 中 PIWIL1 和 PIWIL4 的 mRNA 表达水平，并分析其与临床病理特征的相关性;Kaplan-Meier 生存曲线和 Logistic 回归方法以及 Cox 比例风险模型分析 PIWIL1 和 PIWIL4 表达与 EBVaGC 预后间的相关性。结果 AGS-BX1 中 PIWIL1 与 PIWIL4 mRNA 相对表达量分别是人胃黏膜细胞 GES-1 的 30.6 倍和 28.2 倍，差异具有统计学意义（P<0.01）。PIWIL1 和 PIWIL4 在 EBVaGC 中的表达量分别为（0.556±0.096）、（0.778±0.440），在癌旁组织中的表达量为（0.240±0.121）、（0.501±0.431），分别上调 2.31 倍及 1.55 倍，差别具有统计学意义（P=0.033，P=0.029）。PIWIL1 和 PIWIL4 的表达与肿瘤组织 TNM 分期和 LN 转移都密切相关（P<0.05）。Kaplan-Meier 分析结果显示，PIWIL4 高表达组总生存期（Overall Survial,OS）较低表达组差，差异具有统计学意义（P=0.046）。Logistic 回归方法以及 Cox 比例风险模型分析显示癌组织 PIWIL4 的表达与 EBVaGC 的预后显著相关（P<0.05），是 EBVaGC 预后独立危险因素。结论 PIWIL1 和 PIWIL4 在 EBVaGC 胃癌组织中过表达并与肿瘤的 TNM 分期和 LN 转移密切相关，且 PIWIL4 与总生存期相关、是 EBVaGC 预后的独立危险因素，PIWIL4 有望作为 EBVaGC 预后的重要分子标记物，并可能成为 EBVaGC 治疗新的靶点。

关键词 胃肿瘤；EB 病毒；PIWIL1；PIWIL4；预后

313. Clinical significance of dynamic changes based on markers of inflammation and biochemistry in patients with colorectal cancer

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Background: Recent studies have found that preoperative inflammatory and biochemical biomarkers play a significant role in the prognosis of colorectal cancer (CRC) patients. However, few studies have focused on the effect of dynamic changes of indicators. We elaborated the influence of dynamic changes of neutrophils (Neu) and alkaline phosphatase (Alp) on the outcomes during the perioperation.

Methods: We enrolled 551 patients from Hubei cancer hospital who had undergone radical resection of colorectal cancer, and collected the results of laboratory examination within one week before surgery and the first admission after surgery. We used postoperative neutrophils / preoperative neutrophils (ΔNeu) and postoperative alkaline phosphatase / preoperative alkaline phosphatase (ΔAlp) to reflect the dynamic changes of neutrophils and alkaline phosphatase. Chi-square test, Kaplan Meier survival analysis, univariate and multivariate COX regression were used to evaluate the prognosis of CRC patients.

Results: The disease-free survival (DFS) (70.2%; P=0.003) and overall survival (OS) (84.2%; P<0.001) of low level of ΔNeu were better than high ΔNeu (53.9% vs. 65.0%); the DFS (74.9%; P<0.001) and OS (84.2%;P<0.001) of low level of ΔAlp were better than high ΔAlp (56.2% vs. 72.3%) similarly. Further, we combined ΔNeu and ΔAlp together and draw a conclusion that the group of low ΔNeu and low ΔAlp had best prognosis (DFS: 75.1%, OS: 88.0%, P<0.001), the reverse (high ΔNeu and high ΔAlp) had the worst prognosis (DFS: 42.1%, OS: 57.8%, P<0.001). Above all, ΔNeu (HR, 2.200; 95% CI, 1.351-3.581) and ΔAlp (HR, 1.944; 95% CI, 1.295-2.919) were independent prognostic factors for patients undergoing radical CRC surgery.

Conclusion: Decreasing ΔNeu and ΔAlp were related to better OS and DFS in patients with CRC.

314. Low albumin-to-globulin ratio predicts poor survival in patients with metastatic non-small-cell lung cancer

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Abstract

Objective: The serum albumin to globulin ratio (AGR) may be a useful prognostic factor for various cancers, this study aims to evaluate the prognostic value of AGR in patients with metastatic non-small cell lung cancer (NSCLC).

Methods: A retrospective study was conducted on patients with stage IV NSCLC diagnosed in Hubei Cancer Hospital from July 2012 to December 2013. The formula for calculating AGR value was serum albumin/ (total protein-serum albumin). Chi-square test or Fisher exact test was used to analyze the classified variables. Kaplan-Meier method analyzed the OS (Overall survival) rate and plotted it with R language. The impact of AGR on OS and PFS (Progression free survival) was analyze by Multivariate Cox proportional hazard model.

Results: A total of 399 patients were included in the study population. The optimal cut-off value of OS and PFS were 1.13 and 1.0 respectively determined by X-Tile software. Kaplan-Meier curve showed that the OS rate (32.4 vs 27.4 months, p = 0.04) and PFS (28.3 vs 22.4 months, p = 0.002) in the high AGR group were better than those in the low AGR group. The univariate and multivariate models proved that AGR is an independent risk factor in metastatic NSCLC patients, both in terms of OS (p = 0.01, HR = 0.53, 95% CI=0.33-0.87) and PFS (p = 0.008, HR = 0.61, 95% CI=0.43-0.88).

Conclusion: AGR measured by routine clinical practice is an independent prognostic factor for OS and PFS in metastatic NSCLC, which can sever as a prognostic tool for NSCLC.

Keywords: Serum albumin; Albumin to globulin ratio; Prognosis; Metastatic non-small cell lung cancer; Overall survival; Progression free survival.

315. Advanced Lung Cancer Inflammation Index can serve as an effective prognostic factor for non-small cell lung cancer patients

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Abstract

Introduction： Inflammation plays a crucial role in cancers, in which the advanced lung cancer inflammation index (ALI) is considered to be a potential factor reflecting systemic inflammation.

Objectives: This work aimed to explore the prognostic value of ALI in advanced non-small cell lung cancer (NSCLC) and classify patients according to their potential risks and different prognosis.
Methods: We screened 318 patients who were diagnosed with NSCLC stage IV in Hubei Cancer Hospital from July 2012 to December 2013. The formula of ALI is body mass index (BMI, Kg / m^2) × serum albumin (Alb, g / dl) / neutrophil-lymphocyte ratio (NLR). Categorical variables were analyzed by chi-square test or Fisher's exact test. The OS rates was analyzed by Kaplan–Meier method and plotted with R language. Multivariate Cox proportional hazard model was used to analyze the relationship between ALI and OS.
Results: According to the optimal cut-off value determined by X-tile software, patients were divided into two groups: ALI < 32.6 and ALI ≥ 32.6 and the median OS was 19.23 and 39.97 months respectively (P < .001). Multivariable Cox regression model confirmed that ALI and chemotherapy were independent prognostic factors for OS in patients with non-small cell lung cancer.
Conclusions: The results of our study indicates that patients with low ALI tend to have lower Overall Survival (OS) in advanced NSCLC, and ALI can serve as an effective prognostic factor for NSCLC patients.
Keywords: Advanced lung cancer inflammation index (ALI); Inflammation; Prognosis; Non-small cell lung cancer.

316. 单中心 202 例胶质瘤分子病理特征分析

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目的 分析不同病理类型和分级的胶质瘤分子特征

方法 使用 Sanger 测序法检测 IDH1、IDH2、TP53 基因和 TERT 基因启动子区域突变，使用焦磷酸测序法检测 MGMT 基因启动子区域甲基化，使用荧光原位杂交法检测 1p/19q 共缺失。

结果

1）202 例胶质瘤中，其中男性 112 例，女性 90 例，年龄为 10-85 岁。包括 WHO I 级 8 例；WHO Ⅱ级 46 例，其中低级别胶质瘤 2 例、肥胖细胞型星形细胞瘤 3 例、节细胞胶质瘤 3 例、弥漫型星形细胞瘤 28 例、少突胶质细胞瘤 11 例和室管膜瘤 1 例； WHO Ⅲ级 33 例，其中间变型少突胶质细胞瘤 13 例、间变型星形细胞瘤 17 例、高级别胶质瘤 3 例和星形胶质细胞瘤 1 例；WHO Ⅳ级胶质母细胞瘤 115 例。

2）IDH1 和 IDH2 基因突变共 40 例（51.0%），在 WHO I~ Ⅳ级中分别为 0%、69.6%、48.5% 和 3.5%。包括 IDH1 R132H、R132G、R132S 各 48、1 和 1 例；IDH2 N136S 和 R172K 各 1 例。

3）17 例行 TP53 基因突变检测的胶质母细胞瘤（WHO Ⅳ级）中，5 例发生突变，包括

R248W、N131del、R175H 突变各 1 例和 R273H 突变 2 例。6 例 WHO Ⅱ级胶质瘤中，检测到 1 例存在 D281E 突变，为弥漫型星形细胞瘤。

4）胶质瘤中 TERT 启动子区域突变率为 34.6%，在 WHO I~ Ⅳ级中分别为 0%、22.2%、50%和 48.9%。

5）MGMT 基因启动子区域甲基化胶质瘤共 51.9%，在 WHO I~ Ⅳ级中分别为 12.5%、67.4%、60.6%和 42.1%。

6）共检测到 26 例存在 1p/19q 共缺失。在少突胶质细胞瘤、弥漫型星形细胞瘤、间变型少突胶质细胞瘤、间变型星形细胞瘤和胶质母细胞瘤中的发生率分别为 90.9%、 7.1%、61.5%、11.8%、1.7%。

结论 在不同病理分级胶质瘤中 IDH1 基因突变率和 MGMT 基因启动子区域甲基化发生频率不同，以 WHO Ⅱ-Ⅲ级较为常见。IDH1 基因突变以 R132H 突变最为常见，同时存在其他突变类型。TERT 启动子区域突变最常见于胶质母细胞瘤中。TP53 基因突变类型多样。1p/19q 共缺失最常见于少突胶质细胞瘤和间变型少突胶质细胞瘤中。

317. 生物信息学筛选 miRNA 用于原发性乳腺癌的早期诊断

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摘要：目的 基于肿瘤基因图谱（the cancer genome atlas，TCGA）数据库筛选 microRNA（miRNA）用于原发性乳腺癌的早期诊断。方法 从 TCGA 上下载原发性乳腺癌 miRNA 表达数据，应用多种工具将癌症组与正常组比较获得差异表达 miRNA。分析乳腺癌高频突变基因与差异 miRNA 作用的靶基因之间的关系，得到备选 miRNA，将备选 miRNA 与乳腺癌前 20 名差异表达的 miRNA 求交集，得到目标 miRNA，将目标 miRNA 做 ROC 曲线分析。结果在 TCGA 数据库下载包含原发性乳腺癌组织 1075 例，正常对照乳腺组织 95 例，共有 1870 条 miRNA 的表达数据。共找到差异 miRNA 129 个，上调 miRNA 90 个，下调 miRNA 39 个，并绘制火山图，筛选出了前 20 名差异表达的 miRNA。在 17897 个发生突变的基因中突变发生率大于 5%的基因 12 个。预测 129 个差异 miRNA 的可能作用的基因即靶基因，结果预测到 18413 个靶基因。18413 个靶基因中包含这 12 个高频基因，所以说这 12 个基因为差异 miRNA 的靶基因同时也是高频基因，这些基因能被 63 个 miRNA 作用。将乳腺癌前 20 名差异表达的 miRNA 与这 63 个作用于高频突变的靶基因的 miRNA 求交集，得到 6 个 miRNA，他们是 hsa-mir-4732，hsa-mir-486，hsa-mir-592，hsa-mir-449b，hsa-mir-187，hsa-mir-196a。将这 6 个 miRNA 进行 ROC 曲线分析，预测其作为肿瘤标志物的诊断能力。其中 hsa-mir-592 ROC 曲线

下 AUC 面积为 0.950，hsa-mir-486 为 0.938，说明其作为肿瘤标志物的诊断能力良好。结论 基于 TCGA 数据库的生物信息学方法可简便而可靠地筛选目标 miRNA 进行后续研究，有较高的参考价值。

【关键词】原发性乳腺癌；miRNA；生物信息学

318. 前列腺干癌细胞 CD147 的表达及与患者细胞免疫水平之间的相关性研究

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目的：探讨前列腺癌（Prostate Cancer, PCa）干细胞中 CD147 的表达及与患者细胞免疫水平的相关性。方法：选择 2016 年 3 月-2019 年 6 月入院的 60 例接受手术治疗的转移性前列腺癌患者和未转移性前列腺癌患者作为研究对象，术中收集两组前列腺癌患者的组织标本进行肿瘤干细胞的分离培养。流式细胞仪测定两组样本中 CD147 阳性细胞数；酶联免疫吸附试验测定两组患者血清中白细胞介素-2（IL-2）、白细胞介素-10（IL-10）、白细胞介素-6（IL-6）、和干扰素 γ （INF-r）的表达水平。结果：转移组的干细胞 CD147 表达阳性率明显高于对照组（P<0.05）； 转移组 IL-2 和 INF-r 表达水平高于未转移组，但 IL-10 和 IL-6 表达水平低于未转移组（P<0.05）；转移组干细胞的 CD147 表达与 IL-2 和 INF-r 水平呈正相关性，而与 IL-10 和 IL-6 水平呈负相关（P<0.05）。结论：CD147 在转移性前列腺癌干细胞中呈高表达，且与患者细胞免疫水平具有一定的相关性，在临床疾病的诊断治疗过程中具有应用价值。

319. Lipid Metabolites as Potential Biomarkers for Diagnosis of Hepatocellular Carcinoma with Early-stage

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Objectives: Hepatocellular carcinoma (HCC) is one of the most common malignancies and the leading cause in cancer death. Early diagnosis is essential for improving HCC survival. However, traditional diagnostic biomarkers, such as serum alpha-fetoprotein (AFP), lack of sensitivity and specificity. We aim to identify new diagnostic markers for early-stage hepatitis B virus (HBV) -related HCC via metabolomic study of patients' serum.

Methods: 134 participants (HBV-related HCC at early stages (BCLC stage 0-A), cirrhosis, hepatitis B, and intrahepatic cholangiocarcinoma (ICC)) were obtained from Tianjin Medical University Cancer Institute and Hospital under IRB approval. Advance III IVDr 600MHz nuclear magnetic resonance (NMR) spectrometer (Bruker, USA) was used for metabolomic analysis. Mann-Whitney U test were

applied to evaluate the expression of serum lipid metabolic profiles and to identify early-stage HCC biomarkers. Logistic regression analysis and Receiver operating characteristic curves (ROC) was performed to evaluate diagnostic accuracy, sensitivity and specificity.

Result: We identified a biomarker panel A consists of 18 serum lipid metabolites. Panel A provides a high diagnostic performance in differentiating early-stage HCCs from non-cancerous liver diseases (AUC=0.865，95% CI: 0.791-0.920, sensitivity= 79.63%, and specificity 79.71%). We also identified a biomarker panel B consists of 35 serum lipid metabolites. Panel B provides a high diagnostic performance in differentiating early-stage HCC from cirrhosis (AUC=0.907，95% CI: 0.816-0.963, sensitivity=9 6.30%, and specificity=78.95%). We identified a biomarker panel C consists of 71 serum lipid metabolites. Panel C provides a high diagnostic performance in differentiating early-stage HCC from ICC (AUC=0.944，95% CI: 0.858-0.986, sensitivity=96.30%, and specificity=81.82%).

Conclusions: NMR-based lipid metabolite panels have considerable diagnostic performance for HCCs and therefore may contribute for early-diagnosis of HCC as a new liquid-biopsy approach. Aberrant lipid metabolites may be further investigated for deciphering molecular mechanism of HCC-genesis.

Key words: serum; NMR; HCC; Diagnosis

320. Application value of combined detection of PGI, PGII, CEA, CA19-9 and CA72-4 by antibody chip in the diagnosis of gastric cancer

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Aim: To explore the clinical value of 5 human gastric cancer biomarkers, including CA19-9, CA72-4, CEA, pepsinogen I and pepsinogen II, in the diagnosis of gastric cancer (GC). Methods: Serum samples from 50 patients with GC and 50 patients with non-neoplastic gastric disease (NGD) were collected. Quantibody gastric cancer biomarker arrays were used to quantitative measurement in the above patients. Their content differences between GC and NGD groups and their diagnostic efficacy for GC were compared. Results: The results of single factor analysis showed that all of the five factors had significant differences between the two groups. And the results of multivariate analysis showed that CA19-9, CEA and pepsinogen II were differential proteins. The area under the curve (AUC) of the five biomarkers for the diagnosis of GC ranged from 0.608 to 0.811. Moreover, the AUC combined three differential factors and all of the five factors was 0.866 (95% CI: 0.793-0.939) and 0.875 (95% CI: 0.805-0.945), respectively. Conclusion: Two panals of multiple biomarkers were developed, which are expected to be a new non-invasive method for assistant diagnosis, screening and evaluation of GC.

321. 中国人群中微卫星不稳定不同检测位点敏感性分析

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目的：对比 MSI-H 与 MSI-L/MSS 的临床病理学特征；评价两种不同的 MSI 检测系统各位点的敏感性和特异性，以便于临床更好地选择和应用。

方法：本研究入组南京大学医学院附属鼓楼医院肠癌标本 348 例。肿瘤组织免疫组化法检测 MLH1、MSH2、MSH6 和 PMS2 蛋白。提取肿瘤组织和正常组织 DNA，基于 PCR+毛细管电泳法，分别应用单核苷酸位点检测系统（位点包括 NR-21、NR-27、BAT-25、BAT-26、MONO-27、NR-24）和 2B3D 检测系统（位点包括 BAT-25、BAT-26、D5S346、D2S123、D17S250）评估 MSI 状态，并统计分析结果。

结果：345 例经 MSI 检测的样本中，相较于 MSI-L/MSS 组，MSI-H 组与肿瘤部位、TMN 分期、淋巴结转移、脉管内癌栓及 KRAS/NRAS/BRAF 突变型相关。单核苷酸位点检测系统和 2B3D 检测系统的结果均与 IHC 有着较好的一致性。单核苷酸位点检测系统位点 NR-21 的敏感性和特异性为 95.08%（58/61）和 100%（284/284）；BAT-26 敏感性和特异性为 93.44%（57/61）和 100%（284/284）；NR-27 和 MONO-27 的敏感性均为 91.80%（56/61），特异性分别为 100%（284/284）和 99.65%（283/284）；BAT-25 的敏感性为 90.16%（55/61），特异性 100%（284/284）； NR-24 的敏感性仅为 80.33%（49/61），但特异性为 100%（284/284）。2B3D 检测系统位点 BAT-26 的敏感性相对最高且为 91.30%（21/23），特异性为 98.84%（170/172）；BAT-25 的敏感性 86.96%（20/23），特异性 99.42%（171/172）；D5S346 特异性 99.42%（171/172），敏感性 30.43%（7/23）；D2S123 和 D17S250 的特异性均为 100%（172/172），敏感性分别为 50.17%（12/23）和 34.78%（8/23）。

结论：单核苷酸位点检测系统、2B3D 检测系统均与免疫组化法具有良好的一致性。在单核苷酸位点检测系统中，NR-21 的敏感性和特异性最佳，BAT26 次之；在 2B3D 检测系统中，位点 BAT-25、BA26 的敏感性和特异性相对最佳。

322. Exploration of Reference Intervals for SCCA & CYFRA 211 in Chinese Population

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Background: Tumor makers are a promising method of cancer diagnostics. Appropriate reference interval is key in the clinical usage of tumor markers. We aimed to establish a reference interval of serum SCCA and CYFRA 21-1 for Chinese population. Methods: 1018 subjects apparently health Chinese adults were recruited from 3 research sites. Electrochemiluminescence immunoassays were used to measure the serum SCCA and CYFRA 21-1 levels. Results: Reference intervals of serum SCCA and CYFRA 21-1 were not in agreement with those recommended by the manufacturers. The 95% reference interval is 0.553 to 3 ng/ml for SCCA and 1.06 to 4.93 ng/ml for CYFRA 211. The mean reference values of SCCA and CYFRA21-1 were statistically different according to gender (female, 2.85 ng/ml vs male, 3.29 ng/ml for SCCA, and female, 4.93 ng/ml vs male, 4.905 ng/ml for CYFRA21-1, respectively), and age (≥50 years, 2.82 ng/ml vs <50 years, 3.24 ng/ml for SCCA, and ≥50 years, 5.64 ng/ml vs <50 years, 4.51 ng/ml for CYFRA21-1,), respectively. Conclusion: 3 ng/ml and 4.93 ng/ml are recommended as the upper limit for SCCA and CYFRA 21-1 in Chinese population, respectively.

323. 胃癌细胞源性外泌体趋化极化中性粒细胞促进肿瘤进展

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目的 探讨胃癌细胞能否通过外泌体趋化并极化正常人中性粒细胞。方法 用超速离心法纯化人胃癌细胞源性外泌体（MGC-803-Exos、SGC-7901- Exos、AGS-Exos）和人胃黏膜细胞外泌体（GES-1-Exos），用透射电镜、Western blot、纳米颗粒跟踪分析技术对进行鉴定。Western blot 比较其中包含的趋化因子（CXCL1、2、5、8）和 IFN-β、TGF-β差异。用上述四种外泌体分别干预正常人中性粒细胞，观察中性粒细胞对外泌体的摄取；qPCR 和 Western blot 检测中性粒细胞表面 CXCR1、CXCR2 的变化；Transwell 小室法检测外泌体对中性粒细胞迁移能力的影响；qPCR、Western blot 和 ELISA 检测与中性粒细胞极化相关的酶和因子如 TNF-α、ROS、ICAM-1、NE、MMP-9、LOX。人多通路磷酸化芯片检测外泌体干预中性粒细胞后相关

信号通路的变化。结果 纯化的外泌体在透射电镜下呈双凹碟形，高表达 CD63 和 CD9、不表达细胞色素 C；外泌体的粒径大小均在 30-150nm 之间。胃癌细胞源性外泌体中 CXCL1、2、5、8 和 TGF-β 表达量高于人胃黏膜细胞来源的外泌体。激光共聚焦显微镜下可见外泌体被中性粒细胞摄取。随着 4 种细胞来源的外泌体量的增加，中性粒细胞的迁徙能力增强；胃癌细胞源性外泌体较人胃黏膜细胞来源的外泌体有更强的促进细胞迁移的作用。与对照组相比加入 100、200μg 胃癌细胞源性外泌体可上调 CXCR1、CXCR2 mRNA 和蛋白量。随着 AGS-Exos、SGC-7901-Exos 量的增加，中性粒细胞 LOX、MMP-9、NE mRNA 水平、蛋白量均逐渐升高；TNF-α、ICAM-1、ROS mRNA 水平下调，TNF-α、ICAM-1 蛋白均降低。当 MGC-803-Exos 剂量为 100μg 或 200μg 时，上调中性粒细胞 NE、MMP-9、LOX mRNA 和蛋白量；下调 ROS、TNF-α、ICAM-1 mRNA 水平，TNF-α、ICAM-1 蛋白量减少。外泌体可通过 PI3K-Akt、ErbB 等多条信号通路诱导中性粒细胞极化。结论 胃癌细胞源性外泌体可通过增强中性粒细胞迁移和趋化因子受体表达而趋化中性粒细胞，并诱导中性粒细胞上调 LOX、MMP-9、NE，发挥 N2 型 TANs 的促肿瘤作用。这种作用可能通过 PI3K-Akt 等多条信号通路。

324. Plasma Heat Shock Protein 90alpha as a Biomarker for the Diagnosis of Liver Cancer: in Patients with Different Clinicopathologic Characteristics

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OBJECTS: To investigate the clinical value of Hsp90α in the diagnosis and evaluation of liver cancer, and the clinical significance of combined hsp90 and AFP in the diagnosis of primary hepatocellular carcinoma.

METHODS: A total of 118 patients with liver cancer admitted to the Tianjin Cancer Hospital from September to November 2018 were enrolled in the malignant group, 22 patients with benign liver disease (including liver abscess and hepatic vessels) were benign, and 60 normal subjects were controls. group. The malignant group is divided into static group and dynamic group according to whether or not to receive treatment. The level of hsp90α in the plasma of the sampled patients was detected by ELISA (enzyme-linked immunosorbent assay), and the levels of AFP in the serum of some patients with liver cancer and those with benign liver disease and normal persons were detected by electrochemiluminescence. Compare and analyze the level and expression of each indicator.

RESULTS: The levels of Hsp90α in the benign liver disease group and the malignant group were significantly higher than those in the control group. The Hsp90α level in the malignant group was also significantly higher than that in the benign group. The difference was statistically significant. The

sensitivity of Hsp90α alone in the diagnosis of liver cancer was 0.932, and the specificity was 0.854. The specificity of combined AFP for the diagnosis of HCC was 0.975 with a sensitivity of 0.957. The levels of hsp90α in plasma of patients with primary liver cancer of different ages and genders were not significantly different (P>0.05), but the levels of hsp90α in different groups such as history of hepatitis, history of liver cirrhosis and stage of liver cancer were significantly different (P<0.05). The levels of hsp90α in the plasma of patients with liver cancer who received different treatments were significantly changed (P>0.05). The level of hsp90α in patients with surgical treatment and chemotherapy decreased, and the level of hsp90α in patients with interventional therapy increased. Conclusion: Hsp90α can be used as a tumor marker for early diagnosis of liver cancer, and can be used as a related index to help determine the clinical efficacy of liver cancer patients. Combined with other common tumor markers, it can also improve the specificity and sensitivity of diagnosis.

325. A panel of serum microRNAs serves as biomarkers for noninvasive early diagnosis of biliary tract cancer

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Objective: biliary tract cancer (BTC) is an aggressive malignancy with difficult early diagnosis and poor prognosis. Studies have shown that microRNAs (miRNAs) are expected to be biomarkers of the disease, which indicates that we can diagnose cancers according to the miRNAs with significant changes. The aim of this study was to explore miRNA biomarkers of BTC. Methods: a total of 163 samples were collected and divided into the control group, the benign group and the malignant group. High-throughput low density chips were performed to screen miRNAs with significant changes. Then, the preliminary screening test and the verification test were achieved by quantitative real time PCR (qRT-PCR). Finally, the level of miRNAs in serum exosomes was measured. Results: miR-10a, miR-21, miR-135b, miR-221, and miR-214 were up-regulated in BTC. And miR-221 level was statistically significant when the malignant group was compared with the benign group (P<0.05). Meanwhile, miR-135b and miR-214 were enriched in serum exosomes. Conclusion: five miRNAs in the serum were found to be significantly upregulated in patients with BTC. Among them, miR-221 can be served as early diagnostic marker for BTC patients. MiR-10a, miR-21, miR-135b and miR-214 can be used as biomarkers for the diagnosis of biliary diseases.

326. The Role of GSTT1 In Taxol/Carbo Drug-Resistant Ovarian Cancer Cell Lines

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Objective: As the chemotherapy is widely used for the treatment of ovarian cancer, more chemotherapy resistant occur, leading to fast progress and poor prognosis. We aimed to construct a paclitaxel/carboplatin combined drug-resistant cell lines for ovarian cancer (HO8910-TAX/CBP and SKOV3-TAX/CBP), and study the role of GSTT1 in chemotherapy resistant cell lines, which plays an essential role in.

Methods: Paclitaxel / carboplatin resistant ovarian cancer cell lines (HO8910 and SKOV3) were constructed by increasing concentration gradient method. The expression of GSTT1, p27, Topo1 and MDR1 were detected by real time PCR (qRT-PCR) and Western blot. The localization of GSTT1 was observed by immunofluorescence label. The expression of GSTT1 in chemotherapy resistant cell lines was down regulated by shRNA.

Results: Through the drug sensitivity experiments, we confirmed that the constructed paclitaxel/carboplatin combined drug-resistant cells were significantly higher with survival rate than parent cells and single drug-resistant cells by different concentrations of drugs ($P<0.001$). In the present study, we found that the expression of GSTT1 was increased in chemotherapy resistant cell lines, especially in combined drug-resistant cells. Meanwhile, the expression of resistance-related molecules p27, Topo1 and MDR1 was significantly increased as high as GSTT1. Also the G0/G1-phase of combined drug-resistant cells was significantly higher than that of parent cells and single drug-resistant cells, which indicated a G0/G1-phase arrest in chemotherapy resistant cell lines. Subsequently, as the expression of GSTT1 was down regulated, we found that the cell cycle was arrested at G2/M-phase, as well as the levels of cell cycle protein p27, p53 and cyclinB was decreased. In addition, the sensitivity to paclitaxel/carboplatin was increased by cell apoptosis anlysis and the expression of Topo1 reduced obviously. To investigate the relation between GSTT1 and Topo1, we found that GSTT1 and Topo1 were highly expressed in the combined drug-resistant cell lines and co-localized in the cytoplasm by immunofluorescence label. However, co-immunoprecipitation experiment determined that GSTT1 co-existed with Topo1 inapparently.

Conclusion: Paclitaxel / carboplatin combined resistant ovarian cancer cell lines were successfully constructed. The expression of GSTT1 is associated with paclitaxel / carboplatin resistance in ovarian cancer. Down regulation of GSTT1 can increase the sensitivity of ovarian cancer cells to paclitaxel / carboplatin. It is suggested that GSTT1 can be used as an indicator of drug resistance and therapeutic effect monitoring of ovarian cancer.

327. 低氧与低氧实体瘤

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低氧(hypoxia)不仅存在于高海拔、地下洞穴和深海栖息地等环境中， 在人类急性或慢性缺血后以及低氧实体瘤中也广泛存在。已有大量研究成果证 实，低氧在实体瘤发生发展的各个阶段，都发挥了重要功能，因此实体瘤又被 称为低氧实体瘤(hypoxic solid tumor)。本综述将从两个方面深入总结并讨 论:1)低氧及其相关分子网络关键基因如何影响肿瘤的发生和发展，即关键分 子的直接致癌作用;2)低氧如何改变肿瘤细胞的微环境，进而介导肿瘤的发生 和发展。同时，本综述内容还总结了低氧相关转录因子(HIF1/2a)及其下游应 答基因肿瘤干细胞和肿瘤临床治疗中的最新研究进展和成果。与此同时，本综 述提出利用趋同进化分析方法筛选高原低氧适应新分子，有助于筛选获得低氧 实体瘤的新生物标志物。

328. NCAPH is negatively associated with Mcl‐1 in non‐small cell lung cancer

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lung cancer has a high mortality rate worldwide. non-SMC condensin i complex subunit H (ncaPH) has been identified to be one of the regulatory subunits of the condensin i complex, which is essential for the correct packaging and segre- gation of chromosomes in eukaryotes. NCAPH is abnormally overexpressed in various types of cancer. a pro-survival member of the Bcl‐2 family, myeloid cell leukemia sequence 1 (Mcl‐1) is also frequently overexpressed in multiple cancers and is associ- ated with poorer clinical outcomes for patients. The association of NCAPH and Mcl‐1 proteins with the clinical and pathological features of non‐small cell lung cancer (NSCLC) remains to be elucidated. In the current study, the positive percentage of ncaPH in the non-cancerous lung tissues was revealed to be higher compared with that in NSCLC. However, the positive percentage of Mcl‐1 in the non‐cancerous lung tissues was lower compared with nSclc. in addition, ncaPH high-expression patients had a higher overall survival rate compared with patients exhibiting low expression, whereas the Mcl-1 high-expression group had a lower survival rate. Pairwise association in 260 cases of NSCLC revealed that overexpression of the NCAPH protein was negatively associated with Mcl-1 expression and vice versa. The results of multivariate Cox proportional hazard regression analysis also indicated that ncaPH and Mcl-1 demonstrated potential as distinct prognostic factors that may be used in NSCLC. The expression of NCAPH and Mcl‐1 may be associated with, and act as distinct molecular

marks for the prediction of a poor prognosis in patients with NSCLC.

329. Extracellular vesicles from prostate cancer cells deliver microRNAs to promote osteogenesis

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Introduction: Prostate cancer (PCa) is the most common malignant tumor in male urinary system and osteoblastic bone metastasis is the most observed metastasis in prostate cancer patients. It has been demonstrated that circulating microRNAs contained in extracellular vesicles are potential early biomarkers and therapy targets for many diseases. However, the potential role of microRNAs in prostate cancer bone metastasis, is not yet to be fully explored.

Methods: After isolation and purification EVs using ultracentrifugation from conditioned media of bone metastatic co-opting prostate cancer cells and normal cells , total RNA was extracted. Subsequent to library preparation and small RNA-Seq, differential gene expression analysis was performed. Data were filtered by mean miRNA expression of $\geqslant$ 50 reads, two fold up or down regulation between 2.5 -7.5 and adjusted p-value $\leqslant$ 0.05. The uptake of PCa-sEVs was performed. Three candidate miRNAs (hsa-miR-200c-3p; hsa-miR-1275; hsa-miR-383-5p) were internalized and osteoblast differentiation were detected by qPCR , histochemical staining and protein activity detection.

Results: Total reads of miRNAs in bone metastatic co-opting PCa-EVs exceeded significantly than that in normal EVs ($p<0.001$), indicating that miRNAs delivered by PCa cells play critical role in PCa bone metastasis. PCa-CM enhanced osteoblast differentiation and can be reversed by GW4869. The uptake of PCa-EVs by MC3T3-E1 was efficient. The high expression of the three candidate miRNAs in PCa-EVs was verified by qPCR. All the three candidate miRNAs promoted osteogenesis, verified by mRNA expression of osteoblastic markers (ALP, OCN, RUNX2, OSX), ALP activity, ALP staining and Aliza Red S staining.

Conclusions: These findings suggest that miRNA cargos in PCa-EVs play a pivotal role in the development of osteoblastic bone metastasis of PCa , which can be potential early biomarkers and therapy targets for prostate cancer bone metastasis.

330. Identification of crucial miRNAs and genes predicting Barrett ’ s esophagus progressing to esophageal adenocarcinoma by miRNA-mRNA integrated analysis

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Barrett’s esophagus (BE) is defined as any metaplastic columnar epithelium in the distal esophagus, which predisposes to esophageal adenocarcinoma (EAC). Yet, the mechanism through which BE develops to EAC and relevant driving factors still remain unclear. Moreover, the miRNA-mRNA regulatory network in distinguishing BE from EAC still remains poorly understood. To identify differentially expressed miRNAs (DEMs) and genes (DEGs) between EAC and BE from tissue samples, gene expression microarray datasets GSE13898, GSE26886, GSE1420 and miRNA microarray datasets GSE16456, GSE20099 were downloaded from Gene Expression Omnibus (GEO) database. GEO2R was used to screen the DEMs and DEGs. Gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed by Database for Annotation, Visualization and Integrated Discovery (DAVID). The protein–protein interaction (PPI) network was constructed, functional modules were established using the STRING and Cytoscape . Survival analysis was based on The Cancer Genome Atlas (TCGA) database. A total of 21 DEMs and 446 DEGs were identified. The enriched functions and pathways analysis inclued Epstein-Barr virus infection, herpesvirus infection and TRP channels. GART,TNFSF11,GTSE1,NEK2,ICAM1,PSMD12,CTNNB1,CDH1,PSEN1,IL1B,CTNND1,JAG1,CDH17,ITCH,CALM1 and ITGA6 were considered as the hub-genes for the high degree in PPI network. Hsa-miR-143 was the highest connectivity target gene. JAG1 was predicted as the largest number of target miRNAs. The expression of hsa-miR-181d, hsa-miR-185, hsa-miR-15b, hsa-miR-214 and hsa-miR-496 was significantly different between normal tissue and EAC according to TCGA . CDH1, GART, GTSE1, NEK2, and hsa-miR-496, hsa-miR-214, hsa-miR-15b were found to be correlated with survival and may be used as potential molecular biomarkers to predict the clinical risk of BE patients progressing to EAC.

331. 基于宏基因组学测序的肠道菌群与非小细胞肺癌放疗相关性研究

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中文摘要 目的：从 NSCLC 患者肺部肿瘤放疗前后的菌群变化中找出肠道菌群与肺癌放疗相关性，为 NSCLC 的诊断和防治提供新思路。方法：筛选成都市第五人民医院 10 例经病理学诊断为非小细胞肺癌的初治患者，分别于放疗前、15 次胸部肿瘤放疗后收集粪便样本，采用宏基因组学测序方法进行肠道微生态群落在放疗前后变化。结果：生物标志物的多级 LEfSe 分析发现放疗后有害菌增加，放线菌(LDA 值：4.2 > 4）及链球菌（LDA 值：5.23 > 4）丰度增加具有显著差异。结论：本研究发现，肠道菌群放疗后的多样性改变与放疗敏感性无显著相关性。NSCLC 患者胸部放疗后肠道菌群多样性会发生改变，改变趋势为致病菌增加，有益菌减少。

关键词：非小细胞肺癌；肠道菌群；宏基因组学；放射治疗；炎症

332. 循环血中外泌体源 miR-92a-3p 激活 Ras 通路降低 NSCLC 患者放疗敏感性

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目的：探索与 NSCLC 放疗敏感性相关的血浆外泌体源 miRNAs 及其作用路径。

方法：高通量测序 NSCLC 患者治疗前循环血中 miRNAs，根据患者放疗后的影像学检查结果将血浆样本分 TRG≤30%的 1 组，30%<TRG<50%的 2 组，TRG≤50%的 3 组，分析比较 1、2、3 组差异表达的 miRNAs，取 miRanda 、PITA 和 RNAhybrid 三个软件的交集确认差异表达 miRNAs 的靶基因，并对靶向基因进行 GO 和 KEGG 富集分析和 miR-92a-3p 靶基因的 KEGG 通路分析。

结果：1、2、3 组共同差异表达的 miRNAs 为 miR-92a-3p，对 1、2 组差异表达 miRNAs 的靶基因与 1、3 组差异表达 miRNAs 的靶基因 GO 分析结果，生物学过程均有富集在细胞定位及其建立，细胞组分定位均为细胞内组分、膜结构的细胞器等，分子功能均富集于蛋白结合和键合等，且 DAG 图显示均在蛋白结合的 GO0005515 上交集。KEGG 富集分析示 1、2 组与 1、3 组差异表达 miRNAs 的靶基因在 Ras signaling pathway 和 Endocytosis 上富集明显。miR-92a-3p 的 135 个靶基因中，参与 PI3K-Akt signaling pathway（Ras 基因的下游通路）的靶基因有 4

个，参与 cAMP signaling pathway（Ras 基因的上游通路）的靶基因有 3 个， 2 个靶基因参与 Rap1 signaling pathway（PI3K-Akt 的上游通路）。

结论：循环血中外泌体源 miR-92a-3p 通过 Ras 通路降低 NSCLC 患者放疗的敏感性。

333. New Salivary and Serum Proteomic Biomarkers in Patients with Nasopharyngeal Carcinoma

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Nasopharyngeal carcinoma is a troublesome cancer in South of China. It comes with a high rate of metastases and mortality. It still needs more accurate biomarkers for early diagnosis and prognostic prediction. Radiotherapy has been an important means to treat nasopharyngeal carcinoma and achieved a moderate effect in suppressing cancer growth and maintaining lifespan. Therefore, in order to find new biomarkers for the diagnosis or prognosis of nasopharyngeal carcinoma, we carried out a proteomic analysis of salivary and serum of the patients. Protein profiles was first obtained by use of a solid-phase antibody detection array and then further validated by use of an ELISA assay. We found three protein targets worthy of special interests. These were beta-catenin, cystatin B and E-cadherin. The expression levels of the three targets were correlated with the progression of the disease. Furthermore, we evaluated the dynamic expression index of the three targets with the radiation therapy as a manipulating factor. Our results suggested that these proteomic targets might be used as new diagnostic or prognostic biomarkers for nasopharyngeal carcinoma.

334. 一种同时纯化、富集及检测人体血清游离 DNA 的改性水凝胶运用于肿瘤分子标记物检测

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cfDNA(cell-free DNA)是人体组织排放到血液里的 DNA 片段，不管是正常人还是病人都会发生，现在已经被广泛应用于常见染色体非整倍体无创产前检测(NIPT)、癌症早筛，癌症治疗，治疗后的分子标记物检测等。然而 cfDNA 在血液中含量极低（低至 14-45 ng/mL）以及其已被分解等特性使得临床诊断对其应用进展缓慢，因此对于检测方法的灵敏度及低浓度下定量精确度有较高要求。目前，常规的 cfDNA 纯化和检测方法有磁珠分选法，放射性免疫分析法、实

时荧光定量 PCR、测序法等，但这些方法有的检测成本较高，有的方法复杂且需要特殊仪器。因此建立一种简单易行并能够纯化和检测人血清中目标 cfDNA 的方法具很大临床运用前景。本研究中，研究人员使用一种 DNA 改性水凝胶以及对应的特殊装置实现了人血清样本中的 cfDNA 的同时捕获、纯化、富集以及检测。该套系统对长度 20-100 bp 的单双链核酸的检测均有良好的灵敏度、特异度，可以检测到低至 10 pg/μL 的 DNA，在多次循环后甚至可以得到极其纯净的核酸。

335. Expression and Clinical Significance of GFAP, Vimentin, and AE1/AE3 as Biomarkers in Human Gliomas and Metastatic Brain Carcinoma

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Aim: Evaluating the expression of glial fibrillary acidic protein (GFAP), vimentin, and AE1/AE3 as biomarkers in human gliomas and metastatic brain carcinoma, and their relationship with tumor clinicopathological features.

Methods: Using the SP approach, the expression of GFAP, vimentin, and cytokeratin proteins wAE1/AE3 was assessed in 72 cases of human gliomas and 45 cases of brain metastasis. The relationship among their protein expressions, clinical features and pathological parameters was analyzed. Results: The positive rates of vimentin, GFAP and AE1/AE3 were analyzed and compared between patients with glioma and patients with brain metastasis. Statistical significance was observed for AE1/AE3 (=78.564, P＜0.001), GFAP (=38.416, P＜0.001), and vimentin (=34.594, P＜0.001). Signed-rank tests were performed and statistical significant differences were observed between patients with glioma and patients with brain metastasis for AE1/AE3 (Z=-6.345, P＜0.001), GFAP (Z=-5.792, P＜0.001), and vimentin (Z=-8.993, P＜0.001). the expression of vimentin increased with the increase in grade of gliomas. Vimentin expression was 44.4% in lower-grade gliomas, compared to 84.6% in higher-grade gliomas with a statistical significance between different pathological grades (Z=-2.051, P=0.04). The expression of GFAP in lower-grade gliomas was 88.8%, compared to 46.2% in higher-grade gliomas with a statistical significance between different pathological grades (Z=-2.963, P=0.003). Conclusion: Levels of GFAP, vimentin, and AE1/AE3 may be used as feasibility indexes for differential diagnosis of human gliomas and brain metastasis, especially for tumors that are challenging to be histologically diagnosed.

336. Clinicians, be cautious when you make diagnoses based on the NGS results

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Background: NGS is already used extensively in inherited cancer. It has led to the ability to test for multiple cancer susceptibility genes simultaneously. NGS does not represent a single technique but rather a collection of technologies, which brings both revolution and challenge in inherited cancer diagnosis.

objective: To figure out why the NGS results of the patient, with history of adrenocortical cancer, reported a homozygous pathogenic variant of CHEK2 NM_001005735:c.667C>T, but her daughter's NGS results provided by another commercial laboratory (dLAB) reported no pathogenic germline variant while she should be a carrier theoretically. And clarify the classification of this variant.

Methods: Connected the dLAB to get the sequencing information of the CHEK2 NM_001005735:c.667, to figure out whether she is a heterozygote of the same variant with the patient. Furthermore, we collected the patient's family history, queried the databases and reviewed the literature, to reanalyze the variant and determine the classification of it.

Results: (1) The daughter's sequence information showed that she is indeed a heterozygote of the variant. The reported results of two commercial laboratories didn't match because that the dLAB classified the variant as likely benign and didn't report it. (2) The family history was unremarkable, however the commercial laboratory provided test for the patient (pLAB) overlooked it. (3) pLAB chose the incorrect transcript for analysis. There are multiple isoforms of CHEK2 due to alternative splicing, and according to UniProt and Gtex, the alternative transcript which pLAB chose is much less abundant and biologically relevant than the canonical one. (4) There is no strong evidence supporting that this variant is known pathogenic. The only published article reported it as pathogenic we found was about male in breast cancer, and the researchers also chose the alternative transcript instead of canonical one just like pLAB. (5) Both results of the two commercial laboratories are incorrect. Considering information from family history, literature and databases, we reclassified the variant as uncertain significance.

Conclusion: Variant annotation still be a great challenge since it is a complex process affected by multiple factors. In this example, family histories, alternative transcripts and their tissue-specific expression patterns and quality of evidence were not considered by the commercial laboratories, and that led to the discordant results. All NGS testing laboratories should be more careful to ensure the quality, meanwhile, clinicians need to be more cautious when using the NGS results. We understand that identifying the incorrect NGS results may not be generalizable to all clinic workflows. However, we still wish to highlight the importance for clinicians to carefully consider NGS results especially

when there are family historical or/and phenotypic mismatches, and understand that these results may change with our understanding of genetics over time.

337. microRNA-25 在胰腺癌早期筛查中的临床意义初探

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目的：研究 miRNA-25 在胰腺癌患者与正常对照的表达差异并探究其与糖类抗原 19-9（CA19-9）、癌胚抗原（CEA）等一线胰腺肿瘤标志物联合诊断的临床意义。探索 miRNA-25 的表达水平与胰腺癌临床病理分期之间的相关性。

方法：利用 TIANGEN 总 RNA 提取试剂盒提取血清中 RNA，逆转录后通过荧光定量 PCR 检测 120 例血清样本中 miRNA-25 的浓度（57 例胰腺癌患者血清，7 例干扰疾病样本及 55 例正常人对照）并分析 miRNA-25 的表达与胰腺癌临床病理特征的关系。利用化学发光法检测上述样本中 CA199 和 CEA 的值，分析其表达与胰腺癌临床病理特征及 miRNA-25 表达水平之间的相关性。

结果：miRNA-25 在胰腺癌患者血清中的表达较干扰组（P=0.0008）和对照组（P<0.0001）显著升高，具有统计学差异（P<0.0001）。以病理分期为金标准，miRNA-25 试剂盒总体检测灵敏度达 91.23%；与一线胰腺肿瘤标志物 CA19-9（80.70%）和 CEA（47.37%）相比，miRNA-25 其检测灵敏度更高。联合检测 miRNA-25 和 CA19-9，可提高单 CA19-9 检测的灵敏度及单 miRNA-25 检测的特异度（90.32%）。

结论：miRNA-25 在胰腺癌患者血清中高表达，且在Ⅰ期Ⅱ期胰腺癌患者中检测灵敏度高于 CA19-9 和 CEA，提示 miRNA-25 可能成为胰腺癌早期诊断的具有前景的血清学标志物。miRNA-25 与 CA19-9 联合检测可以提高胰腺癌筛查的特异性，为胰腺癌早期诊断及筛查提供了新的方向，进一步研究 miRNA-25 表达水平与胰腺癌临床病理分期的相关性。

338. The clinical value of the combined detection of sEGFR, CA125 and HE4 for epithelial ovarian cancer diagnosis

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Objective: This study aims to investigate the clinical value of combined detection of serum soluble epidermal growth factor receptor (sEGFR), cancer antigen 125(CA125) and human epididymis protein 4 (HE4) in the diagnosis of epithelial ovarian cancer (EOC).

Patients and Methods: From December 2017 to October 2018, serum samples were obtained from Affiliated Hospital of Xuzhou Medical University, with 30 patients as EOC group, 30 patients with benign ovarian neoplasms as benign group, and 17 healthy subjects as healthy group. Besides, among

30 EOC patients, 9 serum samples were obtained from pre- and post-operative EOC patients. The levels of serum sEGFR were detected by enzyme linked immunosorbent assay (ELISA), while CA125 and HE4 were detected by electrochemiluminescence immunoassay (ECLIA). The diagnostic value was evaluated by Receiver operating characteristic (ROC) curve analysis.

Results: The levels of serum sEGFR, CA125, and HE4 in the EOC group were significantly higher than those in the benign group ($p<0.05$) and the healthy group ($p<0.05$). When using a single tumor marker, the CA125 shows the highest sensitivity (93.30%) and HE4 shows the highest specificity (97.87%). The specificity of combined detection of serum sEGFR, CA125 and HE4 was 100%, which was significantly higher than that using a single tumor marker. The area under the ROC curve (AUC) of combined detection of serum sEGFR, CA125, and HE4 (0.965) was much higher than that of single detection and higher than that of combined detection of CA125 and HE4 (0.940). Moreover, the level of serum sEGFR in post-operative EOC group was significantly lower than that in the corresponding pre-operative EOC group ($p<0.05$).

Conclusions: Our study confirms that combined detection of serum sEGFR, CA125 and HE4 increases the specificity and efficiency in EOC diagnosis, indicating that sEGFR could be a potential biomarker for the diagnosis and prognosis of EOC.

Keywords: sEGFR, CA125, HE4, epithelial ovarian cancer, diagnosis

339. Resident bacteria altered in thyroid cancer tissue with different clinical characters

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Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, the difficulty considered in PTC therapeutic process could be the property. Therefore, it is so important to know the factors that may indicate the progression course of cancer. Previous studies reported that the commensal microorganisms alterations are strongly associated with the oncogenesis and tumor progression. The gut bacteria was related to TC pathogenesis and support conversion of T4 into T3 thyroid hormones in the intestine. However, the composition of the human PTC microbiome that contributes to the natural history of PTC remains incompletely studied.

In this study, we dissect the role of the tumor microbiota in influencing the tumor progression by 16S RNA sequences. The tumor microbiome composition in 80 papillary thyroid carcinoma (PTC) patients were analyzed. We found a predominance of Proteobacteria, Actinobacteriota and Bacteroidota in PTC tissues. At lower taxonomic levels, the most abundant genera were Pseudomonas, Rhodococcus, Ralstonia, Acinetobacter, Sphingomonas, Brevundimonas and Burkholderia-Caballeronia-Paraburkholderia. Furthermore, Higher alpha-diversity in the tumor microbiome of female PTC patients were found compared to the male PTC patients. But similar dominant bacterial community in different subgroups divided by age, gender, stage and lymphatic metastasis were found . The dominant genus was Pseudomonas, with similar abundance in different subgroups. The second dominant genus

was Rhodococcus with higher abundance in patients who is female and age >40y, while with lower abundance in patients in T2 and T3 group. And highest abundance of Enteroccus was found in patients only in T3 group. No obvious deferentially abundant genus was found in patients with or without lymphatic metastasis. Kruskal-Wallis H test analysis found that significantly different abundance of genera among different stages were Pseudomonas, Rhodococcus and Sphingomonas ($p<0.05$). We then used these three genera (Pseudomonas,Rhodococcus,Sphingomonas) to run area under curve (AUC)-receiver operator characteristic (ROC) analysis. We found that the combination of these 3 taxa resulted in an AUC of 0.9 in the cohort (T1/T4), 0.87(T1/T3) and 0.82(T2/T4). Wilcoxon rank-sum test analysis demonstrated that Rhodococcus, Ralstonia, Chryseobacterium and Burkholderia-Caballeronia-Paraburkholderia were more abundance in female PTC patients($p<0.05$). In addition, correlation heatmap analysis showed that UCG-002, Granulicatella, Streptococcus, Parvimonas and Akkermansia were negatively correlated with serum anti-TPO level, Rhodococcus, Sphingomonas and Rhodococcus were positively correlated with serum anti-TG level, Burkholderia-Caballeronia-Paraburkholderia and Klebsiella were negatively correlated with anti-TSHR level. Neisseria was positively correlated with FT4 level, while Klebsiella was negatively correlated with FT4 and T4 level. Treponema was positively correlated with FT3 level, Granulicatella was negatively correlated with T3 level, Carrnobacterium and Prevotella were negatively correlated with TSH level. Escherichia-Shigella was negatively correlated with T4 level.

Overall, the results obtained from all these approaches confirmed the presence of bacteria in PTC samples including some of the species enriched in some subgroup, such as in females, or with different stages. And the data suggested that the presence and abundance of three taxa communities Pseudomonas, Rhodococcus, and Sphingomonas might predict the PTC progression. Moreover, the presence of specific species could influence the thyroid hormones and thyroid-related antibodies.

340. DNA 错配修复蛋白表达与结直肠癌腹膜癌临床病理特征的关系及意义

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目的：检测 DNA 错配修复（mismatch repair, MMR）主要蛋白（MLH1、MSH2、MSH6 和 PMS2）在人结直肠癌腹膜癌（peritoneal carcinomatosis from colorectal cancer, CRC PC）组织中的表达，并分析错配修复缺陷（defective mismatch repair, dMMR）与 CRC PC 临床病理因素及预后的关系。**方法：**采用免疫组织化学染色法检测 4 种 MMR 蛋白（MLH1、MSH2、MSH6 和 PMS2）在 152 例人 CRC PC 组织中的表达，根据 dMMR 确定微卫星不稳定性（microsatellite instability, MSI）的结果，分析 MSI 与 CRC PC 临床病理特征的关系，利用 Kaplan-Meier 法构

建生存曲线分析其与预后的关系。**结果：**免疫组化结果显示在 152 例 CRC PC 组织中，MMR 蛋白表达正常（pMMR）组 136 例（89.5%），MMR 蛋白表达缺失（dMMR）组 16 例（10.5%），其中 MLH1 缺失 10 例（6.6%），MSH2 缺失 3 例（2%），MSH6 缺失 4 例（2.6%），PMS2 缺失 9 例（5.9%），MLH1 和 PMS2 共同缺失 6 例（4.0%），MSH2 和 MSH6 共同缺失 2 例（1.3%）。统计分析结果显示，MSI-H 与 CRC PC 患者年龄（p= 0.777）、性别（p= 0.170）、原发肿瘤部位（p= 0.071）、病理类型（p= 0.775）、有无脉管瘤栓（p= 0.357）、淋巴结有无转移（p= 0.093）及 Ki-67 水平（p= 0.247）无关。Kaplan-Meier 生存分析结果显示 MSI-H 型 CRC PC 患者预后较好，差异具有统计学意义（p= 0.043）。**结论：**152 例 CRC PC 患者汇总 MSI/dMMR 型占比为 10.5%（16/152），结果显示 MSI-H 型 CRC PC 具有预后更好的趋势，与 MSS 间差异具有统计学意义。MSI 状态与 CRC PC 预后的关系尚需进一步深入研究和大样本数据的验证。

341. Prognostic Nutritional Index Identifies Risk of Early Progression and Survival Outcomes in Advanced Non-small Cell Lung Cancer Patients Treated with PD-1 Inhibitors

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ABSTRACT

Background: Prognostic nutritional index (PNI) is associated with the prognosis of cancer patients. However, the prognostic role of PNI in cancer patients who received immune checkpoint inhibitors (ICIs) remains unclear. We conducted the present study to investigate the prognostic value of PNI in predicting early progression and survival outcomes in advanced non-small cell lung cancer (NSCLC) patients treated with programmed death 1 (PD-1) inhibitors.

Methods: We retrospectively analyzed advanced NSCLC patients treated with PD-1 inhibitors from July 2018 to December 2019. Pretreatment PNI was calculated by peripheral lymphocyte count and serum albumin level, and the cut-off value was determined. Subsequently, we explored the relationship between PNI and early progression, and evaluated the prognostic role of PNI on progression-free survival (PFS) and overall survival (OS) by univariate and multivariate Cox regression analyses. Ultimately, based on the results of survival analysis, nomogram was established.

Results: A total of 123 patients were enrolled in our study. Of these, 24 (19.5%) patients had experienced early progression. The median PFS (mPFS) and OS (mOS) were 7.1 and 12.3 months,

respectively. Multivariate logistic analysis showed that low PNI (odds ratio [OR], 3.709, 95% confidence interval [CI], 1.354-10.161; P=0.011) was closely correlated with early progression. In univariate Cox regression analysis, therapy line ≥2 (hazard ratio [HR], 1.918; P=0.003), driver genomic alterations positive (HR, 1.904; P=0.013), bone metastasis (HR, 1.577; P=0.040), and low PNI (HR, 1.089; P<0.001) were associated with poorer PFS; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1-2 (HR, 1.856; P=0.017), therapy line ≥ 2 (HR, 1.898; P=0.020), and low PNI (HR, 7.596; P<0.001) were associated with shorter OS. The multivariate Cox regression analysis suggested that low PNI was an independent risk factor for PFS (HR, 2.698, 95% CI, 1.752-4.153; P<0.001) and OS (HR, 7.222, 95% CI, 4.081-12.781; P<0.001), respectively. The prediction accuracy of nomogram based on PNI is moderate.

Conclusion: PNI is a favourable predictive indicator to evaluate the risk of early progression and survival outcomes in advanced NSCLC patients treated with PD-1 inhibitors. More prospective studies are warranted to verify our results.

KEY WORDS: prognosis nutritional index, non-small cell lung cancer, PD-1 inhibitors, survival analysis, nomogram

342. Predicting the effect of 5-fluorouracil–based adjuvant chemotherapy on colorectal cancer recurrence: A model using gene expression profiles

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It is critical to identify patients with stage II and III colorectal cancer (CRC) who will benefit from adjuvant chemotherapy (ACT) after curative surgery, while the only use of clinical factors is insufficient to predict this beneficial effect. In this study, we performed genetic algorithm (GA) to select ACT candidate genes, and built a predictive model of support vector machine (SVM) using gene expression profiles from the Gene Expression Omnibus database. The model contained four ACT candidate genes (EDEM1, MVD, SEMA5B, and WWP2) and TNM stage (stage II or III). After using Subpopulation Treatment Effect Pattern Plot to determine the optimal cutoff value of predictive scores, the validated patients from The Cancer Genome Atlas database can be divided into the predictive ACT-benefit/-futile groups. Patients in the predictive ACT-benefit group with 5-fluorouracil (5-Fu)–based ACT had significantly longer relapse-free survival (RFS) compared to those without ACT (P = .015); However, the difference in RFS in the predictive ACT-futile group was insignificant (P = .596). The multivariable analysis found that the predictive groups were significantly associated with the effect of ACT (P interaction = .011). Consequently, we developed a predictive

model based on the SVM and GA algorithm which was further validated to define patients who benefit from ACT on recurrence.

343. The expression of herg in musculoskeletal system tumors with different degrees of malignancy

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Background：＇HERG's expression is scarcely reported with common bone tumors and there is a lack of sufficient study situations.

Objective：To explore the expression of HERG in various common musculoskeletal system tumors.

Method：We use the methods such as immunohistochemical staining; RT-PCR and western blot to observe various HERG's expression differences in tissues and cell lines.

Results：Our study showed that HERG is differentially expressed in different malignant tumors both in a different level and different position, but not expressed in normal bone tissue. Some blocker 4-AP can markedly inhibit the proliferation of osteosarcoma cell lines.

Conclusion：HERG was highly expressed in malignant tumors, the blocker of HERG can effectively inhibit the proliferation of malignant tumors.

344. VPS33B modulates c-Myc/p53/miR-192-3p to target CCNB1 suppressing the growth of non-small cell lung cancer.

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VPS33B is reported to be a tumor suppressor in hepatocellular carcinoma, nasopharyngeal carcinoma, colon cancer and lung adenocarcinoma. Here, we observed that reduced VPS33B protein level was an unfavorable factor that promoted the pathogenesis of NSCLC in clinical specimens. We achieved lentivirus-mediated stable overexpression of VPS33B in NSCLC cells. Increased VPS33B reduced cell cycle transition and cell proliferation of NSCLC cells in vivo and in vitro. Knocking down VPS33B restored cell growth. Mechanism analysis indicated that miR-192-3p was induced by VPS33B and acted as a tumor suppressor of cell growth in NSCLC. Further, c-Myc or p53 was identified as a transcription factor that bound to the miR-192-3p promoter and regulated its expression. MiR-192-3p directly targeted cell cycle-promoted factor CCNB1 and suppressed NSCLC cell growth. VPS33B modulated c-Myc/p53/miR-192-3p signalling to target CCNB1 by reducing activation of the

Ras/ERK pathway. Our study reveals a novel molecular basis for VPS33B as a tumor suppressor to participate in the pathogenesis of NSCLC.

345. DNMT3A confers cisplatin resistance in gastric cancer via epigenetic silencing of DDIT3

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Gastric cancer (GC) cells can develop cisplatin resistance by deregulating intracellular epigenetic networks to maintain their intrinsic homeostasis. Aberrant overexpression of DNA methyltransferase 3A (DNMT3A) has been recognized as a key element of epigenetic regulation in gastric carcinogenesis. However, the importance of DNMT3A in chemoresistance has not been fully elucidated. Here, we report that the functional role of DNMT3A in cisplatin resistance of GC and discover the underlying molecular mechanism. DNMT3A is significantly overexpressed in GC tissues and its expression increases in response to cisplatin chemotherapy. Increased DNMT3A expression is positively correlated to the differentiation of GC tissues and poor prognosis in GC patients, suggesting an important role for DNMT3A in GC progression. Using gain- and loss-of function approaches, we reveal that DNMT3A overexpression induce the acquired cisplatin resistance and malignant behavior of GC cells. Through microarray data analysis, several chemoresistance genes and oncogenic signaling pathways are identified as a downstream target of DNMT3A, including DDIT3. Mechanistic studies find that DNTM3A modulates DDIT3 by directly binding to and silencing the DDIT3 gene via promoter hypermethylation. Downregulation of DNMT3A or its inhibition using a small molecule inhibitor effectively restores tumor cells apoptosis signaling and sensitize chemoresistant GC cells to cisplatin. Taken together, all these results suggest that DNTM3A could be a therapeutic target to prevent and treat acquired cisplatin resistance and recurrence in GC. Targeting the DNMT3A-DDIT3 axis may provide a promising therapeutic strategy in the treatment of malignant GC with high DNMT3A expression.

346. Autophagy Regulates the Stemness of Pancreatic Cancer Cells by Affecting the Nuclear Translocation of EHF

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Background: Cancer stem cells are associated with recurrence and metastasis, but the mechanism underlying the stemness of pancreatic ductal adenocarcinoma (PDAC) cells remains unclear. Our previous study found the tumor suppressor role of EHF, and the upregulated level of autophagy also relates to malignant characteristics of PDAC. The relationships between autophagy/EHF and the stemness of PDAC cells need further exploration.

Materials and Methods: Eight pairs of fresh PDAC tissues and noncancerous tissues, and 96 formalin-fixed, paraffin-embedded (FFPE) sections of PDAC specimens were collected from patients who underwent a radical surgery without preoperative radiation or chemotherapy during 2013-2015 at the Tianjin Medical University Cancer Institute and Hospital. Normal FFPE pancreatic tissues were obtained from patients who underwent distal pancreatectomy for benign diseases. Another cohort of 185 pancreatic adenocarcinoma patients with mRNA expression profiling were included from The Cancer Genome Atlas (TCGA) database. Four human PDAC cell lines (PANC-1, MIA-PaCa-2, BXPC-3 and SW1990) were selected for in vitro studies. Luciferase assays, chromatin immunoprecipitation assays, IHC, Immunofluorescence, co-IP and GST-pull down were performed to explore the relationship between P62 (an indicator of autophagy) and EHF. And the effects of the Autophagy-P62-EHF axis on PDAC cells were determined by subsequent functional experiments. Xenograft mouse models were then constructed with Pan02 cells and PDX cells.

Results: In this study, we found that the expression of EHF and P62 were dramatically decreased in PDAC tissues in both our cohort and TCGA cohort. The downregulation of EHF/P62 were correlated with a decrease in survival in PDAC patients. As a transcription factor, EHF could up-regulate P62 and could inhibit the stemness of PDAC cells by restraining the activity of Wnt/β-catenin pathway. In return, P62 could promote the nuclear translocation of EHF by binding directly to EHF protein. The upregulated level of autophagy also affected the nuclear translocation of EHF by reducing the protein level of P62, followed by the downregulation of EHF and the inhibition of the stemness of PDAC cells. Moreover, autophagy inhibition with ULK-101 drastically increased EHF protein levels in nucleus and decreased the volume of tumor growth in a PDAC xenograft mouse model.

Conclusion: These in vitro and in vivo results showed that the Autophagy-P62-EHF axis was involved in the regulation of stemness of PDAC cells, which may clue to the treatment by targeting autophagy in cancer.

Keywords: Pancreatic ductal adenocarcino,Autophagy,EHF,P62,Stemness

347. Association of inflammation-related gene polymorphisms with susceptibility and radiotherapy sensitivity of head and neck squamous cell carcinoma

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Background: Inflammation-related gene polymorphisms are the most important determinants for cancer susceptibility, clinical phenotype diversity and the response to radiotherapy and chemotherapy. However, this relationship with head and neck squamous cell carcinoma remains unclear. The aim of this study was to investigate the role of Inflammation-related gene polymorphisms in the risk and radiotherapy sensitivity of head and neck squamous cell carcinoma. **Methods:** The MALDI-TOF genotyping system was used to genotype 612 individuals for 28 inflammation-related gene polymorphisms. **Results:** The AKT rs1130233 TT, (CT+TT) genotype and rs2494732 CC genotype were associated with reduced risk of head and neck squamous cell carcinoma (P=0.014; P=0.041; P=0.043); PIGR rs291097 CA, (GA+AA) genotype and rs291102 GA genotype are associated with increased risk of head and neck squamous cell carcinoma (P=0.025; P=0.025; P=0.040). IL4RA rs1801275 AA genotype was significantly correlated with increased radiotherapy sensitivity of head and neck squamous cell carcinoma (P=0.030). In addition, the age ≤60 years, non-smokers, and normal levels of SCC were found to be associated with increased radiotherapy sensitivity of head and neck squamous cell carcinoma patients (P=0.033; P=0.033; P=0.030). **Conclusion:** AKT rs1130233, AKT rs2494732, PIGR rs291097 and PIGR rs291102 polymorphisms are significantly related to the risk of head and neck squamous cell carcinoma. IL4RA rs1801275, age ≤60 years, non-smoker and normal level of SCC are significantly associated with increased radiotherapy sensitivity of head and neck squamous cell carcinoma.

348. 核酸适配体功能化磁珠用于转移性大肠癌细胞的靶向捕获研究

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目的：肿瘤转移是肿瘤患者临床致死的主要原因。在肿瘤转移的过程中，脱离原发肿瘤，侵袭并进入循环系统的肿瘤细胞称为循环肿瘤细胞（CTCs），是肿瘤转移和复发的关键。然而 CTCs 数量稀少，目前用于 CTCs 的富集主要是基于上皮细胞黏附因子（EpCAM）的表达，但此方法对于发生上皮间质转化（EMT）的 EpCAM（-）肿瘤细胞无效，而发生 EMT 的肿瘤细胞更能准确预测肿瘤的进展。因此，当前迫切需要发现更为有效的肿瘤标志物用于 CTCs 的富集，为肿瘤的临床诊断、疗效监测和预后判断提供更准确的信息。核酸适配体 W3 是前期利用 Cell-SELEX 技术获得的一段寡核苷酸序列，研究证实 W3 具有转移性肿瘤细胞的结合特异

性。本研究拟通过采用生物素-链霉亲和素的交联，构建能够与转移性大肠癌特异性识别的功能化磁珠，实现对转移性肿瘤细胞的靶向捕获、分离和富集，望为大肠癌患者血样中 CTCs 的分离和检测提供更有效的工具。

方法：利用流式细胞术和荧光显微镜分析核酸适配体在常温和血浆环境下与靶细胞的结合能力和血浆稳定性。利用生物素链和霉亲和素的交联作用构建核酸适配体功能化磁珠（W3-beads），并利用荧光显微镜观察 W3-beads 对靶细胞的特异性识别和在不同比例混合细胞中对靶细胞的靶向捕获，并分析其捕获效率。在此基础上，将靶细胞掺入全血中模拟循环肿瘤细胞进行靶向捕获分析。

结果：流式细胞术和荧光显微镜结果显示核酸适配体 W3 在血浆中不仅保持了很好的生物稳定性，而且在常温下和血浆环境中仍然保持其对靶细胞的结合特异性。 通过采用生物素-链霉亲和素交联方法，将 W3 修饰在磁性微球上，成功制备了能特异性结合转移性大肠癌细胞的核酸适配体功能化磁珠（W3-beads）； W3-beads 能够特异性的捕获靶细胞；在不同的细胞混合比例下，W3-beads 均能够有效的捕获到靶细胞，即使在靶细胞低比例下，W3-beads 对靶细胞仍具有良好的特异性，且 W3-beads 的捕获效率保持在 75%左右，可用作捕获 CTCs 的有效方法。

结论：成功制备了特异性结合转移性大肠癌细胞的核酸适配体功能化磁珠（W3-beads）；该功能化磁珠在对目标细胞的捕获后，利用简单的磁分离手段即可实现对目标细胞的特异性分离和富集；成功实现了对混合细胞及人全血中肿瘤细胞的靶向捕获，为高效富集 CTCs 提供有效的新方法。

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349. Exploration of a novel prognostic risk signature and tumor immune infiltration in nasopharyngeal carcinoma

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is a highly invasive and metastatic cancer, with diverse molecular characteristics and clinical outcomes. In this work, we aim to establish a novel gene signature that could predict prognosis (recurrence, distant metastasis and overall survival) of patients with NPC.

Methods: Here, we enrolled 60 NPC patients from Cancer Hospital Chinese Academy of Medical Sciences, including tumor tissues and paired normal tissues. All these samples were performed transcriptome sequencing. Machine learning and Cox proportional hazards regression model were

used to identify gene signature for NPC prognosis. GSEA and spearman correlation analysis were used to evaluate the function of gene signature.

Results: We utilized machine learning to identify a set of significant feature genes between recurrent/metastatic (RM) samples and no recurrent/metastatic (no-RM) samples. We also found that the combined expression of four feature genes: U2AF1L5, TMEM265, GLB1L and MLF1 was correlated with progression-free survival (PFS) and overall survival (OS) in NPC. Receiver operating characteristic (ROC) and Kaplan-Meier (K-M) plots indicated these genes had good prognostic value for NPC. Moreover, the risk score was an independent predictor for OS and PFS in multivariate Cox regression analyses (HR> 1, P< 0.05). To explore potential biological function of these genes, we used GSEA and revealed they all had a close association with proliferation and immune response, such that expression of GLB1L and TMEM265 were associated with the level of immune infiltrates within the tumor, suggesting that these two genes may affect the prognosis of NPC patients by regulating the host immune response.

Conclusions: our finding identified a novel gene signature predicting prognosis in NPC, which could promote novel therapeutic strategies and more personalized oncology treatment plans.

Keywords: Nasopharyngeal carcinoma, prognostic factor, tumor immune infiltration

350. 局部晚期鼻咽癌患者治疗前外周血乳酸脱氢酶/白蛋白比例与预后的相关性

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摘要：目的：回顾性分析治疗前外周血中乳酸脱氢酶/白蛋白比例（lactate dehydrogenase（LDH）to albumin ratio，LAR）与局部晚期鼻咽癌患者治疗后预后的相关性。**方法：**收集 2014 年 6 月至 2018 年 12 月之间收治入院的 296 例初治III/Ⅳ a，b 期（AJCC 第 7 版分期）鼻咽癌患者为研究对象，采用外周血中 LAR 中位值 3.633 为阈值对所有患者分层。分析治疗前外周血中 LAR 与局部晚期鼻咽癌患者总生存（OS），无局部复发生存（LRFS）和无远处转移生存（DMFS）的相关性。**结果：**高 LAR 组 (≥ 3.633) 与年龄越大（P = 0.000)、死亡（P = 0.000)相关；Cox 风险模型分析显示 LAR 与局部晚期鼻咽癌患者的 OS、LRFS、DMFS 三者均存在相关性，LAR 越高，预示着更差的 OS、LRFS、DMFS。**结论：**治疗前 LAR 是局部晚期鼻咽癌独立的不良预后因素，可用于风险分层及指导辅助治疗。

351. Pericyte-derived exosomes stimulate colorectal cancer revascularization after withdrawal of antiangiogenic drugs

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BACKGROUND & AIMS: Antiangiogenic tyrosine kinase inhibitors (AA-TKIs) have become a promising therapeutic strategy for colorectal cancer (CRC). In clinical practice, a significant proportion of cancer patients temporarily discontinue AA-TKI treatment due to recurrent toxicities, economic burden or acquired resistance. However, AA-TKI therapy withdrawal-induced tumor revascularization frequently occurs and thus the diseases still progress, which hampers the clinical application of AA-TKIs. We investigated the role of tumor vascular pericytes in off-AA-TKI-triggered CRC revascularization.

METHODS: Pharmacological inhibitors (imatinib and PDGFRβ neutralizing antibody) and genetic mouse model (NG2-thymidine kinase mice) were used to deplete pericytes to determine the role of pericytes in off-AA-TKI-triggered CRC tumor revascularization. A new method was developed to isolate CRC pericytes. Pericyte exosomal Gas6 was depleted to evaluate its effect on the recruitment of endothelial progenitor cells (EPCs) that promoted vessel regrowth. An Axl inhibitor R428 was used to inhibit the exosomal Gas6/Axl pathway-mediated EPC recruitment and tumor revascularization. The clinical significance of treatment with regorafenib plus R428 was investigated in mice bearing CRC liver metastases.

RESULTS: This study demonstrates that tumor vascular pericytes mediate tumor revascularization after withdrawal of AA-TKI therapy. Pharmacological inhibition and genetic ablation of vascular pericytes largely attenuate the rebound effect of CRC vascularization in the AA-TKI cessation experimental settings. Mechanistically, pericyte-derived exosomal Gas6 instigates the recruitment of EPCs for tumor revascularization via activating the Axl pathway. Gas6 silence and an Axl inhibitor markedly inhibit tumor revascularization by impairing EPC recruitment. Consequently, combination therapy of regorafenib with the Axl inhibitor improves overall survival in mice metastatic CRC model by inhibiting tumor growth.

CONCLUSIONS: Our data shed new mechanistic insights into pericytes in off-AA-TKI-induced tumor revascularization. Blocking the Axl signaling may provide an attractive anticancer approach for

sustaining long-lasting angiostatic effects for improving the therapeutic outcomes of antiangiogenic drugs.

352. CD38 was critical for tumor survival via enzyme activity

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Background: Our recent study using multiply cancer models addressed that CD38 expression on tumor cells was up-regulated in response to PD-L1 blockade, resulting in the inhibition of CD8+T cell function via adenosine receptor signaling, but a tumor immunotherapy treatment strategy using the combination of PD-L1 and CD38 antibody was shown a discouraged performance. The direct regulatory role of CD38 in neoplastic transformation and tumor progression remained elusive. The present study evaluated the involvement of this new mechanism of CD38 in lung cancer and investigated the associated factors.

Method: The multiplex assays were used to explore changes in CD38 knockout, mutation and over-expression cells. We evaluated the inhibiting effect of CD38 and downstream signals in vivo and in vitro, as well as investigated the value of CD38 in predicting the survival of patients with lung adenocarcinoma tissues.

Result: CD38 enzymatic activity facilitated the tumor formation and survival in lung cancer cells. Mechanistically, cADPR, the hydrolyze product of CD38, bound to TRPM2 iron channel to mediate Ca2+ influx and further increased the expression of Keap1 to boost tumor progression. Finally, our clinical data revealed that the positive expression of CD38 was correlated with poor survival of patients with LUAD.

Conclusion: The generation of cADPR by CD38 could increase the influx of Ca2+ via the opening of the TRPM2 iron channel, accompanied by activation of Keap1 in cancer cells. Our data suggested that CD38 enzymatic activity maybe a promising target for achieving tumor regression.

353. LncRNA TRERNA1 induced by HBx regulates the sensitivity of sorafenib to HCC cells

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HBV X protein (HBx) is mainly considered to contribute to hepatitis B virus (HBV) associated hepatocellular carcinoma (HCC). Sorafenib is a unique targeted oral kinase inhibitor for advanced HCC. LncRNAs have been shown to have critical regulatory roles in the resistance to anti-cancer drugs. However, their contributions to sorafenib resistance in HCC remain largely unknown. We previously investigated that TRERNA1 was significantly induced by HBx. Then, genes expression

profiles by RNA-seq and the effects of TRERNA1 on sorafenib resistance in TRERNA1-overexpressed HepG2 cells and TRERNA1-knockdown HepG2.215 cells were determined and analyzed. Our data indicated that overexpression of TRERNA1 could effectively reduce the sensitivity of HCC cells to sorafenib, and GSEA in TRERNA1 overexpressed HepG2 cells revealed strong correlations between TRERNA1 expression and Wnt signaling pathway. As expected, the overexpression of TRERNA1 could promote expression of Wnt signaling pathway downstream genes. In summary, our study suggested that TRERNA1 contributed to sorafenib resistance by regulating the Wnt signaling pathway.

354. GLUT1 promotes lung cancer progression via EGFR/MET signaling

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Aim: Lung cancer mortality ranks first among malignant tumors and metastasis is the leading cause. Many lung cancer patients have poor prognosis due to distant metastasis. However, the mechanism of lung cancer metastasis remains unclear, which brings many difficulties for drug development and clinical treatment. In this study, we used RNA-seq data to find out the genes that may play an important role in lung cancer metastasis and clarified its function and mechanism.**Methods**: We used RNA-seq data of existing cancer bone-lung metastasis models combined with gene expression microarray data from lung cancer clinical tissue specimens to screen out genes having significant impact on bone-lung metastasis, patient survival, and significant differences between tumors and normal tissues. We performed functional assays to check the effect of a candidate gene on the cell proliferation, migration and invasion in lung cancer cell lines. Quantitative real-time PCR and Western Blot to detect candidate genes mRNA and proteins expression in lung cancer cell lines.**Results**: By comparing two distinct data sets, we selected GLUT1 as a candidate gene to further study its function and underling mechanism. We found that GLUT1 mRNA was significantly increased in bone-lung metastasis samples and significantly higher in lung cancer samples as compared to normal lung tissues, as well as related to poor patient survival. In functional assays, the si-RNA knockdown of GLUT1 resulted in decreased cell proliferation, migration, and invasion in lung cancer cells. GLUT1 knockdown significantly inhibited the expression of E-Cadherin and increased the expression of N-cadherin, indicating GLUT1 may play a role in epithelial-mesenchymal transition (EMT). The increase in expression of PI3K, p-AMPKa and the decrease in expression of p-mTOR suggested that knockdown of GLUT1 may contribute to the autophagy of lung cancer cell lines. More importantly, we also observed significantly decreased expression of EGFR, MET, p-STAT3, and PD-

L1 after GLUT1 knockdown.**Conclusion**: Increased GLUT1 expression in lung cancer and related to poor patient survival indicating GLUT1 may be potential a diagnosis/survival marker. GLUT1 affects the malignant phenotypes of lung cancer may via EGFR/EMT oncogenic pathway, which provides a potential drug target for the prevention and treatment of lung cancer metastasis.

355. 持续质量改进在结直肠癌围手术期全程营养管理中的应用

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摘要：目的 观察持续质量改进（CQI）在结直肠癌手术患者全程营养管理中的效果。**方法** 通过对 2019 年 7 月-12 月的 30 例在我科行结直肠癌手术治疗患者的营养管理调查分析，发现存在的主要问题，并针对问题对我科 2020 年 1 月-6 月的 30 例行结直肠癌手术治疗患者实施 CQI 全程营养管理，通过 PDCA 四步法（计划、实施、核查、行动），对结直肠癌手术患者实施全程营养管理。比较实施 CQI 前后结直肠癌患者患者术后营养指标及术后恢复情况。结果 实施 CQI 全程营养管理后，结直肠癌患者舒适度明显提高，实验室指标显示较对照组有改善。结论 实施 CQI 全程营养管理在结直肠癌围手术期术后康复中起到积极作用。

1.对象与方法

1.1 研究对象：采用先后对照方法选取 2019 年 7 月-12 月在我科室进行结直肠手术患者为对照组；2020 年 1 月-7 月行结直肠手术患者为实验组，各 30 例。

1.2.1 通过对 30 例对照组实施营养管理过程进行调查分析，发现存在主要问题：

1.2 研究方法 成立 CQI 团队，护士长为总负责人，1 名营养学组的资深护士、一位主任医师和 2 名责任组长，科内其余 15 名护士和 2 名结直肠组医生为组员，特别纳入了营养师和病区 PICC 专科护士，共同组建 CQI 团队。护士长负责组织培训，循证查询，2 名责任组长负责收集实施过程汇总的问题，并进行归纳和总结，通过 PDCA 四步法（计划、实施、核查、行动）制定患者全程营养管理实施方法，并在实践中不断调整方案。

3.讨论 本研究结果显示，实施 CQI 全程营养管理后，结直肠癌患者术后舒适度明显提高，非计划性拔管没有发生，实验室各项指标显示患者术后营养恢复较干预前好。并通过持续质量改进形成了营养管理标准化、档案化管理以及全程连续性，确保了患者整个治疗过程营养照护的连续性。

综上，持续质量改进能改变结直肠癌手术患者的营养管理规范性，提高临床护士营养知识、降低手术并发症。此外，家庭营养延续性护理的开展，能维持患者的体重，为患者平稳度过恢复期提供保证；通过分层培训，组织营养支持护理的相关学习，可促进护理人员为患者提供更全面优质的护理服务。

356. Quantification of programmed cell death pathways revealed heterogeneity in breast cancer with distinct immune microenvironment and immunoregulatory function of ferroptosis

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Clinical significance and biological functions of programmed cell death (PCD) pathways were addressed in all aspect of cancer regarding multi-omics level, however, the status of each pathway was hardly evaluated. The aim of this study is to comprehensively analyze the putative biological, pathological and clinical functions of programmed cell death pathways in breast cancer on pathway level. By adopting the bioinformatic algorithm “pathifier”, we quantified five PCD pathways (KO04210 Apoptosis; KO04216 Ferroptosis; KO04217 Necroptosis; GO:0070269 Pyroptosis; GO:0048102 Autophagic cell death) in breast cancer patients, comprehensively analyze were done focusing on the clinical significance and correlation of programmed cell death pathways in breast cancer. We featured the clinical characteristics and prognostic value of each pathway in breast cancer, found significantly activated PCD in cancer patients, among which ferroptosis was demonstrated significant correlation with early recurrence and progression of breast cancer. Correlation analysis between PCD pathways identified intra-tumor heterogeneity of breast cancer. Therefore, clustering of patients based on the status of PCD was done. Comparisons between subgroups highlighted specifically activated ferroptosis in cluster 2 and opposite clinical significance of ferroptosis between cluster 2 and cluster 5, indicating differentially altered functions between groups. Further functional enrichment identified distinct status of tumor immunity and microenvironment between clusters, which diversely correlated with ferroptosis. In cluster 2, ferroptosis pathway showed good prognostic value in predicting response to the treatment of immune checkpoint inhibitor (ICIs). A 3-gene panel was constructed as selective biomarker of cluster 2 and further validated in external independent cohorts, among which, GADD45GIP1 was identified an important role in the process of ferroptosis and may works as an putative biomarker for ferroptosis. In conclusion, the status of PCD significantly correlated with the clinical outcomes and intra-tumor heterogeneity of breast cancer. The immunological function of ferroptosis differs between patients. In cluster 2 patients, ferroptosis pathway was hyperactivated and can function as a predictive biomarker for immunotherapy with the activation of ferroptosis indicating better responsiveness and GADD45GIP1 was identified as an putative biomarker for ferroptosis.

357. KIF4A enhanced cell proliferation and migration via activation of Hippo signaling and predicted a poor prognosis in esophageal squamous cell carcinoma

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Purpose: In this study, we aim to explore and clarify the function of KIF4A in esophageal squamous cell carcinoma (ESCC).

Patients and methods: The microarray data were extracted from the Gene Expression Omnibus (GEO) database. The GEO2R method was used to analyze differentially expressed genes (DEGs) in ESCC tissues. Then, we used the database for Annotation, Visualization, and Integrated Discovery (DAVID) to perform the Gene Ontology function (GO) and KEGG Orthology-Based Annotation System (KOBAS) to perform Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. The 6 core candidate genes were identified using protein–protein interaction (PPI) network analysis and Cytoscape software with MCODE plug-in. Among them, the expression of KIF4A were validated by UALCAN database from the Cancer Genome Atlas (TCGA)($P<0.05$). Western blotting, qRT-PCR and IHC were used to detect the expression of KIF4A in tissues. Cell experiments (transwell migration assays, wound healing assay, CCK8 assay, clone formation experiment) were utilized to verify the roles of KIF4A on the ESCC cells. Western blotting was used to explore the mechanism of KIF4A in ESCC.

Results: The expression level of both mRNA and protein of KIF4A were upregulated in ESCC samples compared to those in paracancerous normal tissues. Transwell migration, wound healing assay showed overexpression of KIF4A significantly promoted the migration of ESCC cells. CCK8 assay analysis showed that overexpression of KIF4A promoted proliferation of ESCC cells. Western blotting detection found that KIF4A could affect the phosphorylation level of Hippo signaling pathway related proteins.

Conclusion: In summary, KIF4A promotes ESCC cell proliferation and migration by regulating the biological function of ESCC cells through the Hippo signaling pathway. These experimental results further explain the role of KIF4A in ESCC, and provide a new biomolecular target for the treatment of ESCC.

358. Study on the activity of glutamine cyclase inhibitor luteolin

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Abstract: Luteolin, a natural plant flavonoid compound, exists in many kinds of vegetables, fruits and herbs in the form of glycosides. Similar to many other flavonoids, luteolin has anti-oxidation, anti-tumor, anti-inflammatory, cardiovascular protection, immune regulation and other pharmacological properties, especially its anti-tumor effect has gradually attracted people's attention. However, past research only focused on its inhibition of tumor cell proliferation and induction of apoptosis, and little is known about the relationship between luteolin and tumor immunity. Cancer cells can evade immune surveillance by expressing inhibitory ligands, which inhibit ligand binding to homologous receptors on immune effector cells. The cell surface expression of CD47 protein generates a "don't eat me" signal on tumor cells by binding to SIRPα expressed on myeloid cells. Glutamine cyclase-like protein (QPCTL) is the main component of the CD47-SIRPα checkpoint. Soon after biosynthesis, glutamine cyclase is essential for the formation of pyroglutamate at the SIRPα binding site on CD47. After multiple rounds of cytometry screening and enzyme activity detection, we determined here that luteolin enhances the antibody-dependent phagocytosis and cytotoxicity of tumor cells through pharmacological interference with glutamine cyclase activity. These data indicate that luteolin is a new natural small molecule inhibitor that interferes with the CD47 pathway through glutamine cyclase, thereby increasing the possibility of luteolin therapy as a new anti-cancer therapy.

359. Prognostic Value of the Glasgow Prognostic Score on Overall Survival in Patients with Advanced Non-Small Cell Lung Cancer

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BACKGROUND: Findings from previous studies regarding the relationship between Glasgow Prognostic Score (GPS) and overall survival of advanced non-small cell lung cancer (NSCLC) patients was limited. This study set out to investigate the prognostic value of GPS in advanced NSCLC patients after adjusting for potential confounding factors.

METHODS: A retrospective cohort study was conducted in a total of 494 patients with advanced NSCLC between 2009 to 2019. Clinicopathological characteristics (including GPS) were analyzed to determine predictors of overall survival (OS) using univariate and multivariate Cox proportional hazards models. Survival curves were estimated using the Kaplan-Meier method.

RESULTS: Of the enrolled patients with advanced NSCLC, 66.46% were male, 53.85% were age < 60 years. The percentage of GPS of 0, 1, 2 was 36.44%, 36.03%, 27.53%, respectively. The median

OS of GPS 0, 1, 2 group were 23.27, 14.37 and 10.27 months, respectively (Log-rank P <0.0001). Higher GPS was independently associated with the increased risk of death (P for trend = 0.0004) after full adjustment for potential confounders. The risk of death increased by 77% in GPS of 1 (HR= 1.77, 95% CI= 1.22-2.57, P=0.0027), 109% in GPS of 2 (HR=2.09, 95%CI=1.36-3.22, P=0.0008) compared to GPS of 0 after adjustment. We did not find significant heterogeneity among the analyzed subgroups apart from sex (P interaction=0.017).

CONCLUSION: Pretreatment high GPS is independently associated with decreased overall survival of advanced NSCLC patients. GPS should be considered in patient counseling and decision-making and need to be further validated by large-cohort and perspective studies.

360. 基于 TCGA 数据库分析分化型甲状腺癌免疫相关指标的临床意义

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目的：探索基于 TCGA 数据库计算免疫相关指标在分化型甲状腺癌中的临床意义。

方法：TCGA 数据库（The Cancer Genome Atlas Database）中下载 506 例分化型甲状腺癌 mRNA 的表达数据及患者临床数据。通过 R 软件的 ESTIMATE 数据包计算每位患者的 ESTIMATE 评分（ESTIMATEScore，ES）、肿瘤浸润免疫细胞评分（ImmuneScore，IS）及基质细胞评分（StromalScore，SS）。利用方差分析肿瘤大小（TMN 分期中 T1 和 T2）与免疫评分的关系。将 IS 及 SS 以中位值均分为高低 2 组，利用 limma 数据包对评分的高低组 mRNA 表达数据进行差异表达分析。然后，对差异表达基因取交集后，进行 GO 富集和 KEGG 通路分析。对差异表达基因利用 Kaplan-Meier 法绘制生存曲线。

结果：T1 期肿瘤比 T2 期肿瘤的 ES、IS 及 SS 均显著升高（分别为，P=0.004，P=0.021 和 P=0.001）。以|LogFC|＞1，FDR＜0.05 为阈值，获取 IS 表达上调基因 914 个，表达下调基因 73 个；获取 SS 表达上调基因 954 个，表达下调基因 315 个；共同上调基因 789 个；共同下调基因 65 个。GO 功能分析发现共同差异表达基因富集于 T 细胞活化与调节、淋巴细胞迁移、细胞间粘附的正向调控等生物学过程。KEGG 通路分析发现共同的差异表达基因富集于细胞因子相互作用、趋化因子信号通路及粘附分子等通路。共同差异表达的基因中 28 个表达水平与预后相关（P＜0.05）。蛋白质互相作用（STRING 数据库）分析发现共同上调的 GZMK、XCL2、IL2RB、TBX21、PRF1、GZMM 基因编码的蛋白质相互作用密切。共同下调基因编码的蛋白未发现密切的相互作用关系。

讨论：SS 和 IS 预测肿瘤样本中浸润基质和免疫细胞的水平，从而构成推断肿瘤纯度的 ES 的基础。T1 比 T2 的 ES、IS 及 SS 均显著升高，提示 2~4cm 的肿瘤中肿瘤纯度增加，可能不利于免疫系统控制肿瘤，为积极外科干预提供证据。该评分代表肿瘤免疫微环境的一个方面，尚需联合其他细胞指标优化算法。我们差异基因分析发现 28 个与预后相关的基因，可能成为预测 DTC 预后的指标。先前的研究发现 30 个与肿瘤微环境相关的基因，其中 CXCL10 被认为核心基因，上述基因需进一步实验验证其表达情况及功能。

361. 液体活检肿瘤标志物对肝癌诊断价值的网状 Meta 分析

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摘要:背景：肝癌是目前世界上发病率和死亡率较高的恶性消化道肿瘤之一。 2018 年，世界卫生组织发布的全球范围内恶性肿瘤的流行状况显示肝癌的新发病例数在所有恶性肿瘤中排名第六，死亡人数排名第四，因此针对防治肝癌是一项非常重要的公共卫生政策。在肝癌的二级预防中，提高肝癌的早期诊断能力是至关重要的。虽然现在已发现了许多新的标志物，并且它们已经进行了相关的研究，然而在众多的研究中，我们并未明确哪种肿瘤标志物对肝癌的诊断效能更高，更具有潜在的研究价值。而我们本次研究的目的在于尝试运用网状 meta 分析的方法来评价液体活检的肿瘤标志物诊断肝癌的能力。方法：我们在 PubMed、Cochrane 图书馆、EMBASE 和 Web of Science 数据库中查找与 microRNA、lncRNA、circular RNA 对肝癌诊断有关的研究，时间截止为 2020 年 7 月 14 日，共发现 3001 篇研究，最后符合纳入排出标准的研究共纳入 63 篇，随后通过双人录入的形式来提取数据并 QUADAS 量表来评估文献质量。我们使用 STATA15.1 软件中的 mvmeta 和 network 程序进行了分析，验证了网状 meta 分析的同质性、相似性和一致性假设；对于诊断结局变量，效应大小采用比值比（OR）估算；最终通过累积排序图来得出排序结果。结果：通过 Q 检验我们进行了同质性的分析，并选择了各自相应的模型进行拟合；选用的研究人群纳入的是临床确诊患有肝细胞癌的病人和健康对照（P），采取的干预措施指诊断方法分别有 circular RNA、LncRNA、microRNA 三种（I），并且都以临床病理结果作为比较的金标准（C），结局变量分为两类，包括病人和健康者（O），保证了研究的相似性；随后又采用了 3 种不一致性分析的方法进行分析，发现我们的研究并不存在不一致性；在本研究满足网状 meta 分析三个假设的前提下，以健康人群为对照，我们制作了证据网络图、研究贡献图、一致性分析图、预测区间图以及累积排序图和发表偏倚图。然而，在我们的研究结果中并未发现三种标志物对肝癌的诊断效能存在明显差异，但累积排序结果显示出了 circular RNA＞long no-code RNA＞microRNA 这种趋势。结论：虽然基

于目前的研究并未得出较明确的结果，但 circular RNA 很有可能成为潜在的最优标志物，但是我们还需要更多的符合标准的研究来证实这个结果。

362. YTHDF2 介导 m6A 去甲基化酶 ALKBH5 表观沉默 PLXNB1 促进胶质母细胞瘤侵袭与复发的分子机制研究

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目的：胶质母细胞瘤向周围浸润性生长，手术无法根除，极易复发，且机制不明，因此寻找调控胶质母细胞瘤侵袭与复发的关键分子已成为亟待解决的难题。本研究旨在明确 m^6A 去甲基化转移酶 ALKBH5 参与胶质母细胞瘤侵袭与复发过程，并探讨 m^6A 识别蛋白 YTHDF2 介导 ALKBH5 调控 PLXNB1 表达在胶质母细胞瘤侵袭与复发中的作用及潜在分子机制。

方法：通过公共数据库挖掘及生信分析筛选出在复发胶质瘤中差异高表达 m^6A 修饰酶 ALKBH5，同时利用 m6A-MeRIP-seq 及 mRNA-seq 高通量测序数据进行生信分析筛选出 ALKBH5 下游靶基因 PLXNB1；应用平板克隆实验、Transwell 与划痕实验检测沉默 ALKBH5 后胶质瘤细胞的增殖与侵袭迁移能力的变化情况；采用 Pulldown、RIP、MeRIP-PCR 等技术验证 ALKBH5 与 PLXNB1 的 RNA 结合情况及沉默 ALKBH5 后 PLXNB1 的 m6A 修饰水平变化；应用 CHIP 与 MeRIP 技术分析 m6A 识别蛋白 YTHDF2 与 PLXNB1 的 m6A 修饰区域结合情况；应用原位成瘤动物模型及临床数据库验证 YTHDF2 介导 m6A 去甲基化酶 ALKBH5 调控 PLXNB1 的表达促进胶质母细胞瘤侵袭与复发。

结果：平板克隆、Transwell 及划痕实验结果显示沉默 ALKBH5 显著抑制胶质瘤细胞的增殖与侵袭迁移，进一步功能回复实验证实 ALKBH5 调控 PLXNB1 参与胶质瘤的增殖与侵袭迁移；Pulldown 与 RIP 实验证实 ALKBH5 与 PLXNB1 的 RNA 相互结合，同时 MeRIP 结果表明 ALKBH5 催化 PLXNB1 的 m6A 去甲基化修饰；RIP 实验证实 YTHDF2 与 PLXNB1 的 pre-mRNA 结合；敲低\过表达 YTHDF2 可相应的增加或降低 PLXNB1 的 m^6A 修饰水平，同时沉默 ALKBH5 可显著降低 YTHDF2 与 PLXNB1 的 pre-mRNA 结合量。

结论：本研究证实 m^6A 去甲基化转移酶 ALKBH5 调控 PLXNB1 参与胶质母细胞瘤增殖与侵袭迁移，m^6A 识别蛋白 YTHDF2 结合 ALKBH5 催化的 PLXNB1 m^6A 去甲基化修饰，介导 ALKBH5 表观沉默 PLXNB1 促进胶质母细胞瘤的侵袭与复发。

363. Long noncoding RNADANCR contributes to pancreatic cancer progression by sponging miR-125b-5p

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Long noncoding RNAs differentiation antagonizing non-protein coding RNA (DANCR)has been involved in tumorigenesis of several human cancers, but its precise biological role in pancreatic adenocarcinoma(PC) remains largely unclear. Here, we found that DANCR was increased in PC tissues and PC patients with high DANCR expression had a shorter overall survival time. Furthermore, loss-of-function and gain-of-function were performed to explore the function of DANCR in the progression of PC. Mechanistically, miR-125b-5p can bind to DANCR and decrease its oncogenic effect, and ectopic expression of miR-125b-5p reversed the effects of DANCR-induced cell proliferation and invasion. Taken together, our findings indicated that DANCR promoted the malignant properties of PC by sponging miR-125b-5p.

364. A Recurrent Ovarian Cancer Patient Tested Negative for All Immune biomarkers Responded to Pembrolizumab Monotherapy：A Case Report

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Ovarian cancer has the highest mortality rate among all gynecological malignant tumors. There is currently no standard treatment for refractory and recurrent ovarian cancer.The development of targeted and immune drugs has opened up many options for the treatment of ovarian cancer.The objective response rate of monotherapy with immune checkpoint inhibitors for ovarian cancer is not satisfactory even in PD-L1-positive patients, Therefore PD-L1 alone is not sufficient for patient selection for anti-PD-1 / PD-L1 therapy.In this case, a recurrent ovarian cancer patient tested negative for all immune biomarkers responded to pembrolizumab monotherapy for 8.7 months and responded again after local artery perfusion of pembrolizumab. Multiple fluorescence immunohistochemistry indicated that her tumor tissue was significantly infiltrated with CD8+T cells and NK cells, which could be a potential explanation for the benefit of immunotherapy.

365. 结肠腺癌微环境中免疫细胞浸润模式及其预后评估

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摘要：

背景和目的 结直肠癌（CRC）是主要的致死性肿瘤之一，其中结肠腺癌（COAD）是结直肠癌中最常见的类型。目前，免疫疗法已被临床验证为许多肿瘤有效治疗的选择。肿瘤浸润免疫细胞作为肿瘤免疫微环境中的主要成分，其与 COAD 患者预后之间的关联尚未明确。本研究旨在探索 COAD 微环境中免疫细胞的浸润模式及其预后价值，为临床个体化治疗提供新方向。

方法 通过 CIBERSORT 软件包从癌症基因组图谱（TCGA）数据库筛选 17 例正常结肠组织样本及 277 例 COAD 患者癌组织样本，利用标准化后的基因表达谱数据对 22 种浸润免疫细胞进行提取和量化，描绘并分析免疫细胞在正常组织和癌组织中的浸润模式和表达差异。运用多因素 COX 回归构建 Nomogram 风险预测模型。

结果 本研究发现活化的 $CD4^+$记忆性 T 细胞、M0 巨噬细胞、活化的肥大细胞在结肠腺癌组织中浸润显著增多。随着肿瘤的转移，M1 型巨噬细胞、活化的 $CD4^+$记忆性 T 细胞及滤泡辅助性 T 细胞在结肠腺癌微环境中的浸润量均显著减少（$p<0.05$），而活化的肥大细胞水平显著增多（$p=0.025$)。此外，未活化的 NK 细胞、活化的 $CD4^+$记忆性 T 细胞、滤泡辅助性 T 细胞的浸润量随着疾病的恶化而整体呈减少趋势（$p<0.05$），且滤泡辅助性 T 细胞减少还伴随着淋巴结播散的恶化（$p=0.002$）。利用患者年龄、性别、临床病理分期、TNM 分期、组间分析具有差异的免疫细胞构建 Nomogram 风险预测模型，模型预测 1 年、3 年和 5 年生存率的 ROC 曲线 AUC 分别为 0.828、0.794 和 0.754。将 COAD 患者按照风险评分分为高低风险组并进行 Kaplan-Meier 分析，结果显示高风险组 COAD 患者预后较差（$p<0.001$）。同时，基于高低风险组的基因集富集分析（GSEA）提示 COAD 患者预后与氨基酸代谢通路密切相关。

结论 肿瘤浸润免疫细胞中的幼稚 B 细胞、浆细胞、活化的 CD4 记忆性 T 细胞、单核细胞、M0 巨噬细胞、未活化的肥大细胞及活化的肥大细胞在 COAD 患者疾病进展中具有重要作用，预后模型为 COAD 患者的生存评估提供了理论和数据支持。

关键词：结肠腺癌；免疫细胞； Nomogram

366. Hyperprogressive Disease caused by PD-1 inhibitors for the treatment of various malignant tumors

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Abstract

Objective Nowadays PD-1/PD-L1 inhibitors are widely used to treat various malignant tumors and the treatment has achieved good results. However, during the immunotherapy in a few patients, a flare-up of tumor growth occurred. This new pattern of progression is called Hyperprogressive Disease (HPD). The purpose of this study was to describe the incidence of HPD of pan-cancer when using PD-1 inhibitors, and to explore their possible related factors and predictive markers. **Methods** The retrospective study of single center included 377 patients with malignant tumors treated with PD-1 inhibitors (Nivolumab/Pembrolizumab) in the Chinese PLA General Hospital from January 2015 to January 2019. The evaluation of tumors was based on Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Tumor growth rate (TGR) was calculated before and during treatment. HPD was defined as TGR difference exceeding 50% between the first assessment within 6-8 weeks after the immunotherapy and previous treatment. **Results** In 38 (10.08%) of 377 patients, HPD occurred after treatment with PD-1 inhibitors. Including 14 with lung cancer, 7 with pancreatic cancer, 2 with esophageal cancer, 5 with colorectal cancer, 3 with cholangiocarcinoma, 2 with liver cancer, 1 with lymphoma,1 with ampullary carcinoma, 1 with cervical carcinoma and 2 with gastric cancer. Factors related to HPD include more than 2 metastatic sites before immunotherapy (68.4% [26 of 38] vs 22.4% [76 of 339]; $P<0.01$), ECOG performance status≥2 (13.2% vs 3.5%; $P=0.02$), hepatic metastases (73.7% vs 28.9%; $P<0.01$) and lactate dehydrogenase level greater than normal upper limit (52.6% vs 34.5%; $P=0.03$). KRAS status was counted only in patients with non-small cell lung cancer and colorectal cancer，and its result was statistically significant in patients with colorectal cancer (80.0% [4 of 5] vs 23.5% [4 of 17]; $P=0.04$). Before radiological evaluation, the best diagnosis of HPD was achieved when characteristic tumor markers (such as CEA in colorectal cancer, AFP in liver cancer, etc.) increased by 31.48% (efficacy,74.2%; sensitivity,83.3%) within 1 month after treatment with PD-1 / PD-L1 inhibitors. **Conclusion** HPD was related to some clinicopathological features. including the number of metastatic sites, ECOG performance status, hepatic metastases and lactate dehydrogenase level, etc. The tumor markers rising above a certain range within one month after immunotherapy might indicate the occurrence of HPD. Close clinical observation is required to decide the next treatment with discretion.

Keywords: HPD, immunotherapy, PD-1 inhibitors, TGR

367.姜黄素通过调控 miR-21 抑制乳腺癌细胞 MCF-7 增殖促进细胞凋亡机制研究

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摘要：目的 研究姜黄素通过调控 miR-21 对乳腺癌细胞 MCF-7 细胞增殖的抑制作用及其机制。方法 将体外培养的 MCF-7 细胞分为对照组、不同浓度姜黄素实验组(1、5、10、20、40μmol/L)，实时荧光定量 PCR (qRT-PCR)检测对照组及实验组 MCF-7 细胞 miR-21 表达情况；MTT 比色法测定 MCF-7 细胞增殖程度；Transwell 法观察 MCF-7 细胞迁移能力；Caspase-3 活性检测 MCF-7 细胞凋亡。结果 qRT-PCR 结果显示姜黄素可调控 MCF-7 细胞 miR-21 呈现低表达水平；不同浓度的姜黄素能抑制 MCF-7 细胞增殖并促进其凋亡；随着姜黄素浓度递增，Caspase-3 的表达增加呈剂量依赖性(P＜0.01)。结论 姜黄素通过下调 miR-21 的表达，抑制乳腺癌细胞 MCF-7 细胞增殖,并促进其凋亡。

关键词：姜黄素；miR-21；MCF-7；细胞增殖；细胞凋亡

368.基于生物信息学分析探讨 CD59 在肺癌中的表达及其临床意义

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肺癌是发病率和死亡率较高的恶性肿瘤，临床上肺癌早诊水平低，急需筛选高灵敏度高特异性的肿瘤标志物用于肺癌早诊，以提高患者生存率。早期肺癌患者肿瘤自身分泌的抗体进入血液或肿瘤发生阶段引起血液中免疫相关的分子变化，可作为早期肺癌筛查标记物。前期我们采集自华中科技大学同济医院的早期 NSCLC 患者和健康志愿者外周血液样本，在无菌环境下采集的血浆用红细胞裂解液裂解，分离得到白细胞送至华大基因进行转录组测序。用 HiseqTM 2000 平台（Illumina）进行双末端测序，测序后的 RNA-seq reads 数目用 TopHat 与人的基因组进行比对，再用 Cufflinks 软件分析差异表达的基因。转录组数据分析发现免疫分子 CD59 在早期肺癌患者外周血白细胞中表达下调。本研究利用 Oncomine、GEPIA、COMSIC、cBioportal 和 Kaplan-Meier 等数据库分析了 CD59 在肺癌中的表达及其与患者生存期的关系。结果表明，CD59 在肺鳞癌中表达显著下降，在肺腺癌中有降低趋势，DNA 频率改变则可能是其表达下降的原因之一。蛋白相互作用网络分析发现，CD55、C9、CD47、ITGAM 和 CEACAM8 等蛋白与 CD59 具有明显相互作用，其中大部分蛋白参与免疫反应或与细胞粘附作用有关。CD59 表

达与肺癌患者生存期相关，CD59 低表达的肺癌患者生存期更短。本研究为肺癌发生、诊断及预后监控提供参考。

369. PAQR4 Regulated Chemoresistance in Non-Small Cell Lung Cancer through Mediating Nrf2 Protein Ubiquitination and Stability

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Lung cancer is the predominant cause of cancer related deaths. Within the main types of lung cancers, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), NSCLC accounts for approximately 85% of all lung cancer, with a poor 5-year survival of only ~15%.Despite the huge advances in treatment options, prognosis remains poor because of the presence of locally advanced metastatic tumors in most patients at the time of diagnosis. We recently reported that PAQR4 promotes chemoresistance in non-small cell lung cancer through inhibiting Nrf2 protein degradation, providing new paths for developing PAQR4 as a biomarker and therapeutic target for non-small cell lung cancer treatment.The previous studies identified many differentially expressed genes (DEGs) from large scale pan-cancer dataset using the Cross-Value Association Analysis (CVAA) method. The authors provided evidence showing that PAQR4 is increased in NSCLC patients and cancer cell lines, and identified many mutations in PAQR4 in non-small cell lung cancer (NSCLC) tissues. We demonstrated that PAQR4 high expression correlates with a worse clinical outcome, and that its knockdown suppresses cell proliferation by inducing apoptosis. Importantly, overexpressed PAQR4 physically interacts with Nrf2, blocking the interaction between Nrf2 and Keap1. Nrf2 is stably expressed and accumulated in the nucleus, which activates a series of antioxidant stress and resistance-related genes. This study found a new mechanism to regulate the ubiquitination and protein stability of transcription factor Nrf2, suggesting that screening for lead compounds that specifically inhibit PAQR4 function in combination with chemotherapy drugs in the future can achieve better clinical efficacy.

370. The role of TSHR D727E polymorphism in nodular goiter and differentiated thyroid cancer depends on TSH status

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TSHRis one of the important candidate genes in the pathogenesis of thyroid diseases. To investigate TSHRD727E polymorphism, 17 nodular goiter (NG) patients and 20 differentiated thyroid cancer (DTC) patients under low TSH levels were enrolled. 10 patients respectively diagnosed as NG and DTC with normal TSH levels were selected as controls. DNA was extracted from 57 tissue samples for TSHRexome sequencing.Results demonstrated that TSHRD727E GC+GG genotype was similarly distributed in NG (37.0%) and DTC (33.3%). Subgroup analysis revealed that the incidence of GC+GG genotype (52.9%) of NG patients in low TSH state was significantly higher than normal TSH subgroup (10%) (p=0.042). This phenomenon had not been found in DTC patients (35% vs 30%, p=1). For NG, the GC+GG genotype exhibited a trend of greater median age (61 vs 48 years, p=0.083) and smaller median lesions size (2.45 vs 3.00 cm, p=0.241) than CC type, andthis trend only appeared in the low TSH subgroup. In DTC patients, the GC genotype displayed the same trend regarding age (42.5 vs 36.5 years, p=0.373) and tumor size (0.75 vs 0.95 cm, p=0.530). GC-type DTC patients in the low TSH subgroup also disclosed less infiltration rate (0/7 vs 3/13, p=0.168) and less lymph node metastasis rate (1/6 vs 6/12, p= 0.171), though no statistical difference. Moreover, GC genotype presented a dominant position among female DTC patients (9/19), instead of male (1/11) (p=0.032), which was contrast to NG patients (5/20 vs 5/7, p=0.029). TSHRD727E GC+GG genotype may be relevant to the occurrence of NG under low TSH, however there was no obvious correlation in DTC. In the low TSH state, the GC+GG genotype had a protective effect on the progression of NG and DTC. GC+GG genotypes had different occurrences of NG and DTC in different genders.

371. FABP5 调控 YAP1 表达促进胃癌进展的研究

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目的 探讨脂肪酸结合蛋白 5（FABP5）调控 YAP1 表达在胃癌进展中的作用及其相关机制 **方法** 通过胃癌组织芯片的免疫组化法检测 FABP5 的表达，采用小干扰 RNA(small interfering RNA,siRNA)技术在胃癌细胞系 AGS、MGC803 中干扰 FABP5 表达，用 CCK-8 检测细胞活性、Edu 检测细胞增殖、采用膜联蛋白 V(Annexin V)/碘化丙啶(PI)双染,流式细胞仪检测细胞凋亡情况；在 AGS 细胞系中过表达 FABP5，CCK-8 检测细胞活性；裸鼠成瘤实验观察 FABP5 对细胞成瘤能力影响；转录组测序结合生物信息学分析 FABP5 影响的信号通路，通过 RT-PCR、Western Blot 检测 YAP1 等 RNA 或蛋白表达情况； PPI 数据库寻找 FABP5 相结合蛋

白，JASPAR 数据库预测转录因子与 YAP1 启动子结合；免疫荧光显示 FABP5 与 RXRa 表达情况，细胞免疫共沉淀探索 FABP5 与 RXRa 结合情况。 **结果** 低分化胃癌组织相对于中高分化胃癌组织，高表达 FABP5 （$\chi 2=8.44, P<0.01$），高表达 FABP5 患者预后较差（$\chi 2=61.610, P<0.01$）；干扰 FABP5 表达后，AGS、MGC803 细胞系增殖受到抑制（$P<0.05$），细胞凋亡增加（$P<0.05$）。裸鼠成瘤实验发现敲低 FABP5，细胞成瘤能力减低。转录组测序发现，干扰 FABP5 后 YAP1 表达下降，HIPPO 通路受抑制。免疫荧光显示 FABP5 与转录因子 RXRa 存在细胞核共定位，CO-IP 实验显示 FABP5 和 RXRa 存在内源性结合，干扰 RXRa 表达会导致 YAP1 蛋白表达下降。 **结论** FABP5 表达与胃癌分化程度及胃癌患者预后相关， FABP5 表达与胃癌细胞增殖、凋亡有重要关系,其机制可能是与转录因子 RXRa 结合，通过调控 YAP1 表达过程实现。

372. ORMDL1 is up-regulated and associated with favorable outcome in colorectal cancer

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Background: The mammalian ORMDL family gene (ORMDL1, 2 and 3, ~ 80% homology) are a set of small membrane-bound proteins of the endoplasmic reticulum, mediating feedback suppression of the de novo synthesis of sphingolipids by inhibiting a key enzyme serine palmitoyl transferase in response to high ceramide levels. The functionality of ORMDLs in disease context had been extensively focused on allergic airway disease like asthma. However, it has not been well studied in tumor-related context, especially for ORMDL1 gene. Furthermore, ORMDL1 was identified as a differentially expressed gene in one of our cohort studies related to metastatic colorectal cancer (CRC). Therefore, the expression and prognostic value of ORMDL1 in CRC remain to be explored.

Methods: TCGA CRC cohort mRNA expression date was downloaded; qRT-PCR, and immunohistochemistry (IHC) were used to examine the ORMDL1 mRNA and protein level in cohort from our center. The association between ORMDL1 expression and various clinical characteristics were analyzed by Chi-square tests. CRC patients' overall survival (OS) was analyzed by Kaplan-Meier analysis. In vitro and in vivo cell-based assays were performed to explore the role of ORMDL1 in cancer cell proliferation, invasion and migration. Transcriptional changes of cells either with ORMDL1 knockdowned or overexpressed were compared and analyzed. List of differentially expressed genes was subjected to GO, pathway enrichment analysis.

Results: ORMDL1 was upregulated in CRC tissues either in TCGA cohort (mRNA level) or in our cohort (both mRNA and protein level). In 41 cases with tissues of normal, peri-tumor, primary tumor and metastatic tumor all matched, metastatic tumor had the highest expression level of ORMDL1.

Interestingly, its expression level was significantly lower in patients with metastasis compared to patients without metastasis, and different distant organ metastasis groups expressed different levels of ORMDL1. Survival analysis showed that high ORMDL1 expression group had longer OS than low expression group in overall. For cancer cell-based assay, knockdown of ORMDL1 expression can promote proliferation, colony formation and invasion, but attenuate migration in CRC cell lines. In opposite, forced overexpression of ORMDL1 reduced cell proliferation, colony formation and invasion, while enhanced cell migration. Epithelial-to-mesenchymal transition (EMT) related genes were enriched among differentially expressed genes when ORMDL1 was knockdowned in cells, which was consistent with morphologic change by microscopy observation. Finally, stable knockdown of ORMDL1 can promote cancer cell proliferation in vivo in nude mice model to some extent.

Conclusion: For the first time we demonstrate the association of ORMDL1 expression and clinical characteristics of CRC. Although it was generally up-regulated in CRC, patients with different distant organ metastasis had different levels of ORMDL1, suggesting its potential role in regulating cancer cell metastasis specific to distant organs. Cell-based assays indicated that ORMDL1 plays multiple roles in CRC tumorigenesis and progression, yet the underlying mechanisms need to be dissected. Patients with heightened ORMDL1 expression had longer OS. Therefore, ORMDL1 expression is potentially to be a promising biomarker for favorable outcome.

373. Increased ERO1A expression relates poor patient survival and promotes lung cancer progression via EGFR/MET signaling

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Aim: lung cancer is one of the most incident cancers in the world, and the overall five-year survival rates of lung cancer is only 19%. While the mechanism of lung cancer metastasis is not clear. In this study, we explore the mechanism of lung cancer metastasis and uncover new biomarkers of lung cancer.

Methods: We firstly selected the potential lung cancer metastasis related genes through two data sets, RNA-seq of bone-lung metastasis model and gene expression array of 442 lung cancer tissues. ERO1A is one of the top genes by combining analysis of these two data sets. Next, functional studies such as colony formation, cell proliferation, migration and invasion were performed. Western blot, RT-qPCR, RNA-seq and IP were performed to explore the mechanism in lung cancer cells.

Result: The expression of ERO1A was increased in bone-lung metastasis cells as compared to original cells. In clinical data, ERO1A expression in tumor tissues is higher than that in normal tissues

and higher ERO1A expression patients had worse overall five-year survival. Colony formation ability and cell proliferation were decreased after ERO1A knock-down by siRNAs. Transwell experiments shows that silencing ERO1A reduced the cell migration and invasion ability of lung cancer cells. Western blot showed that the expression of MET and EGFR were decreased after ERO1A knock-down. Interestingly, ERO1A expression was up regulated in hypoxia condition, and MET and EGFR were up regulated too indicating that ERO1A may be related to lung cancer hypoxia adaptation.

Conclusion: ERO1A was significant increased in lung cancer and related to poor patient survival suggested that ERO1A could be used as a biomarker for lung cancer. ERO1A promoted cancer progression via MET and EGFR signaling indicating that ERO1A may be potential a drug target for lung cancer treatment.

Key words: Lung cancer, Metastasis, Proliferation, ERO1A, MET, EGFR

374. TTK1 involved in platinum-resistance of serious ovarian cancer by activating PI3K/AKT signaling pathway

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Objective: Cis-diamminedichloro-platinum (best known as cisplatin or CDDP), is a platinum compound widely used in various solid tumors including ovarian cancer. Drug resistance and recurrence, however, are significant contributors to the poor prognosis of serous ovarian cancer (SOC). Therefore, this study aimed to investigated the role of TTK1 in the CDDP resistance in ovarian cancer.

Methods: Platinum resistant ovarian cancer cell lines (A2780DDP) was constructed by increasing concentration gradient method. The related signaling pathways of TTK1 in CDDP-resistant ovarian cancer cells were analyzed by RNA-seq, and the expression of TTK1、PI3K、p-PI3K、AKT、p-AKT were detected by Western blot.

Results: We found that there was a significant increase in the expression of TTK1 in ovarian cisplatin-resistant cells, and Knockdown or inhibition of TTK1significantly affected biological phenotype of CDDP-resistant ovarian cancer cell, suggesting that TTK1 may be involved in platinum resistance in ovarian cancer. To explore the role of TTK1 in platinum resistance, we analysed the related signaling pathways of TTK1 in CDDP-resistant ovarian cancer cell by RNA-sequencing (RNA-seq).

Conclusion: We demonstrated that TTK1 was highly expressed and played a vital role in platinum-resistant ovarian cancer. Knockdown or inhibition of TTK1 expression significantly inhibited CDDP-resistant ovarian cancer cell proliferation, colony formation, and promoted cell apoptosis under CDDP

treatment. Moreover, we found that TTK1 involved in the progress of platinum-resistance by activating the PI3K/AKT signaling pathway in ovarian cancer. These findings are expected to inform new approaches for ovarian cancer treatment.

375. Identification of the key genes related to stemness of colon adenocarcinoma and T lymphocyte infiltration by WGCNA analysis

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Background

Colon adenocarcinoma (COAD) is one of the most common malignant tumors worldwide. The stemness of tumor tissue is closely associated with tumor pathological staging, medical treatment and patient's prognosis. Tumor with high stemness has the characteristics of cancer stem cells and leads to poor outcome of immunotherapy and chemotherapy. However, the genes and mechanism driving COAD to self-proliferation and regulating resistance of adaptive immune cell surveillance are still unknown.

Methods

The mRNAsi scores were used to quantify the stemness of COAD. Gene expression data of normal colon and COAD tissues were obtained from The Cancer Genome Atlas (TCGA) database. Different expressed genes(DEGs) between normal colon tissues and COAD were screened. The Weighted Gene Co-expression Network Analysis (WGCNA) was applied to classify DEGs and modules correlated with mRNAsi scores. Functional enrichment analysis was performed to annotate the genes from the key modules. The Real-time PCR (RT-PCR) was applied to validate the expression of key genes. The correlation between expression of key genes and drug sensitivity was analyzed in the CellMiner database. Then, docking site and docking energy between protein as receptor and compound as ligand was predicated by Autodock Vina and Pymol software. CIBERSORT algorithm were used to analyze the proportion of immune cells infiltrating in COAD microenvironment.

Results

The mRNAsi scores was significantly higher in COAD than that in normal colon tissues. In addition, the mRNAsi scores decreased as COAD progress to distant metastasis and lymphatic metastasis. Five genes in the gene set from WGCNA analysis, which had highest correlation coefficient with mRNAsi scores, was identified as key genes, including PLK4, TTK, CHEK1, KIF18A and BUB1. GO analysis revealed that the genes in the the gene set with the lowest correlation coefficient and the gene set with the highest correlation coefficient were enriched in mitotic division and cell cycle. In KEGG analysis result, the genes in the two modules mainly involved in cGMP−PKG signaling and cell cycle

pathway. The expression of PLK4 was positively correlated with drug sensitivity of Nelarabine and there was potential docking site of PLK4 with Nelarabine. The binding energy of PLK4 with Nelarabine is (−2.68 kcal/mol). After calculating the infiltration of immune cells in the immune microenvironment by CIBERSORT analysis, we found that the infiltration of activated memory CD4+ T cells was lower, while the Tregs was higher in COAD with high mRNAsi scores.

Conclusions

Five key genes were identified to be positively correlated with stemness of COAD, and Nelarabine might bound to,PLK4, which might be the potential drug for COAD. Moreover, the high stemness of the COAD is associated with the low infiltration of activated memory CD4+ T cells and the high infiltration

376. 血清自身抗体检测在多种肿瘤诊疗中的应用初探

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目的 探讨血清自身抗体在食管癌及乳腺癌诊疗中的应用价值。**方法** 70 例食管癌患者、70 例乳腺癌患者以及 100 例正常人对照被纳入本课题研究。运用酶联免疫吸附法（ELISA）分别对食管癌、乳腺癌及各组正常人对照的血清自身抗体进行定量检测，并对结果进行统计，分析其与临床病理参数的关系，再经二元 logistic 回归后筛选得到自身抗体组合的敏感度和特异性。**结果** 食管癌患者组、乳腺癌患者组的自身抗体检测结果与正常人对照组的检测结果均存在显著性差异。对 70 例食管癌和 50 例正常人对照进行自身抗体 Anti-P53、Anti-P62、Anti-c-Myc、Anti-HCCR、Anti-CyclinE、Anti-KOC、Anti-P16、Anti-P90、Anti-IMP1 的检测，结果筛选 Anti-P53、Anti-HCCR、Anti-KOC、Anti-P90 和 Anti-P16 进行组合；对 70 例乳腺癌和 50 例正常人对照进行自身抗体 A（P19012902）、抗体 D（P180603）、抗体 E（P16081502）、抗体 G（P180915）、抗体 H（P16080303）、抗体 I（P16111401）、抗体 K（P17121201）的检测，结果筛选自身抗体 A（P19012902）、抗体 D（P180603）、抗体 E（P16081502）、抗体 G（P180915）、抗体 I（P16111401）进行组合。食管癌患者组根据 ROC 曲线计算各血清自身抗体浓度的 CUTOFF 值，再经二元 logistic 回归后计算自身抗体组合的 OcScore 值得到总敏感度是 75.71%，总特异性 88.00%；乳腺癌患者组根据 ROC 曲线计算各血清自身抗体浓度的 CUTOFF 值，再经二元 logistic 回归后计算自身抗体组合的 OcScore 值得到总敏感度是 81.43%，总特异性 84.29%。**结论** 血清自身抗体的测定在食管癌及乳腺癌的诊疗中具有一定的应用价值，可作为早期诊断的辅助指标。自身抗体组的联合可有效提高早期诊断的特异性和灵敏度。

377.应用于肿瘤临床标志物挖掘的人类基因组调控区域数据库（HGR2DB）开发

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特征性表观遗传修饰可用以注释人类基因组非编码区中富含的转录调控元件如启动子、增强子等，有助于复杂疾病如癌症的发病机制及临床标志物研究，全基因组关联研究中获得的非编码区位点注释等。人类基因组测序计划完成后，随着高通量测序技术的迅猛发展，世界范围内开展了多项国际协作的人类基因组调控区域注释计划（如 ENCODE、ROADMAP 等），从而积累了大量与人类健康和疾病相关的功能基因组调控区域，特别是参考表观基因组的数据。

为有效统一收集于不同公共数据库中的人类基因组调控区域数据，使之可便利地应用于大规模肿瘤临床标志物研究，本研究首先制定了各大公共数据库中的信号数据、元数据、实验协议的格式标准，规范了分析软件参数设定和数据分析的标准流程，从而开发了人类基因组调控区域数据库（Human Genome Regulation Region Database，HGR^2DB）。HGR^2DB 基于 Apache/MySQL/PHP 后端，利用高性能计算集群资源管理、分析和整合来自不同公共数据库的数据，是一个平台型数据库。HGR^2DB 包含三个层次，即第一层的信号层数据，整合来自健康人群和不同疾病人群的多种组织、细胞类型的多种表观遗传修饰数据（包括 DNA 甲基化、组蛋白修饰、染色质可及性和非编码 RNA 表达调控等）；第二层的调控元件数据，整合来自 SCREEN 等调控元件数据库中收录的利用生物学先验知识和相关软件鉴定出人类基因组表观遗传调控元件信息；第三层为调控关系数据，运用 ChromHMM 和 Segway 等算法对基因组中调控元件与基因的调控关系进行预测，并合并已知数据库中的调控关系获得的全面调控关系数据。数据库提供了特定人类基因组调控区域的检索功能，可以根据关键字检索、筛选并导出包含组织类型、细胞类型、疾病类型、实验类型、信号类型、基因组版本、450k、850k 芯片位点、基因名、突变位点、转录调控元件、表观遗传修饰信号位置及量化数据等信息的 bed 文件。

作为数据库应用的一个示范案例，本研究中通过检索血液系统中功能基因组调控区域的甲基化亚硫酸盐测序数据，快速鉴定了与急性髓细胞白血病（AML）相关的 55 个甲基化区域。进一步，建立了这些区域与其靶基因的调控关系。这些区域的鉴定为进一步研究 AML 的发病机制及筛选潜在 AML 诊断及预后的标志物奠定了基础，验证了 HGR^2DB 数据库在肿瘤临床标志物应用方向的应用价值。

378. Identification of autoantibodies based on GEO database and construction of diagnostic model for esophageal squamous cell carcinoma

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Aim: Esophageal cancer (EC) is highly aggressive and one of the most common gastrointestinal cancers, especially in China. There is currently no specific blood test for detecting EC. Autoantibody against tumor associated antigens (TAAb) can exist stably in the serum of cancer patients, and have the potential to be biomarkers for early immunodiagnosis of cancers. The aim of the present study was to screen and verify TAAbs associated with esophageal squamous cell carcinoma (ESCC). **Methods:** Gene Expression Omnibus (GEO) database was adopted to screen potential TAAs from ESCC tissues. Differential gene analysis, KEGG analysis and GEPIA database were employed to attain candidate TAAs. Enzyme linked immunosorbent assay (ELISA) was used to explore the expression level of the corresponding autoantibodies in serum samples of 243 ESCC patients and 243 normal controls. A total of 486 serum samples were randomly divided into the train set and validation set according to the ratio of 2:1. ROC curve was employed to evaluate the diagnostic value of TAAbs, and the evaluation indexes included sensitivity, specificity, AUC and coincidence rate. Logistic regression analysis, recursive partition analysis (RPA) and support vector machine (SVM) were used to build diagnostic models. **Results:** Nine candidate TAAs (MSH6, COL4A1, SLC2A1, MMP9, CXCL8, MMP1, CKS2, LAMC2 and FN1) were screened out by bioinformatics methods. Among the 9 autoantibodies, the expression level of 5 autoantibodies (MSH6, CXCL8, MMP1, LAMC2 and SLC2A1) in the case group was higher than that in the control group($P<0.05$). In the train set, the AUC of the five autoantibodies ranged from 0.58 to 0.74, with the sensitivity ranging from 22% to 36%, and with the specificity ranging from 90% to 93%. In the validation set, the AUCs were distributed in the range of 0.60-0.74, and the sensitivities ranged from 12% to 27% when the specificity was greater than 90% and the Yoden index was the highest. In the constructed logistic regression model, decision tree model and support vector machine model, the AUCs in training set and validation set were 0.76(95%CI:0.71-0.81), 0.85(95%CI:0.85-0.89), 0.95 (95% CI: 0.92-0.97) and 0.75(95%CI:0.67-0.83), 0.71 (95%CI:0.63-0.79), 0.73(95%CI:0.66-0.81), respectively. Considering the diagnostic performance and stability of models, the optimal diagnosis model was logistic regression model consisting of 3 anti-TAA autoantibodies (MSH6, LAMC2 and MMP1). The AUC, sensitivity, specificity and accuracy of the model in the train set and the validation set were,66%,77%, 71% and 73%, 69%, 71%, respectively. the AUCs of diagnose early and advanced patients in the train set and validation set were

0.77, 0.71 and 0.86, 0.69, respectively. **Conclusions:** The model including 3 TAAbs was identified as potential diagnostic model for the immunodiagnosis of ESCC patients, especially for early patients.

Key words： autoantibody; detection; esophageal squamous cell carcinoma; GEO database

379. MYSM1, H2A deubiquitinase, affects the proliferation of Hs578T breast cancer cells

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Abstract

Objective: Epigenetics is bound up with the tumor, and post-translational modification of histones, especially. Breast cancer is one of the biggest causes of death among women, in which histone post-translational modification plays a significant role. In this study, we explored the function of MYSM1, a H2A deubiquitnase (DUB), in breast cancer.

Methods: The Cancer Genome Atlas (TCGA) datasets results analyzed by GEPIA Bioinformatics. The MYSM1 expression level of carcinoma and para-carcinoma was detected through The Cancer Genome Atlas (TCGA) datasets results analyzed by GEPIA Bioinformatics. The mRNA level of MYSM1 was also detected in 40 para-carcinoma and carcinoma tussue samples from surgical patients diagnosed as breast cancer at the Department of Breast Surgery, Fudan University Shanghai Cancer Center (Shanghai, China) during 2016. The over expressing and downregulating MYSM1 Hs578T cell lines were established. Protein and mRNA levels were tested by Western Blot and quantitative RT-PCR. Cell proliferation and colony formation assay were carry out to measure the proliferation ability. Cell cycle was detected by flow cytometry.

Results: According to the bioinformatio analysis and tissue mRNA levels, MYSM1 expressed lower in breast carcinoma. The MYSM1 overexpression cell line was established in Hs578T cell line. The growth curve of PCDH and OE groups showed a significant difference. The proliferation of MYSM1 overexpression cells was suppressed. Colony formation assay showed that MYSM1 overexpression decreased the colony numbers of breast cancer cells. Knocking down MYSM1 leaded to the opposite biological effects of MYSM1 overexpression cells, evidenced by accelerating growth potentials according to CCK8 assays. Consistently, flow cytometry revealed a change in cell cycle distribution. After knocking down MYSM1, the S phase increased, which leaned a cell cycle arrested at S phase. Furthermore, colony formation was performed. Fewer cell colonies of stably transduced shMYSM1-1 and shMYSM1-3 were formed than shCON groups'($P<0.01$)

Conclusions: The up-regulation of MYSM1 expression in Hs578T cells can slow down cell growth, while down-regulation of MYSM1 expression can accelerate cell proliferation and affect cell cycle

process. This biological effect of changing MYSM1 expression in breast cancer cell lines suggests that MYSM1 act a specific part in the occurrence and development of breast cancer and can be viewed as a candidate new therapeutic target for breast cancer.

380. 血清骨钙素的测定在肺癌骨转移评估中的应用价值

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目的 探讨血清骨钙素的测定在肺癌骨转移病人的诊断以及治疗评估中的应用价值。**方法** 283 例非小细胞肺癌患者、43 例小细胞肺癌患者和 90 例其它癌种患者纳入本次研究。患者分别依据是否发生骨转移分为未骨转移组和骨转移组，应用 ELISA 方法定量测定其血清骨钙素水平并比较差异。另将非小细胞肺癌患者分为鳞癌患者和腺癌患者，并依据性别、年龄、是否经过治疗以及是否发生远处转移等因素进一步分为若干亚组，对测定结果进行比较和分析，评估该因素对血清骨钙素测定结果的影响。**结果** 非小细胞肺癌患者骨转移组血清骨钙素水平高于未骨转移组，其他癌种患者骨转移组骨钙素水平高于未骨转移组，鳞癌和腺癌骨转移患者未经治疗组骨钙素水平高于经过治疗组，以上差异均有统计学意义（$P<0.05$）。**结论** 血清骨钙素的测定在肺癌骨转移评估中具有一定的应用价值，可作为骨转移诊断的可靠指标，该指标对未经治疗患者诊断的意义更显著。

381. 基于高通量转录组测序技术寻找多发性骨髓瘤诊断和预后评估的新靶点

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研究目的：基于高通量转录组测序结果筛选参与 MM 发生发展的关键基因，以获得可能用于 MM 诊断、治疗及预后判断的相关分子标志物。**研究方法：**对 23 例初诊高危、15 例初诊标危和 36 例复发的 MM 患者及 3 例正常人进行高通量基因表达谱分析。使用 R 语言 DESeq2 package 筛选差异基因。对 GSE13591 和 Zhan Myeloma 进行荟萃分析，对我们的差异基因结果进行验证。使用 DAVID 进行差异基因的功能富集分析。使用 STRING 和 Cytoscape 制作蛋白质互作网络（PPI）并用 MCC 算法筛选出 hub 基因，制作 ROC 曲线评估 hub 基因的诊断价值。使用 GSE2658、GSE4452 和 GSE9782 构建 Cox 风险比例回归模型，绘制 Kaplan-Meier 曲线来评估 hub 基因的预后价值。**研究结果：1.**初诊和正常人比较，根据|logFC|>=1 和 FDR<0.05 选出 1396 个 DEGs。生存分析显示 788 个基因与病人预后不良相关。对 GSE13591 和 Zhan Myeloma 进行荟萃分析，筛选出 477 个高表达与病人预后不良相关的基因。绘制 Venn 图找出

我们与公共数据交集的 39 个基因。功能富集显示其与蛋白酶体通路最相关。构建 PPI 并筛选出评分>100 的 hub 基因为 PSMB3、PSMD4、COPS6、PSMB7、PSMB4、VHL。制作 ROC 曲线评估这 6 个基因的诊断价值，p 值全部<0.05。**2.** 初诊高危与标危患者比较，筛出 1032 个 DEGs。DEGs 通路分析显示与 MAPK 信号通路、cAMP 信号通路等相关。270 个基因与病人预后不良相关,其中 84 个基因高表达与病人预后不良相关。构建 PPI 并筛选出前 10 位的 hub 基因为 EGFR、ITGA5、NTRK2、MYCN、ANXA1、COL5A1、MMP14、ABCB1、PTPRC、GHRHR。绘制 Kaplan-Meier 曲线，p 值全部<0.05。**3.** 初诊与复发患者比较，筛出 1462 个 DEGs，其在 1 号染色体上分布最多（9%）。DEGs 功能富集分析显示其与 PD-1 信号通路、T 细胞分化等免疫通路显著相关。其中 131 个基因高表达与病人预后不良相关。构建 PPI 并筛选出前 10 位的 hub 基因为 KIF23、KIF2C、NEK2、CASC5、CENPF、MKI67、ASPM、TRIP13、PLK1、TPX2。绘制 Kaplan-Meier 曲线，p 值全部<0.05。

382.肿瘤相关成纤维细胞 CAFs 与免疫浸润在乳腺癌中的研究

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乳腺癌是一种常见的恶性肿瘤，其患病人数呈逐年增高的趋势，发病率已居女性恶性肿瘤首位。随着人类对肿瘤研究的不断深入，越来越多的研究表明，恶性肿瘤的生物学行为不仅取决于肿瘤细胞本身，肿瘤微环境对肿瘤的发生发展也起着决定性的作用。肿瘤微环境由细胞外基质(extracellular matrix，ECM)和各种肿瘤间质细胞(包括成纤维细胞、免疫细胞等)组成。其中，肿瘤相关成纤维细胞(cancer-associated fibroblasts，CAFs)是最丰富的肿瘤间质细胞，研究表明，它可分泌多种成份，参与多种癌症的发生发展过程。CAFs 是肿瘤微环境最重要的细胞成份之一，它不仅参与微环境血管和淋巴管形成、细胞外基质重塑，而且促进乳腺癌的发生，癌细胞增殖、侵袭和转移，其标志分子也可作为乳腺癌临床诊断、靶向治疗和预后的生物标志。ACTA2（actin alpha 2）是一种肌动蛋白，包括主动脉平滑肌或 α 平滑肌肌动蛋白 (α-SMA)，α-SMA 是应用最广且发现最早的 CAFs 细胞表面标志物。基于癌症基因组图谱 TCGA 数据库中关于乳腺癌的样本数据进行生物信息学分析。通过将 ACTA2 的表达量分组做差异分析，可得到的 165 个差异基因。将差异基因进行基因本体（GO）和京都基因组百科全书（KEGG）富集分析并构建 PPI 蛋白互做网络图，接着通过 COX 分析找到预后相关的基因，将其和 PPI 中的基因取交集得到预后相关的核心基因进行单基因分析。根据单基因还可进行生存分析、差异分析、临床相关性分析、GSEA 分析以及免疫细胞浸润分析来找出乳腺癌中在肿

瘤相关成纤维细胞上潜在的靶点。还可根据差异基因的 fdr 值由大到小排序，取前 25 个基因进行验证，将表达量高且免疫细胞浸润相关性高的基因作为目标基因进行单基因分析，来了解 CAFs 通过哪些调控机制来影响乳腺癌的侵袭转移，为乳腺癌治疗提供新的靶点。

383. 应用生物学信息综合分析筛选三因乳腺癌的关键基因和通路

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三阴性乳腺癌（TNBC）是指雌激素受体(ER) 、孕激素受体(PR) 及人表皮生长因子受体 2(HER2) 都是阴性的乳腺癌亚型。三阴性乳腺癌具有高度异质性，也是目前乳腺癌治疗中最棘手的一种，死亡率最高、且最容易复发。三阴性乳腺癌对激素和靶向治疗都不敏感，治疗方法几乎只有化疗。随着人们对 TNBC 的研究，与 TNBC 相关的生物标志物层出不穷， 但这些生物标志物在临床上取得的进展是有限的。为了提高 TNBC 的预后，与 TNBC 发病机制相关的 特异性通路的新的靶向治疗的开发是未来研究的主要目标。基于 GEO 数据集中下载了 GSE76275 的基因表达谱。基因芯片超级系列集由 265 例样本的基因表达数据组成，其中包括 67 例非 TNBC 和 198 例 TNBC。其次，通过 R 语言操作包对样本进行免疫打分，分为基质评分，免疫评分，和总体评分，分别以打分中位数为准分为 HIGH、LOW 两组，识别出所有 p0.01、折叠改变≥1.5 或≤-1.5 的双向表达基因(DEGs)，然后取免疫细胞表达基因和基质细胞表达基因 Venn 集，以求寻找共同表达的标志性关键基因。对 56 个上调基因和 151 个下调基因进行了基因本体(GO)和京都基因组百科全书(KEGG)富集分析。然后对基因芯片整体的免疫浸润进行评估，再次验证交集基因是否差异表达并与预后、免疫、分期等有关。总之，所发现的这些途径和基因可能有助于理解 TNBC 的发生机制。此外，ACTA2、TAGLN、CNN1、AP000892.4、LMOD1、DKK3、MYLK、AP001107.5、FGF1、ACTA2-AS1、ACTG2 等关键基因和通路可能是 TNBC 治疗的有希望靶点。

384. 鼻咽癌早期诊断的相关分子标志物的研究进展

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鼻咽癌是我国常见的恶性肿瘤之一，在头颈部恶性肿瘤中占首位。鼻咽癌的发生发展过程在表型上和生理上具有细胞增殖信号的过度表达、生长抑制信号的不敏感、逃避凋亡、无限制的复制潜能、维持血管生成及组织侵袭和转移等六方面的能力。每个能力的获得不仅促进鼻咽癌的发生，而且都受到相关的信号传导通路的异常调节。通过研究发现，除了与鼻咽癌发生密切相

关的 EB 病毒基因和相关蛋白外，鼻咽癌相关凋亡基因 p53 与 MDM2 蛋白结合后发挥的负性调节作用，参与细胞周期停滞和细胞凋亡；同时，某些抑癌性 miRNA(miR-212)的异常低表达与促癌性 miRNA(miR-151)的异常高表达也与鼻咽癌的产生有明显的组织相关性，这都提示鼻咽癌发生发展以及转移的复杂性。除此之外，由于鼻咽癌发病部位隐蔽、鼻咽部组织构成复杂，治疗方式较单一、缺乏特异性治疗药物，且不同的鼻咽癌患者在病理类型，肿瘤分化程度对放化疗敏感性方面都存在着不同程度的差异，因此及时准确的早期诊断和个体化治疗对于提高患者的生存率和预后具有重要意义。这就提示我们寻找鼻咽癌早期诊断及预后相关的特异性分子标志物对实现鼻咽癌的早期诊断及个体化治疗具有深远意义。

385. 外泌体在乳腺癌中的现状及研究进展

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外泌体是一种由细胞主动分泌的纳米级的脂质囊泡，随着研究不断深入，外泌体在多种领域中被广泛提及，如心血管系统，内分泌代谢以及肿瘤治疗，其在肿瘤方面的研究最为广泛。在过去十多年的研究中，大量结果表明外泌体可影响乳腺癌发生发展过程中的相关信号通路，如成纤维细胞(CAFs）分泌的外泌体可通过 Wnt-细胞平面极性信号通路来促进肿瘤的侵袭转移。外泌体还能够在乳腺癌肿瘤微环境中起作用，与肿瘤的血管生成，细胞侵袭和转移密切相关。外泌体对于乳腺癌的诊断，治疗都有很大的潜在价值，可以作为乳腺癌诊断的分子标志物与治疗载体，现在已经发现部分外泌体可以通过多种机制调控来起到抑制肿瘤细胞增殖以及促进肿瘤细胞侵袭转移的作用，比如 miRNA-128 可以负向调控乳腺癌中细胞株 MCF-7，从而抑制了肿瘤的生长。外泌体与乳腺癌发生发展密切，其独特功能功能对于临床诊断和治疗乳腺癌有些很大的潜在价值。

386. 百里醌衍生物(TQ-19)调节乳腺癌治疗的机制探索

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【目的】

初步探讨百里醌（TQ）新型衍生物（TQ-19）对乳腺癌的作用及其调控机制。

【方法】

将乳腺癌细胞（4T1、231、BT549）和正常乳腺细胞 MCF-10A 按 1×10 ^4/孔，接种于 96 孔板予 0 μmol/L 、10 μmol/L、 20μmol/L、40 μmol/L、80μmol/L TQ-19 培养 24 h/48h，应用 CCK-8 法检测 TQ-19 对 22RV1 细胞的毒性作用程度；蛋白质印迹法（Western blot）检测：加 0

μmol/L、 2.5μmol/L、5 μmol/L、 10 μmol/L TQ-19 于乳腺癌细胞（468、231、4T1、BT549、T47D 、 Mcf-7 ） 孵 育 24h 后 测 P-AMPK-α 、 AMPK-α 、 Bad 、 Bcl-2 、 Bax 、 Bcl-xl 、Caspase3/7/8/9、cleaved caspase-3、p70 S6、P-p70 S6、P-mTOR、mTOR、CDK 等蛋白表达；细胞生长、迁移和侵袭实验：将乳腺癌细胞（4T1、231）悬液(4T1：1×10 ^4 个细胞/ml，231:4×10 ^4 个细胞/ml)分别接种于 16 孔 E-Plate 板中。用 CMI 平板进行细胞迁移和侵袭指数分析，下室填充趋化诱导剂(10%血清补充培养基)，上室填充无血清培养基悬浮的 100ul(4T1：1×10 ^3 个细胞,231：4×10 ^3 个细胞)细胞。细胞侵袭实验用稀释的基质凝胶(目录号354277,BD Biosciences, USA)涂布 CMI 平板的膜接种前用 1×PBS 缓冲液(1:40)。每 15min 检查细胞迁移和侵袭情况。细胞迁移和侵实验在实时细胞分析仪(xCELLigence RTCA DP, Roche，德国)中进行，所有分析均至少进行两次。

【结果】

TQ-19 呈浓度依赖性降低乳腺癌细胞（4T1、231、BT549）存活率，而对乳腺正常细胞 MCF-10A 影响较小。细胞生长、迁移和侵袭实验结果表明：TQ-19 能有效抑制乳腺癌细胞（4T1 和 231）的迁移和侵袭。Western blot 结果表明乳腺癌细胞（4T1、MCF-7）的 AMPK、P-AMPK、Pten 随着 TQ-19 浓度增加而增加；未见其他的蛋白随 TQ-19 浓度增加而改变。

【结论】

TQ 新型衍生物（TQ-19）in vitro 抑制乳腺癌的生长、迁移和侵袭。它可能是通过 AMPK/Pten 信号通路进行的。进一步的功能及调节机制有待深入研究。

387. 基于机器学习算法的结直肠癌肝转移关键基因预测

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目的：预测筛选结直肠癌肝转移的关键基因。**方法**：从基因表达数据库获取结直肠癌患者全转录组表达谱数据，采用差异表达分析、基因加权共表达网络（weighted gene co-expression network analysis，WGCNA）筛选核心基因集，采用基因本体学（Gene Ontology，GO）和京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes，KEGG）分析核心基因集功能富集情况，采用随机森林（ Random Forest，RF）模型筛选结直肠癌肝转移关键基因，随后在外部验证集中采用 ROC 分析验证关键基因的预测性能。最后采用人类蛋白图谱数据库（The Human Protein Atlas，HPA）验证关键基因在正常结直肠组织与结直肠癌组织中的蛋白表达模式。**结果**：经过数据筛选与预处理，获取原发性结直肠癌患者转录组表达谱数据共 235 条，结直肠癌肝转移患者转录组表达谱数据共 44 条，外部验证数据集共 457 条。差异表达分

析得到 862 个差异表达基因，WGCNA 分析得到两个显著性模块，与结直肠癌肝转移正相关系数最高的为青绿色模块，整合上述结果得到核心基因集，数量为 804 个基因。GO 分析显示核心基因集大多富集参与细胞增殖、血管生成、细胞基质黏附和 p53 类信号转导调控等生物学过程，并具有 RNA 绑定、组蛋白乙酰转移酶活性和转录因子活性激活等分子功能；KEGG 分析显示核心基因集大多富集在病毒性心肌炎、血管生成、细胞黏附分子、癌症中的转录失调和 ABC 转运蛋白等信号通路。选取四个不同种子利用 RF 算法进行训练，特征为 804 个基因，每次生成 50 颗树，训练集与测试集错误率均<0.05，整合变量重要性结果显示 GRIK1 为结直肠癌肝转移关键基因。外部数据集 ROC 分析显示 GRIK1 区别结直肠癌肝转移 AUC 值为 0.83。免疫组化结果显示，GRIK1 在正常结直肠癌组织中的阳性表达率显著高于结直肠癌组织，差异具有统计学意义。**结论：**结直肠癌肝转移与细胞增殖、血管生成、细胞黏附分子激活、转录失调和 ABC 转运蛋白等信号通路密切相关。进一步确定 GRIK1 为结直肠癌肝转移的关键基因，GRIK1 表达下调促进癌细胞的增殖、迁移、侵袭和上皮-间充质转化，GRIK1 不仅可作为结直肠癌患者肝转移的预警关键基因，还可以为结直肠癌肝转移患者的免疫疗法提供新的研究思路。

388. A novel nutritional risk score and prognosis of oral cancer patients: A prospective study

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Abstract

Objectives: To evaluate the prognostic performance of a novel nutritional risk score based on serum iron, hemoglobin, Body Mass Index (BMI) in oral cancer patients, and to predict the response to chemotherapy in patients with different nutritional status.

Methods: This prospective study, which included 671 patients, was conducted in Fujian, China. X-tile analysis was performed to determine the optimal cut-off values of serum iron, hemoglobin and BMI in predicting the prognosis of oral cancer. A nutritional risk score was established by using the HR values of serum iron, hemoglobin and BMI. Kaplan-Meier curve and multivariable Cox proportional

hazards models were used to evaluate the prognostic value of the nutritional risk score in overall survival (OS) and oral cancer specific survival (OCSS) in oral cancer.

Results: Serum iron, hemoglobin and BMI were all inversely related to the prognosis of oral cancer. The adjusted HR of serum iron, hemoglobin and BMI were 1.562(95% CI: 1.135-2.148), 1.886(95% CI: 1.225-2.904), 1.465(95% CI: 1.054-2.036) for OS, and the adjusted HR were 1.653(95% CI: 1.163-2.350), 1.865(95% CI: 1.183-2.942), 1.443(95% CI: 1.018-2.044) for OCSS. The established nutritional risk score was also found to be significantly associated with the prognosis of oral cancer. Patients with higher nutritional risk score (Quartile 4 vs Quartile 1) had a poorer OS (HR = 2.657, 95% CI: 1.488-4.742) and poorer OCSS (HR = 2.086, 95% CI: 1.221-3.563). Additionally, we observed that chemotherapy was only significantly associated with improved OCSS in oral cancer patients with the lowest nutritional risk score [HR=0.370, 95% CI: 0.183-0.749), but not in patients with higher nutritional risk score.

Conclusions: Nutritional risk score is of prognostic value in patients with oral cancer. Favorable response to chemotherapy may only be observed in well nourished oral cancer patients with lower nutritional risk score.

Keywords: Serum iron; Hemoglobin; Body Mass Index; Oral cancer; Prognosis

389. Expression and Prognostic Analysis of FEN1 in Hepatocellular Carcinoma and Lung Adenocarcinoma by Bioinformatics

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Background: Flap structure-specific endonuclease 1 (FEN1) is a member of XPG/RAD2 endonuclease family, which is one of ten essential proteins for cell free DNA replication. FEN1 differential expression and mutations were closely correlated with carcinogenesis and disease progression. In this study, we used bioinformatics analysis to investigate FEN1 expression level and explore its prognostic and diagnostic value of hepatocellular carcinoma and lung adenocarcinoma. **Materials and Methods:** Clinical data for patients, expression levels of FEN1 gene and protein expression data were extracted and analyzed from ONCOMINE, DriverDBv3, UALCAN and The Human Protein Atlas (HPA). The survival data of patients were analyzed by GEPIA and Kaplan-Meier Plotter. FEN1 related functional networks were found within the STRING. And Metascape was used to analyze Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathways (KEGG). The cBioPortal was used to explore the effect of FEN1 mutations for patients. **Results:** The expression levels of FEN1 were remarkably higher in hepatocellular carcinoma and lung adenocarcinoma than in normal tissues. FEN1 and its 20 related genes were significantly

enriched in several biological processes and pathways including cellular component organization or biogenesis, DNA repair, DNA strand elongation and DNA recombination. High expression of FEN1 is a potential diagnostic and prognostic biomarker. **Conclusion:** Knowledge of the expression levels of FEN1 gene could provide a sensitive strategy for predicting diagnosis and prognosis in hepatocellular carcinoma and lung adenocarcinoma.

390. Phylogenetic Tree Inference: A Top-Down Approach to Track Tumor Evolution

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Recently, an increasing number of studies sequence multiple biopsies of primary tumors, and even paired metastatic tumors to understand heterogeneity and the evolutionary trajectory of cancer progression. Although several algorithms are available to infer the phylogeny, most tools rely on accurate measurements of mutation allele frequencies from deep sequencing, which is often hard to achieve for clinical samples (especially FFPE samples). In this study, we present a novel and easy-to-use method, PTI (Phylogenetic Tree Inference), which use an iterative top-down approach to infer the phylogenetic tree structure of multiple tumor biopsies from same patient using just the presence or absence of somatic mutations without their allele frequencies. Therefore PTI can be used in a wide range of cases even when allele frequency data is not available. Comparison with existing state-of-the-art methods, such as LICHeE, Treeomics, and BAMSE, shows that PTI achieves similar or slightly better performance within a short run time. Moreover, this method is generally applicable to infer phylogeny for any other data sets (such as epigenetics) with a similar zero and one feature-by-sample matrix.

391. 基于主成分分析的膳食脂肪酸模式与口腔癌的关系研究

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目的 探讨膳食脂肪酸模式与口腔癌发病的关联。**方法** 采用病例对照的研究设计，收集 2013 年 11 月至 2019 年 3 月间福建医科大学附属第一医院口腔颌面外科确诊的 225 例口腔癌新发病例作为病例组，收集同期在同一家医院进行健康体检的人群以及就诊于其他科室的患者共 524 例作为对照组。通过面访式问卷调查收集研究对象的一般资料及膳食数据。采用秩和检验比较病例和对照组间的膳食脂肪酸摄入水平；采用主成分分析确定本地区居民的膳食脂肪酸模式；采

用非条件 Logistic 回归模型、分层分析等方法对膳食脂肪酸模式与口腔癌发病风险的关系进行探讨，并对膳食脂肪酸模式与相关因素如年龄、饮酒等进行相乘交互作用分析。**结果** 经总能量摄入量调整后，病例组的辛酸、癸酸、十一烷酸、月桂酸、肉豆蔻酸、十五烷酸、棕榈酸、十七烷酸、硬脂酸、花生酸、山萮酸、肉豆蔻油酸、棕榈油酸、油酸、十六碳二烯酸及花生四烯酸等膳食脂肪酸的每日摄入量均明显高于对照组(P<0.05)。主成分分析提取了共 6 种膳食脂肪酸模式，包括模式 1（以肉豆蔻酸、十五烷酸、棕榈酸、硬脂酸等长链饱和脂肪酸，肉豆蔻油酸、油酸、棕榈油酸等单不饱和脂肪酸以及花生四烯酸为主）、模式 2（主要包括辛酸、癸酸、十一烷酸、月桂酸等中链饱和脂肪酸以及部分十六碳二烯酸、EPA、DHA 等多不饱和脂肪酸）、模式 3（以十五碳烯酸、二十碳烯酸及亚油酸为主）、模式 4（主要包括的花生酸、二十二烷酸、十七碳烯酸、亚麻酸及二十二碳四烯酸）、模式 5（以十七烷酸、十九烷酸等奇数碳饱和脂肪酸以及二十二碳烯酸、二十碳二烯酸、二十二碳三烯酸及 DPA 等多不饱和脂肪酸为主）和模式 6（主要包括己酸、十三烷酸及二十碳三烯酸）。非条件 Logistic 回归分析结果显示，以人群中占比最大的模式 6 为参照组，模式 1 和模式 2 均可降低口腔癌的发病风险，其调整后的 OR 及其 95%CI 分别为 0.47（95%CI :0.25～0.86）、0.45（95%CI : 0.21～0.98）。进一步分层分析结果表明，模式 1 及模式 2 与口腔癌发病风险的关联在低年龄人群中更为显著，而在高年龄人群中仅发现模式 5 可增加口腔癌的发病风险。且模式 1、模式 2 及模式 5 和年龄均存在相乘交互作用。**结论** 相对于模式 6，模式 1 及模式 2 能降低口腔癌的发病风险，尤其在低年龄人群中模式 1 及模式 2 与口腔癌发病风险的关联更为显著，而模式 5 在高年龄人群中则可增加口腔癌的发病风险。

392. 中链饱和脂肪酸与口腔癌发病的关联性研究

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3.福建医科大学附属第一医院口腔颌面外科

目的 探讨膳食中链饱和脂肪酸与口腔癌发病的关联，为从膳食途径防治口腔癌提供参考依据。**方法** 采用病例对照的研究设计，以 2010 年 1 月至 2019 年 12 月福建医科大学附属第一医院口腔颌面外科经病理确诊的 225 例口腔癌患者作为病例组，以同期前往该医院的健康体检人群及其他科室的患者共 527 例为对照组。采用 χ^2检验对病例组及对照组的一般人口学特征进行均衡性检验；采用残差法及秩和检验，检验病例组及对照组中经能量校正后的膳食中链饱和脂肪酸含量分布是否存在差异；采用非条件 Logistic 回归计算各中链饱和脂肪酸和生活方式因素

与口腔癌发病风险的 OR 及其 95%CI；进一步根据吸烟、饮酒状况进行分层，分析各中链饱和脂肪酸与口腔癌发病风险的 OR 及其 95%CI，最后进行相乘交互作用分析。**结果** 均衡性检验结果显示，病例组与对照组在性别、居住地及肿瘤家族史等方面均衡可比（P>0.05）。采用残差法对各类中链饱和脂肪酸的每日摄入量进行总能量校正后，病例组的辛酸、癸酸、十一烷酸及月桂酸等中链饱和脂肪酸的每日摄入量均明显高于对照组，差异具有统计学意义（P<0.05）。多因素分析发现，总中链饱和脂肪酸高水平组患口腔癌的风险是低水平组的 3.19 倍(95%CI :2.17～4.69)；此外，高水平组的辛酸、癸酸、十一烷酸及月桂酸等均可显著增加口腔癌的发病风险，其调整后的 OR 及其 95%CI 分别为 2.54(95%CI :1.75～3.69)、2.56(95%CI :1.76～3.71)、5.00(95%CI :3.27～7.64)和 3.09(95%CI :2.10～4.54) 。分层分析发现，在不吸烟者中，辛酸和癸酸是口腔癌的危险因素，且无论是否饮酒，其均能增加口腔癌的发病风险；各亚组均发现高总中链饱和脂肪酸、十一烷酸及月桂酸摄入量与口腔癌发生风险呈正相关。此外，总中链饱和脂肪酸、辛酸、癸酸、十一烷酸及月桂酸每日摄入量均与饮酒之间存在相乘交互作用，其调整 OR (95%CI) 分别为 3.50(2.11～5.83)、2.74(1.65～4.55)、2.85(1.71～4.73)、2.00(1.23～3.25)及 3.09(1.87～5.11)。而吸烟仅与十一烷酸之间存在相乘交互作用，调整之后的 OR(95%CI)为 2.00(1.23～3.25)。**结论** 较高水平的膳食中链饱和脂肪酸可能会增加口腔癌的发病风险。

393. The prognostic value of three inflammation related biomarkers in patients with oral squamous cell carcinoma: a large-sample prospective study

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Objectives: The purpose of the present study was to evaluate the prognostic value of three systemic inflammation related indexs, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) in patients with oral cancer (OC). **Methods**: A total of 1149 patients newly diagnosed with primary oral cancer that was confirmed by histology were

enrolled in a prospective study. Descriptive statistics for patient demographics and clinical characteristics were analyzed by Chi-square test. PLR, NLR and SII were included in the study as binary variables by using the optimal cut-off value identified by X-tile analysis. Log rank test, univariate and multivariate Cox regression were performed to explore the prognostic value of these indicators. **Results**: During the follow-up, 329 (28.63%) deaths were identified. All patients' demographic and clinical characteristics, among them, the mean age was 58.92 years (range: 18-80 years, SD: 12.52 years), the ratio of females to males was 1:1.90 (396/753). More than half (53.23%) of the patients with oral cancer were well differentiated. The majority clinical stage of the patients (60.87%) was III-IV, and 65.24% (717) of the patients were with lymph node metastasis. The optimal cut-off value of PLR, NLR and SII identified by X-tile were 153.6, 1.9 and 672.8, respectively. Univariate analysis revealed that patients with higher PLR, NLR and SII level had worse overall survival. PLR, NLR and SII were inversely related to the prognosis of oral cancer patients, with a HR=1.383 (95%CI: 1.114-1.718), 1.678 (95%CI: 1.333-2.111) and 1.775 (95%CI: 1.428-2.208) respectively. Similar results were observed by Kaplan-Meier curve and log rank test (all P<0.003). Next, correlation analyses demonstrated that varied degrees of correlation were found among the three systemic inflammation marker, moderate correlation exists between PLR and NLR (r=0.5105), PLR and SII (r=0.5836), and relative strong correlation exists between NLR and SII (r=0.9633). Univariate analysis and log rank test revealed that elevated PLR, NLR and SII were significantly associated with worse survival outcome. Multivariate Cox regression analysis also showed that patients with higher PLR, NLR or SII were prone to have higher all-cause mortality, with HR = 1.394(95%CI: 1.088-1.785) for PLR, HR = 1.516(95% CI: 1.169-1.967) for NLR, HR = 1.558(95% CI:1.210-2.005) for SII. Furthermore, we compared the prognostic value of these indicators, and concordances were observed in terms of the discrimination power between PLR (AIC =3058.669), NLR (AIC =3055.387) and SII (AIC = 3053.955). A combination of PLR with NLR (AIC = 3056.230) did not improve the discrimination power compared with PLR and NLR alone, or SII. **Conclusion**: PLR, NLR and SII are of prognostic value in the prognosis of oral cancer. Concordance in terms of the discrimination power was observed between PLR, NLR, SII.

394. Machine Learning Classification Models for Grades of Clear Cell Renal Cell Carcinoma based on Magnetic Resonance Imaging Texture Features

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Abstract

Objective: This study aims to develop and validate classification models to discriminate the low-grade, the International Society of Urologic Pathologists (ISUP) grade I-II, and the high-grade, ISUP III-IV, clear cell renal cell carcinomas (ccRCCs) based on the magnetic resonance imaging (MRI) texture features.

Materials and methods: We retrospectively evaluated patients in two cohorts. The first cohort contained 63 patients, including 39 low-grade and 24 high-grade ccRCCs. The second cohort contained 31 patients, including 19 low-grade and 12 high-grade ccRCCs. The regions of interest (ROIs) of all tumors in the first cohort were manually drawn by three radiologists, independently, at the maximum lesion level of the cross-sectional corticomedullary phase (CMP) sequence images. The dataset generated by one of the radiologists was used as the training set, and the datasets generated by the other two radiologist sets were used for initial validation. The software package, MaZda, was used to extract quantitative texture features, including histogram, co-occurrence matrix, run-length matrix, gradient, autoregressive model and wavelet transformed features. Reproducibility of the texture features was assessed with the intra-class correlation coefficient (ICC). Six supervised learning algorithms, support vector machine (SVM), multilayer perceptron (MLP), naïve Bayes, k-nearest neighbors (KNN), linear discriminant analysis (LDA) and random forest (RF), were applied to develop classification models. The performance of the models on independent datasets was verified on the second cohort.

Results: Among 269 features, all features have an ICC value equal to or higher than 0.80 (excellent reproducibility). The 20 most important features were selected based on the importance coefficients assigned to the features by the random forest model. Among them, we further screened out 7 features for final modeling. The six classifiers were trained on the training set, and the performance of the model was evaluated with ten-fold cross-validation. We found that SVM performed best among six classifiers. The AUC values are 0.89 and 0.90, respectively, on the first cohort using the features from the other two radiologists. The AUC value is 0.81 on the second cohort.

Conclusions: An SVM model was developed to classify ccRCCs into low and high grades using the MRI texture features. The model is helpful for radiologists to mine the information embedded in the MRI images.

Keywords: Machine learning, Magnetic resonance imaging, Texture analysis, Clear cell renal cell carcinoma

395. 基于生物信息学方法鉴定去分化脂肪肉瘤的关键基因及初步验证

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背景和目的：高分化/去分化脂肪肉瘤（WD/DDLPS）是脂肪肉瘤最常见的亚型，其中 DDLPS 恶性程度高，易复发转移。本研究拟通过生物信息学的方法鉴定 DDLPS 的关键差异基因，尝试揭示其相互作用的分子机制，并进行初步验证。

方法：首先，从 Gene Expression Omnibus 数据库中提取 DDLPS 和正常脂肪的基因表达谱，通过 GEO2R 鉴定差异表达基因，并利用 GO、KEGG 分析 DDLPS 中发生显著变化的生物学途径、分子功能、细胞组分及分子通路。用 Cytoscape 软件构建蛋白质相互作用网络并计算 hub gene。然后从 TCGA 数据库下载 Adult Soft Tissue Sarcomas（TCGA，Cell2017）数据集，用 cBiopotal 分析 50 例 DDLPS 中关键差异基因的表达相关性，以及关键差异基因与间质增生基因、CAF 相关基因的表达相关性。最后，收集正常脂肪组织 10 例，WDLPS 组织 10 例，DDLPS 组织 40 例，通过 qPCR 检测关键差异基因的表达水平，分析差异基因与临床病理特征的相关性以及各基因之间的相关性。

结果：GEO 数据库方面，筛选出 DDLPS 和正常脂肪差异表达大于 4 倍的基因 193 个；GO 和 KEGG 分析显示脂肪细胞分化、PPAR 信号通路、ECM-受体相互作用等在 DDLPS 中发生了显著变化；Cytoscape 鉴定出 10 个 hubgene。而 TCGA 数据库方面，cBiopotal 结果显示，PPARG 与脂肪分化基因 CEBPA 等呈正相关，而与 CAF 相关基因 FAP 等呈负相关。CEBPA 与脂肪分化基因 FABP4 等呈正相关，与间质增生基因 THBS2、FN1 以及 CAF 相关基因 FAP 等呈负相关。THBS2 与间质增生基因 COL1A1 等、CAF 相关基因 FAP 等均呈正相关。最后，qPCR 初步验证结果表明，与正常脂肪组织相比，DDLPS 中 PPARG、CEBPA 等表达降低，THBS2、FN1、FAP 等表达增加。复发患者的肿瘤组织 CEBPA、LPL、ADIPOQ 表达较低；发生转移的患者肿瘤组织 FAP 表达增加；FN1、MMP2 表达与 DDLPS 的组织学分级呈正相关。

结论：我们的研究鉴定出一组 DDLPS 关键基因，其中 PPARG、CEBPA、THBS2 分别与 DDLPS 脂肪分化程度、间质增生及 CAF 浸润相关，能够预测复发和肿瘤进展，有望成为 DDLPS 潜在的生物标志物和治疗靶点。

396. 免疫检查点 Siglec-15 与 PD-L1 在腹膜后脂肪肉瘤中的表达及预后相关性研究

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背景与目的:

程序性死亡受体-配体 1（programmed cell death protein 1/programmed cell death ligand 1, PD-1/PD-L1）在肿瘤发生发展中起到重要作用。唾液酸结合性免疫球蛋白样凝集素-15（Sialic acid-binding Ig-like lectin- 15， Siglec-15）是新发现的免疫检查点，也是肿瘤免疫逃逸的另一重要机制。本研究旨在探讨 Siglec-15 与 PD-L1 蛋白在腹膜后脂肪肉瘤中的表达及其相关性，并分析其与临床病理特征及预后的相关性。

方法：

收集 94 例腹膜后脂肪肉瘤患者的肿瘤标本及其临床病理和随访资料,采用免疫组织化学染色法检测肿瘤组织中 Siglec-15 和 PD-L1 的表达水平，并分析其与临床病理特征的关系及对预后的影响。

结果：

Siglec-15 在 94 例腹膜后脂肪肉瘤中的阳性率 83.0%，显著高于 PD-L1 的阳性率 23.4%。同时，siglec-15 与 PD-L1 的表达呈负相关(r=-0.218，P<0.05)。Siglec-15 与患者年龄、肿瘤大小、病理类型均无相关性。PD-L1 与患者肿瘤分级相关（P=0.02），与患者年龄、肿瘤大小、病理类型均无相关性。生存分析显示，Siglec-15 的低、高表达组的中位无进展生存期（disease free survival，DFS）分别为 70.3 个月（95%CI:27.3-113.3）和 17.4 个月（95%CI:12.71-22.1）,差异具有统计学意义（P=0.044），而 PD-L1 的低、高表达组的中位 DFS 无统计学差异；Siglec-15 的低、高表达组的中位总生存期（overall survival, OS）分别为 74.7 个月（95%CI:25.3-124.15）和 28.7 个月（95%CI:15.84-41.5）,差异不具有统计学意义，而 PD-L1 的低、高表达组的中位 OS 差异也无统计学意义。此外，多因素 Cox 回归分析表明 Siglec-15 为腹膜后脂肪肉瘤患者 DFS 的独立影响因素(P=0.026)。

结论：

PD-L1 在腹膜后脂肪肉瘤中的表达较低，而 Siglec-15 表达较 PD-L1 高，且与 PD-L1 表达存在明显的负相关，提示其所在通路可能是 PD-1/PD-L1 通路的重要补充。同时 Siglec-15 与 DFS 密切相关，提示可将其作为预后评价的指标，并有望成为治疗新靶点。

397. Singel cell RNA sequening reveal an Immunosuppressive role of TREM2 in intrahepatic cholangiocarcinoma

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Checkpoint Immunotherapy regarded as potential treatment strategys for intrahepatic cholangiocarcinoma (ICC) patients.Massive of myeloid cells were infiltrated in ICC tumors and cooperate with tumor immune escape. The treatment of myeloid cells is lacking. We performed single-cell RNA sequencing (scRNA-seq) for nine ICC patients. We discovered new immune subsets by profiling different intracellular signatures of immune signaling, transcription factor combinations, and metabolic activity. TREM2 is expressed by tumor-infiltrating macrophages. Here, we found that Trem2–/– ICC patients are more resistant to growth of various cancers than other ICC patients and are more responsive to anti-PD-1 immunotherapy. Furthermore, treatment with anti-TREM2 mAb curbed tumor growth and fostered regression when combined with anti-PD-1. TREM2 might be potential myeloid target and augment checkpoint immunotherapy for ICC patietnts.

398. Differential expression and bioinformatics analysis of circRNAs in non-small cell lung cancer

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Background: Circular RNAs (circRNAs) are special type of non-coding RNA with covalently closed loop. Increasing evidences have revealed that circRNAs have important roles in several diseases, especially in cancers. Some circRNAs may act as ceRNA, sponge to corresponding microRNA (miRNA) and further affect the expression of relative messenger RNA (mRNA). However, the roles of circRNAs in the progression of non-small cell lung cancer (NSCLC) are still largely unknown. Our study aimed to describe the regulatory mechanisms in NSCLC by constructing a regulatory circRNA-miRNA-mRNA network.

Methods: Whole transcriptome sequence was performed in five NSCLC tissues and paired adjacent normal tissues. The expression of the selected circRNAs were detected by quantitative real-time

polymerase chain reaction (qRT-PCR). MiRNAs and mRNAs expression profiles were obtained from The Cancer Genome Atlas (TCGA) database. We predicted the relationships between circRNAs and miRNAs by using Circular RNA Interactome (CRI). Meanwhile, Targetscan, miRWalk and miRDB were used to predict the target genes of the miRNAs. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway revealed the functions and signaling pathways associated with the target genes. Furthermore, a circRNA-miRNA-mRNA regulatory network was constructed by Cytoscape.

Results: A total of 66 circRNAs (FC>2, P<0.05) were dysregulated in whole transcriptome sequence, of which 11 were up-regulated and 55 were down-regulated in NSCLC tissues compared with the corresponding adjacent normal tissues. Then, top three down-regulated circRNAs and top three up-regulated circRNAs were selected for further analysis. The three down-regulated circRNAs (hsa_circ_0000348, hsa_circ_0077837, has_circ_0086414) were verified by qRT-PCR detection. Through the bioinformatics prediction, we gained 7 target miRNAs and 137 relative mRNAs were connected with the three down-regulated circRNAs. GO and KEGG pathway analysis revealed that differentially expressed genes were mainly linked to the PI3K-Akt signaling pathway, EGF receptor signaling pathway and MAPK signaling pathway. Furthermore, the circRNA-miRNA-mRNA regulatory network were constructed based on the top three down-regulated circRNAs, 7 miRNAs and 137 mRNAs, allowing us to better understand its underlying mechanisms in NSCLC.

Conclusion: The study constructed a circRNA-miRNA-mRNA regulatory network associated with NSCLC and explored the potential functions of circRNAs in the progression of NSCLC.

Keywords: NSCLC, circRNA, competitive endogenous RNA, microRNA

399. Identification of IgM autoantibodies by protein array based on cancer driver genes for early diagnosis of lung adenocarcinoma

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Background: In China, lung cancer owns the highest morbidity and mortality. And, lung adenocarcinoma (LUAD) is the most common histological subtype of lung cancer, accounting for about 40%. The mutations of cancer driver genes (CDGs) cause the occurrence and development of cancers. As the early appeared antibodies in humoral immunity when stimulated by antigens, IgM autoantibodies might be a kind of excellent biomarkers for early detection of diseases, so we aimed to discover and identify the novel IgM indicators and explore a biomarkers panel for early diagnosis of LUAD. **Methods:** We customized a protein array contained 154 human recombinant proteins based

on 138 CDGs to explore the level of IgM autoantibodies to proteins encoded by these genes in discovery cohort with 68 LUAD patients and 68 normal controls (NCs) matched by age and gender, and discover the IgM autoantibodies with potential diagnostic value to be candidate indicators. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expression of the selected IgM autoantibodies, and the diagnostic performances of candidate IgM were evaluated in the validation cohort with 147 LUAD patients and 147 matched NCs. Logistic regression analysis was applied to integrate the meaningful IgM and carcinoembryonic antigen (CEA) to construct the diagnostic model for improving the diagnostic accuracy of LUAD. **Results:** Based on the protein array, 31 IgM autoantibodies were observed with the potential ability of distinguishing LUAD from NCs in discovery cohort ($P < 0.05$). According to the ranking of the 31 IgM autoantibodies' area under the receiver operating characteristic curve (AUC), the top five (TSHR, ERBB2, Survivin, PIK3CA and JAK2) were selected to explore their diagnostic performance in validation cohort by ELISA. And, these IgM autoantibodies also possessed the diagnostic capacity in validation cohort with AUCs of 0.599, 0.613, 0.579, 0.601 and 0.633, respectively ($P < 0.05$). Moreover, the model that constructed by logistic regression including five biomarkers (JAK2, TSHR, PIK3CA, Survivin and CEA) yielded the AUC of 0.827, sensitivity of 72.3% and specificity of 84.3%, which was superior to CEA (AUC = 0.692) or single IgM alone. Interestingly, the model showed the AUC of 0.743 and 0.861 in early stage and late stage LUAD, respectively ($P < 0.05$). **Conclusions:** The protein array based on cancer driver genes was a productive method for screening biomarkers in LC. The biomarkers panel with IgM autoantibodies and traditional tumor marker may provide a more accurate method to distinguish LC patients from healthy individuals.

400. 单细胞测序在表征颅咽管瘤分子特征研究中的应用

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摘要

目的

颅咽管瘤是颅内最常见的先天性肿瘤，具有术后易复发、生存质量差等特点。目前对部分颅咽管瘤的发生发展的分子机制仍不清楚。本研究应用单细胞测序技术研究肿瘤的微环境，探讨其发生与发展机制。

方法

采用 10X Genomics 技术平台对 13 例颅咽管瘤进行了单细胞转录组和 VDJ 测序分析，结合临床信息研究肿瘤细胞的发展机制。使用 SingleR 对 scRNA-Seq 数据进行细胞类型注释，并结合

CTNNB1 基因突变状态对上皮肿瘤细胞进行个性化分析，比较携带突变基因的肿瘤细胞和未突变上皮细胞之间的分子差异；使用免疫分子标志对免疫细胞进行亚群分析，比较不同肿瘤间的免疫微环境差异；利用 cellphnoedb 工具分析肿瘤细胞和免疫细胞之间互作的情况。

结果

单细胞转录组数据表明颅咽管瘤可以分为 CTNNB1 基因三号外显子突变细胞和野生细胞，而突变细胞显著聚集于肿瘤细胞簇中，比例介于 48.44%-84.21%。而野生型细胞分布较为分散，大多数聚集在巨噬细胞和成纤维细胞中。在上皮细胞内部同时存在突变细胞和野生细胞，通过研究这两种细胞之间差异，我们发现上皮细胞内部可以分为几个特征不同的亚群，主要有 Wnt 激活型、角质化型和核糖体激活型细胞簇，分别显著富集到 Wnt 信号通路，角质化通路和核糖体通路。以上现象表征了肿瘤细胞的多样性和异质性，有助于了解肿瘤的发生发展机制。针对肿瘤细胞与免疫细胞之间的互作情况，我们发现了一些趋化因子受体配体对，如 CXCR6_CXCL16，CCL3L1_CCR1，CCR6_CCL20 等，暗示了肿瘤细胞的发展途径。

结论

CTNNB1 突变细胞表征了颅咽管瘤肿瘤细胞的特征，同时基于细胞互作情况揭示了肿瘤细胞的微环境对肿瘤细胞的影响，有助于我们进一步了解颅咽管瘤中肿瘤的发展机制。

关键词：颅咽管瘤 单细胞测序 突变 CTNNB1 基因

401. Expression of SQSTM1 in hepatocellular carcinoma involving hepatitis B virus infection and aflatoxin B1 exposure

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This study aims to clarify the relationship and mechanism between expression of autophagy-related protein SQSTM1 and prognosis of patients with hepatocellular carcinoma (HCC) involving chronic hepatitis B virus (HBV) infection and aflatoxin B1 (AFB1) exposure. HCC patients who underwent resection were divided into three groups: HBV(+)/AFB1(+) (n = 26), HBV(+)/AFB1(-) (n = 68), and HBV(-)/AFB1(-) (n = 14). The groups were compared in terms of mRNA and protein levels of SQSTM1, disease-free survival (DFS), and overall survival (OS) and the expression of NRF2, Nqo1, and AKR7A3 in SQSTM1 high-expression and low-expression group. HBV(+)/AFB1(+) group has lower DFS and OS, and higher SQSTM1 expression than in the other two groups. SQSTM1 expression generally correlated with elevated NRF2 and Nqo1 expression, and reduced AKR7A3

expression. Patients expressing high levels of SQSTM1 showed significantly lower DFS and OS rates than patients expressing low levels. HCC involving HBV infection and AFB1 exposure is associated with relatively high risk of tumor recurrence, and this poor prognosis may relate to high SQSTM1 expression. High SQSTM1 expression activates the NRF2 pathway, promotes tumor recurrence. The downregulation of AKR7A3 also reduced liver detoxification of aflatoxin B1

402. 食管癌中 p53 突变体的功能及机制研究

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目的：食管鳞癌是食管癌在中国主要的病理类型，是食管癌中恶性程度高、预后差的一种类型，其中最重要的驱动基因 TP53 突变频率超过 75%。我们对 663 对食管鳞癌样本进行了全基因组测序，全面解析 TP53 的突变类型，频率最高的突变包括错义突变和无义突变，主要分布在 DNA binding domain。一些 p53 突变体不但失去了野生型 p53 的抑癌功能，而且还获得了一系列类似癌基因的功能，促进了肿瘤的进程。本研究中，我们拟在食管癌细胞中明确 p53 突变体的功能，并深入地探讨 p53 突变体在食管癌中发挥功能的分子机制。

方法：生物学功能方面，首先选择食管鳞癌样本测序突变病例数较高的突变体，构建稳定可诱导表达的 p53 野生型和突变体食管癌细胞系；并通过 Western Blot 方法检测食管癌细胞系中 p53 野生型和突变体表达情况，通过 Transwell、克隆形成及 CCK8 等实验明确 p53 突变体对食管癌细胞功能的影响。分子机制方面，通过蛋白质免疫共沉淀试验及质谱分析，确定与 p53 突变体的相互作用蛋白；并通过体外 IP 试验进行验证；同时利用 Chip-seq 试验分析 p53 突变体影响的下游相关信号通路及对下游靶基因的调节。

结果：Western Blot 方法分析表明成功的构建了稳定可诱导表达的 p53 野生型和突变体食管癌细胞系；此外，功能试验表明，在食管癌细胞系中 p53 突变体失去了野生型 p53 的抑癌功能，且大部分 p53 突变体还表现了促癌功能。分子机制方面，蛋白质免疫共沉淀试验及质谱分析发现有的 p53 突变体与 EIF4A1 和 RUVBL2 互作，与转录翻译能量代谢相关；有的 p53 突变体与 HNRNPA1、HNRNPA2B1 及 RBMX 互作，与 mRNA 剪接翻译相关。Chip-seq 试验表明 p53 突变体改变了野生型 p53 对下游靶基因的调节关系。

403. Identification of the Gemcitabine Resistant Signature for Predicting Prognosis in Patients With Pancreatic Cancer

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Background: Pancreatic cancer (PC) is one of the most lethal cancers. Gemcitabine resistance can result in treatment failure, thus leading to cancer recurrence and poor survival in PC patients. Therefore, identifying effective strategies to overcome gemcitabine resistance would have a significant clinical impact for PC patients. This study aimed to find the target genes of gemcitabine resistance and constructed a gemcitabine-resistance based prognosis signature in order to improve the individualized treatment.

Methods: In this study, we conducted the first exploration of genes associated with gemcitabine resistance in 3 different PC cell lines (Bxpc-3, CFPAC-1, PANC-1) and generated a gemcitabine resistant-based signature (GRS) to predict the survival and responses to gemcitabine of PC patients. We selected the whole exome sequencing data (GSE140077, GSE80616) of gemcitabine-resistant PC cell lines and corresponding non-resistant PC cell lines from GEO database. The gene expression profiles and clinical information of 179 pancreatic cancer patients with an initial pathologic diagnosis from 2001 to 2013 and the gene expression profiles of 165 healthy donors were retrieved from UCSC. The GRS was constructed using the bioinformatics method that classifies cases as high vs. low-risk groups per OS.

Results: The formula of GRS was: [Expression level of SLAIN2 * (0.0546)] + [Expression level of KITLG * (0.0219)] + [Expression level of MAP1B * (-0.0816)] + [Expression level of MT1X * 0.0025]. GRS was an independent prognostic factor for PC patients and was positively correlated with T staging and lymph node metastasis.

Conclusion: This was the first comprehensive gemcitabine resistant analysis of PC patients. We built a reliable, clinically feasible GRS for the prognosis and gemcitabine response prediction. SLAIN2, KITLG and MT1X might act as new targets for pancreatic cancer treatment and chemotherapy resistance in the future. We hope these findings can facilitate the personalized therapy of PC patients in future.

404. 循环 miRNA 生物标志物在多发性骨髓瘤诊断、预后评估中的作用研究

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目的：多发性骨髓瘤（Multiple Myeloma，MM）是好发于中老年人群的浆细胞克隆增殖性血液系统肿瘤，其发生率占血液肿瘤 10%，所有肿瘤的 1%。MM 肿瘤细胞呈全身散在分布，基于单一位点的穿刺活检仅反应穿刺局部肿瘤细胞特征，在疾病监测、疗效评估等应用中具有一定局限性。血清样本具有采集方便，可短期内反复获取等优势，是生物标志物理想的组织来源。因此本研究通过大规模 MM 患者血清标本探讨血清 miRNA 在 MM 诊断、预后评估中的作用。

方法：本研究分别采集和分离初诊 MM 患者（NDMM）和健康供者血清标本，提取其游离小 RNA 分子，进行二代测序。分析 MM 患者血清游离 miRNA 表达谱特征及其与正常人血清中差异表达 miRNA 分子。采用 RT-PCR 验证上述 MM 患者血清差异表达 miRNA 分子，并分析

结果：二代测序结果显示，MM 患者（n=15）循环血清与正常对照（n=6）相比，存在 104 个差异 miRNAs，其中表达上调 26 个（25%），下调 78 个（75%）。对其中差异表达的 miRNAs (log2FC>2，log2FC<-2，p<0.01)进行扩大样本的 RT-PCR 验证 (HD n=120 MM n=45)，证实 6 个在 MM 及 HD 中存在显著差异表达的 miRNAs，包括 miR-27b-3p、miR-342-5p、miR-30e-3p、miR-145-3p、miR-628-3p。ROC 分析显示，miR-19a-3p/miR-27b-3p/miR-145-3p 三者联合，曲线下面积可达 98.7%（AUC=0.987）。生存分析结果显示，NDMM 患者血清中低表达 miR-19a-3p、miR-27b-3p 提示患者有较短的 PFS（P<0.05）和 OS（P<0.05）。NDMM 患者血清中低表达 miR-30e-3p、miR-145-3p、miR-628-3p 与患者缩短的 PFS（P<0.05）有关。利用 DIANA TOOLS 软件对这些与 MM 生存密切相关的 miRNA 分子参与的信号通路进行分析，结果显示这些 miRNAs 参与到 TGF-beta、p53 以及 mTOR 等信号通路。提示这些 miRNAs 参与 MM 细胞增殖、存活、迁移等过程，从而促进 MM 疾病的发生发展。

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405. 多发性骨髓瘤循环 miRNA 生物标志物的发现研究

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目的：多发性骨髓瘤（Multiple Myeloma，MM）是好发于中老年人群的浆细胞克隆增殖性血液系统肿瘤，其发生率占血液肿瘤 10%，所有肿瘤的 1%。MM 肿瘤细胞呈全身散在分布，具有明显时间及空间异质性。基于单一位点的穿刺活检仅反映穿刺局部肿瘤细胞特征，在疾病监测、疗效评估等应用中具有一定局限性。近年研究发现 miRNA 分子可在人类及动物的血清和血浆中稳定存在，疾病状态下独特的血清 miRNA 表达模式，可将肿瘤患者与健康人群区分。由于血清样本具有采集方便，可短期内反复获取等优势，是生物标志物理想的组织来源。因此本研究系统探讨了 MM 患者血清、血浆、血清外泌体、骨髓浆等循环 miRNA 表达谱，明确可作为生物标志物的 miRNA 分子。

方法：本研究分别采集和分离初诊 MM 患者（NDMM）血清、血浆、骨髓浆、血清外泌体及肿瘤浆细胞（CD138+细胞）等组织标本，提取不同标本的 RNA（MM n=8 HD n=2），对 RNA 分子进行二代测序。系统分析不同组织样本中 MM 相关 miRNAs 谱。

结果：小 RNA 二代测序结果显示 MM 患者血清、血浆、骨髓浆、血清外泌体及其健康对照样本的 miRNA 表达谱存在明显差别。MM 细胞与正常浆细胞 miRNA 表达谱存在明显不同，MM 细胞中有 376 个差异表达 miRNAs，其中上调表达 293 个（78%），下调表达 83 个（22%）。与 MM 浆细胞 miRNAs 差异表达谱结果进行韦恩分析发现，MM 患者血清中有 36 个 miRNAs 与浆细胞中差异表达 miRNAs 一致，占血清差异 miRNAs 的 48.6%。骨髓浆与浆细胞有 39 个共同的差异 miRNAs，占骨髓浆差异 miRNAs 的 52.7%。外泌体差异 miRNAs 与浆细胞有 8 个共有的差异 miRNAs，占血清外泌体差异表达 miRNAs 的 61.5%。循环 miRNA 的来源主要有三种：（1）破裂的细胞或受损的组织被动释放；（2）经由外泌体主动分泌；（3）不被外泌体包裹，与 RNA 结合蛋白结合被分泌。循环 miRNAs 来源的多样性以及不同细胞的来源导致游离差异 miRNAs 的多样性。MM 患者存在稳定、特异的循环 miRNA 表达谱，MM 患者血清、血清外泌体、骨髓浆与健康供者血清、血清外泌体、骨髓浆 miRNA 表达谱存在明显差异，其游离 miRNAs 是 MM 理想的生物标志物组织来源。

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406. EP9-A3 评价两种方法学检测 SCCA 结果的一致性

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目的 在常见的妇科恶性肿瘤中，宫颈癌的发病率仅次于乳腺癌，宫颈癌初期无典型的临床症状，发现时通常已处于浸润期，预后效果很差。因此，宫颈癌死亡率的降低有赖于早期的筛查诊治。SCCA 是宫颈癌尤其是宫颈鳞癌特异性很好的肿瘤标志物，结合临床信息，通过比对两种不同的免疫检测系统测定鳞状细胞癌抗原（SCCA/SCC Ag）结果的可比性，以评估磁微粒化学发光法检测 SCCA 是否能够满足临床需求。

方法 收集医院正常随机体检血清样本 100 例，宫颈癌患者血清样本 43 例，食管癌患者 25 例，肺癌 27 例，肺炎 19 例，妇科相关疾病 33 例（宫颈炎、阴道炎、盆腔炎），胆囊炎 18 例，皮肤病 21 例，以雅培 化学发光（Architect i2000sr)为参考方法，安图 Auto Lumo A2000 Plus 磁微粒化学发光法（CMIA）为待评价方法，根据美国临床和实验室标准协会（CLSI）新指南 EP9-A3 文件的要求，对两种方法学检测 SCCA 的结果进行方法学比对和偏移评估。

结果 在 0.6-68.8ng/ml 范围内，两种方法学的 SCCA 检测结果具有较好的相关性，相关系数 r=0.9912，截距 0.1118。

结论 安图 Auto Lumo A2000 Plus 磁微粒化学发光法和雅培化学发光法检测 SCCA 结果具有可比性。

关键词：鳞状细胞癌抗原；SCCA；EP9-A3；SCLC；方法学比对

407. 时间序列转录组分析乳腺癌 MCF-7 细胞系对他莫昔芬产生抗性的动态过程

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目的：他莫昔芬治疗是 ER+乳腺癌最常见的治疗手段。虽然大部分患者在治疗初期对他莫昔芬有响应，但随着治疗时间的推移约有 1/3 的患者产生耐药性。尽管有大量研究探讨乳腺癌对他莫昔芬的耐药机制，但抗性产生的过程仍不清楚。本研究旨在通过对中长期持续药物处理的 MCF-7 细胞系转录组的时间序列分析，探究 ER+乳腺癌对他莫昔芬产生抗性的动态过程。

方法：在 LINCS 数据库中收集经他莫昔芬短期处理的 MCF-7 细胞系 Level 5 数据（6 h，共 18 个处理样本和 60 个对照样本; 24h，共 18 个处理组样本和 69 个对照组样本）。在 SRA 数据库中收集经他莫昔芬长期处理的 MCF-7 细胞系 RNA-Seq 转录组数据（项目访问号 PRJDB4496：处理时间为 1–12 周；每个时间点各 5 个处理组样本和 5 个对照组样本）。在 GEO 数据库中收

集经他莫昔芬诱导耐药的 MCF-7 及其亲本细胞系的基因芯片转录组数据（GSE67916：8 个亲本细胞系和 10 个耐药细胞系）。首先，利用 CellComp 算法识别他莫昔芬长期处理组相对于对照组的差异表达基因；然后，分析差异表达基因在他莫昔芬短期处理和诱导耐药的细胞系中的表达情况；最后，对经他莫昔芬长期处理的 MCF-7 细胞系进行时间序列分析，探索他莫昔芬耐药的动态发展机制。

结果：研究发现 MCF-7 在经过他莫昔芬短期处理 6 h 或 24 h 后，PRSS23 基因的表达水平显著降低；然而，在耐药细胞系与亲本细胞系间，PRSS23 基因的表达水平无显著差异。为了进一步理解这个矛盾现象并探索 PRSS23 基因在他莫昔芬耐药中的作用，对经他莫昔芬处理 1 到 12 周的 MCF-7 细胞系的转录谱进行时间序列分析，根据基因表达值的变化趋势将差异基因分为 9 个簇。PRSS23 基因所在簇的基因在短期药物处理后表达水平显著下调；但是随着药物处理时间增加，其基因表达水平逐渐回调。PRSS23 基因所在簇的基因主要富集到 DNA 复制、错配修复及细胞周期等生物学通路，可能与克服药物毒性存在关系，其具体机制有待于进一步探索。簇 5 涉及的基因表达水平随着药物处理时间增加，逐渐下降，其基因主要富集到雌激素信号通路、MAPK 信号通路及 EGFR 酪氨酸激酶抑制剂耐药通路等。

结论：ER+乳腺癌获得性耐药是一个复杂的动态生物学过程。PRSS23 基因在抗性产生中发挥一定作用，是一个潜在克服耐药靶点。

关键字：ER+乳腺癌，PRSS23 基因，时间序列分析，耐药

408. Tumor sequencing big data management and analysis platform and clinical application

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Background: In recent years, more and more hospitals and laboratories use tumor sequencing-related technologies and have made tremendous progress in genomics research. However, they have also generated and accumulated a large number of large-scale sequencing sample data, which inevitably Generate complex data management, storage, security and analysis issues. Faced with a large amount of sequencing data, we urgently need a secure sequencing information management and automated data analysis system to correctly process, upload, store, and analyze batch data, manage system access rights for different users, unify uploaded data formats, and quickly To correlate patient clinical information with genome sequencing data.

Method: The tumor sequencing information management system we developed is a web-based interface designed for user management, batch data upload, storage and management, and a platform that calls automated analysis processes for biological information analysis. It combines a simple user

interface and independent The server-side automated data analysis process. This system is built on the Windows environment based on the Django framework, mainly written in Python language, and also used to write data processing and analysis scripts. The database uses SQLite for data storage, runs on the uWSGI server infrastructure, and the development tool uses JetBrains PyCharm. The system is applied to the multidimensional omics sequencing data set for testing and compared with other similar tools to verify the performance of the system.

Result: This system allows users to log in to the system with the verified user name and password through email registration and verification. Logged-in users can retrieve limited data information from the database server according to different permissions, and upload, manage, and download information through an intuitive operation interface to ensure data security. The system prompts the input rules of data information through friendly forms to realize standardized and unified management of data. After the user imports the original sequencing data, the system performs complete processes such as quality control, sequence comparison, and sequencing data analysis in an automated and repeatable manner. During the data analysis process, detailed information such as the progress status of the sequencing task and error messages can be displayed. The whole analysis process does not require manual intervention. After the analysis is completed, an email is automatically sent to the user to inform the user to log in and view the analysis result.

Conclusion: This system is an integrated user management, sample information upload, tumor sequencing information management, and workflow management system. It can manage multidimensional omics sequencing data and call related data analysis processes for biological information analysis. Safe and efficient information management and automated workflows can save time for bioinformatics scientists to analyze and interpret results instead of data processing. Especially the application of this system to clinical research requires not only faster and more convenient data management and operation interface, so that inexperienced users can quickly query the analysis result information related to patient diagnosis through this system, but also need to improve the accuracy and safety.

Keywords: Next Generation Sequencing;User management; Information management; Workflow management; Automated analysis platform

409. The diagnostic value of serum anti-PIDD1, anti-STC1, and anti-FOXA1 autoantibodies as biomarkers in ovarian cancer

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Aim: Ovarian cancer (OC) is the major cause of death of gynecologic malignancies worldwide. Serum autoantibodies against tumor-associated antigens (TAAabs) can be potential biomarkers for OC. This study aims to evaluate serum autoantibodies against five TAAs, including EDNRB, PIDD1, STC1, SPA, and FOXA1, as biomarkers in the immunodiagnosis of OC.

Methods: The serum titer of five aforementioned TAAabs were measured using Enzyme-linked immunosorbent assay (ELISA) in 94 OC patients and 76 healthy controls (HCs) in the research group. The diagnostic values of significant TAAabs were validated in another independent validation group which consisted of 136 OC patients, 136 HCs, and 181 benign ovarian disease controls (BODCs). We applied two independent sample t-test and Mann-Whitney U test to compare the differences of five TAAabs between OC patients, HCs, and BODCs. The area under curve (AUC) values was used to evaluate the diagnostic performances of autoantibodies. $P<0.05$ was considered to be statistically different. All statistical analyses were performed by IBM SPSS, version 21.0.

Result: In the research group, three promising autoantibodies (anti-PIDD1, anti-STC1, and anti-FOXA1) had higher serum titer in OC patients compared with HCs. The AUCs of anti-PIDDI, anti-STC1, and anti-FOXA1 autoantibodies for discriminating OC patients from HCs were 0.910, 0.879, and 0.817 (all $P < 0.05$). Whereas anti-EDNRB and anti-SPA autoantibodies showed no significantly discriminating ability between OC and HCs with AUC of 0.544 and 0.558, respectively (both $P > 0.05$). In the validation group, autoantibodies against three TAAs (PIDD1, STC1, and FOXA1) showed AUCs of 0.759, 0.760, and 0.817 for discriminating OC patients from HCs, with AUC of 0.718, 0.729, 0.814 for discriminating OC patients and BODCs, respectively. Further analyses showed that anti-PIDD1, anti-STC1, and anti-FOXA1 autoantibodies can discriminate early stage (stage I and stage II) OC patients from HCs with AUC values of 0.738, 0.718, and 0.818, respectively (all $P < 0.05$). The cutoff values (the OD value corresponding to the maximal Youden index at specificity over 90%) were used to determine positive reactivity for each autoantibody. The sensitivity of anti-PIDD1, anti-STC1, and anti-FOXA1 autoantibodies were 48.53%, 41.91%, 47.79% at 90.44% specificity. Parallel analyses were initiated using anti-PIDD1, which had the highest sensitivity in the three biomarkers, to enhance the autoantibodies detection in OC. Combination utilization of anti-PIDD1 and anti-FOXA1 autoantibodies achieved the optimal diagnostic performance with the sensitivity

increased to 58.1% at 86.8% specificity. With the addition of anti-STC1, the sensitivity increased to 59.6% and the specificity slightly dropped to 84.6%.

Conclusion: Serum autoantibodies against PIDD1, STC1, and FOXA1 have the potential to detect OC. Combinational utilization of serum anti-PIDD1 and anti-FOXA1 autoantibodies can increase the sensitivity in OC detection.

Keywords: Ovarian cancer, autoantibody, tumor-associated antigens, diagnosis

410. pH responsive polymer micelles based on amphiphilic block copolymer PEG-HES-PLA for delivery of emodin to breast cancer cells

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Emodin (Emo) is a natural anthraquinones with pharmacological activities in anti-tumor effects. However, emodin suffer from the poor water solubility, low biocompatibility, rapid systemic elimination and off-target side effects, resulting in unsatisfactory treatment outcome. Nanotechnology-based drug delivery systems have been demonstrated to have passive or active tumor targeting behaviors, with great potential for cancer chemotherapy. Herein, the amphiphilic block copolymer CD44 peptide-conjugated polyethylene glycol- hydroxyethyl starch- poly(L-lactic acid) (CD44p-conjugated PEG-HES-PLA) was synthesized and self-assembled to form pH-responsive and Emo-loaded polymeric micelles (Emo@CD44p-PM) targeted to breast cancer. Hydrophilic PEG chain conjugated to HES via an acid-labile acetal bond. When in blood circulation, the PEGylation of polymeric micelles Emo@CD44p-PM reduced the absorption of plasm proteins, prolonged the circulation and shielded targeting peptide CD44p. Emo@CD44p-PM accumulated in tumor tissue via EPR effect. Once the polymeric micelles Emo@CD44p-PM entered acidic tumor microenvironment (pH<6.8), the acid-labile acetal bond hydrolyses gradually and led to the detachment of PEG layer, which resulted in the exposure of CD44p to enhance the cellular internalization of Emo@CD44p-PM effectively. The in vitro results showed good biocompatibility, effective tumor targeting and anti-tumor effect. Therefore, the polymeric micelles Emo@CD44p-PM provide a promising delivery strategy of targeted therapy of breast cancer.

411. Identification of novel autoantibodies based on the human proteomic chips and evaluation of their performance in the detection of gastric cancer

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Aim: Gastric cancer (GC) is one of the most important causes of cancer death in the world. At present, the commonly used diagnostic methods for GC are gastroscopy and biopsy. Their application in large-scale population screening is restricted due to the invasiveness and high cost. Several serum biomarkers including carcinoembryonic antigen (CEA), carbohydrate antibody 199 (CA199), and carbohydrate antibody 724 (CA724) have been used in clinics to evaluate the effectiveness of therapy. However, these serum biomarkers have limited sensitivity and specificity for cancer screening. Autoantibodies against tumor-associated antigens (TAAabs) can be used as potential biomarkers in the detection of cancer. This study aims to identify novel TAAabs to detect GC based on human proteomic chips and construct a diagnostic model to distinguish GC from healthy controls (HCs).

Methods: The titer of TAAabs in serum samples from 10 GC cases and 10 HCs were measured by human proteomic chips. Further, 80 GC cases and 80 HCs were selected as the verification cohort to detect selected serum TAAabs by ELISA. Next, 192 GC cases, 128 begin gastric disease (BGD) cases and 192 HCs were selected as the validation cohort to validate the performance of serum TAAabs. All GC cases and HCs were matched by age and gender. Then, the cohort with larger sample size was used as the training group to construct a model by logistic regression analysis, and another cohort was used as the testing group to evaluate the model.

Results: Eleven candidate TAAabs were identified, including INPP5A, F8, NRAS, MFGE8, PTP4A1, RRAS2, RGS4, RHOG, SRARP, RAC1, and TMEM243 by proteomic chips. The titer of INPP5A, F8, NRAS, MFGE8, PTP4A1 and RRAS2 were significantly higher in GC cases while the titer of RGS4, RHOG, SRARP, RAC1 and TMEM243 showed no difference in the verification group. MFGE8 showed the highest diagnostic value with an AUC of 0.75 (95%CI: 0.68-0.82), and the optimal sensitivity and specificity were 71.3% and 72.5%, respectively. Next, 6 potential TAAabs were validated by ELISA in the validation cohort. The titer of F8, NRAS, MFGE8, RRAS2, and PTP4A1 were significantly higher in GC cases. Among them, MFGE8 showed the best diagnostic value with an AUC of 0.80 (95%CI: 0.76-0.84), the optimal sensitivity and specificity were 69.3 % and 77.1%, respectively. Besides, the titer of NRAS and PTP4A1 in GC cases were significantly higher than that in BGD cases. Then, logistic regression analysis was performed to establish the diagnostic model, and NRAS, MFGE8, PTP4A1, and RRAS2 entered the model. The AUC, sensitivity, specificity, and accuracy of the model in the training cohort and the testing cohort were 0.87 (95%CI:0.83-0.90),

75.5%, 83.3%, 79.4% and 0.83 (95%CI:0.76-0.90), 76.3%, 81.3%, 78.8%, respectively. Stratification analyses of the diagnostic model according to the clinical characteristics showed no significant differences (all $P > 0.05$).

Conclusion: The panel of 4 TAAabs (NRAS, MFGE8, PTP4A1, RRAS2) is promising for distinguishing GC cases from HCs.

Keywords: Gastric cancer, proteomic chip, tumor-associated antigen (TAA), autoantibody, diagnostic model, immunodiagnosis

412. PCDH7 overexpression is correlated to poor patient survival and silencing impairs cell proliferation and invasion via EGFR signaling in lung cancer

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Purpose: Lung cancer is the major cause of morbidity and mortality throughout the world. The overall 5-year patient survival is only 19%, which may due to the higher recurrence and metastasis rate, as well as the underling complicated molecular pathology. PCDH7 (protocadherin 7) belongs cadherin superfamily and plays role in cancer metastasis. Here, we further explore PCDH7 expression pattern and the potential mechanism in lung cancer metastasis, as well as look for potential molecular markers of lung cancer.

Methods: We first intergraded analyzed RNA-seq data from animal model of lung cancer to brain metastasis and microarray data from lung cancer tissues in which clinical information are included. Therefore, PCDH7 was selected for further study. The cell proliferation, colony formation, migration and invasion were performed after PCDH7 siRNA-mediated gene knockdown in H1299 and H1975 lung cancer cells. Western blot, qRT-PCR, RNA-seq and IP, Co-IP were performed to explore the underling mechanism of PCDH7 in cancer progression.

Results：We found that PCDH7 was significantly increased in tumors with brain metastasis in animal model. PCDH7 expression was higher in lung adenocarcinoma as compared to normal lung tissues, and PCDH7 overexpression was significantly associated with overall poor patient survival. PCDH7 knockdown with siRNAs inhibited tumor cell migration, invasion, colony formation and proliferation in lung cancer cells. Mechanistically, we found that PCDH7 depletion reduced the expression of EGFR and MET, and it affected EGFR and MET signal pathway to affect tumor cell metastasis and proliferation.

Conclusion：High expression of PCDH7 was related to poor patient survival and tumor metastasis in lung cancer suggested that PCDH7 may be used as a molecular marker for prognostic prediction and potential therapeutic target of lung cancer.

Key words: lung cancer, PCDH7, prognosis, metastasis

413. 肾透明细胞癌诊断及预后相关生物标志物的组学预测

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目的 筛选肾透明细胞癌诊断及预后相关分子标志物。 **方法** 整合 GEO 与 TCGA 数据库中肾透明细胞癌患者全转录组表达谱数据，采用差异表达分析、基因加权共表达网络（weighted gene co-expression network analysis，WGCNA）筛选核心基因集，采用基因本体学（Gene Ontology，GO）和京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes，KEGG）分析核心基因集功能富集情况，采用蛋白互作网络（protein-protein interaction，PPI）和生存分析筛选与诊断预后相关的分子标志物。随后进一步验证诊断及预后相关分子标志物在肿瘤组与正常组之间的诊断价值与表达差异。 **结果** GSE53757 与 TCGA-KIRC 差异表达分析分别得到 2013 与 3747 个差异表达基因，WGCNA 分别得到 4 与 11 个显著性模块，其中与癌症组正相关系数最高的均为棕色模块，整合上述结果最终得到 280 个潜在核心基因。GO 分析显示，潜在核心基因大多富集在质膜、胞外间隙和细胞表面，参与免疫细胞的增殖和迁移、细胞周期、细胞粘附等生物学过程，并具有趋化因子激活、氧化还原酶激活等分子功能；KEGG 分析显示，潜在核心基因大多富集在细胞粘附分子、细胞凋亡、免疫细胞分化与迁移、肿瘤相关信号通路。PPI 与生存分析筛选得到 4 个与诊断及预后相关的分子标志物，分别为 FCGR2B、ITGAM、IL10RA、TYROBP。进一步验证发现，在 GSE6344 数据集中，诊断预后相关分子标志物表达水平在癌症组与正常组之间存在显著差异。ROC 分析显示，诊断预后相关分子标志物在 GSE53757 与 TCGA-KIRC 中的诊断 AUC 值均>0.70，联合诊断 AUC 值均>0.95。免疫组化结果显示，FCGR2B、ITGAM、TYROBP 在肾细胞癌肿瘤组织中的阳性表达率均高于正常肾脏组织，差异具有统计学意义。 **结论** 肾透明细胞癌的发生发展与免疫细胞的增殖和迁移、细胞粘附分子、细胞凋亡、肿瘤相关等信号通路密切相关。进一步确定了 FCGR2B、ITGAM、IL10RA、TYROBP 等 4 个核心基因，它们不仅可作为肾透明细胞癌诊断与预后的分子标志物，还可以为肾透明细胞癌的免疫疗法提供新的治疗靶点。

414. HIF-1α combining histone lysine methylation biomarkers for predicting survival in patients with esophageal squamous cell carcinoma

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Backgrounds and aims: Hypoxia is a potent micro-environmental factor promoting tumor progression. The expression of the hypoxia-inducible transcription factors HIF-1α is associated with increased poor survival in various types of tumors. Histone methylation markers play vital roles in the evolution of hypoxia/HIF-1α-related tumorigenesis through multiple unclear mechanisms and their alterations have been developed as clinical biomarkers for diagnostic, prognostic, and therapeutic applications. Here, we investigate that HIF-1α and histone methylation markers as potential indicators of prognosis in esophageal squamous cell carcinoma (ESCC).

Patients and methods: HIF-1α and histone methylation markers protein expression was examined by IHC in ESCC tissues array. The prognostic value of levels was analyzed using Kaplan–Meier survival analysis.

Results: HIF-1α protein expression was higher in ESCC tumors than in paracancerous tissues. H3K9me3, H3K27me3, H3K4me3, and H4K20me3 were significantly upregulated in ESCC tissues. Importantly, HIF-1α was only positively correlated with H3K9me3, and H3K4me3 expression. H3K27me3 expression maybe is affected by HIF-1α level although there is no positive association between upregulated HIF-1α and increased H3K27me3. Kaplan-Meier analysis indicated H3K9me3, H3K27me3, H4K20me3, and H3K36me3 were independent indicators of prognosis for ESCC. Furthermore, epigenetic markers and HIF1α were selectively combined to serve as a novel prognostic marker for ESCC.

Conclusions: This study identified a pattern of epigenetic methylation markers and HIF-1α expression in ESCC, and their combined evaluation might improve survival prediction for ESCC patients.

Key words: ESCC, HIF-1α, histone methylations, prognosis

415. Neutrophil-to-Lymphocyte Ratio/Prealbumin is a Superior NLR-derived Prognostic Marker for Patients with Biliary Tract Cancer after Surgical Resection

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Background. The neutrophil-to-lymphocyte ratio (NLR) is a well-known prognostic marker associated with some inflammation-based scores, and has showed a prognostic ability in biliary tract cancer (BTC). This study aimed to compare the prognostic value of different NLR-derived scores and establish a new prognostic staging system based on inflammation markers.

Methods. More than 800 patients undergoing surgical operation at the Peking Union Medical College Hospital（PUMCH） between 2003 and 2017 or at China-Japan Friendship Hospital (CJFH) between 2014 to 2020 with confirmed BTC who underwent surgery between 2003 and 2017 were enrolled retrospectively. Kaplan-Meier analysis and time-dependent receiver operating characteristic (ROC) analysis were performed. Independent predictors of overall survival (OS) and disease-free survival (DFS) were evaluated using Cox regression. Nomograms constructed using the training cohort were not only internally but also externally validated. Our novel staging system was compared with the American Joint Committee on Cancer TNM staging system.

Results. All the NLR-derived inflammation scores, derived neutrophils/(leukocytes minus neutrophils) ratio (dNLR), NLR/albumin ratio (NLR/ALB), NLR/prealbumin ratio (NLR/PA), and the systemic immune-inflammation index (SII), were related to OS and revealed significant survival difference between the two groups in survival curve analysis. The NLR/PA was independently prognostic in multivariate analysis. Patients with a high NLR/PA score showed significantly decreased OS and DFS. The area under the ROC curve of NLR/PA was superior to that of other scores in prognostic value, based on which a new and effective staging system was established. The nomogram, C-index, and survival curves of the new model showed accuracy and efficiency not only in our study cohort but also in the external cohort for predicting the OS of patients with BTC (all $P<0.05$). Our model showed excellent discrimination performance compared to the TNM staging system in the Kaplan-Meier analysis for the whole population as well as for subgroups.

Conclusions. For predicting OS and DFS in BTC patients post-surgery, the NLR/PA is independently prognostic, and is superior to other NLR-derived inflammation indicators. The new clinical staging system based on NLR/PA is a promising tool for prognostic evaluation and is a good complement to the AJCC TNM staging system for BTC and its subtypes.

416. EP9-A3 评价两种方法学检测糖类抗原 125 结果的一致性

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目的:卵巢癌在女性生殖系肿瘤的发病率占第 3 位，死亡率确占第 1 位对女性生命造成了严重的威胁，已有研究表明，糖类抗原 125（CA125）是卵巢肿瘤细胞表面肿瘤相关抗原，CA125 是 1981 年由 Bast 等从上皮性卵巢癌抗原检测出可被单克隆抗体 OC125 结合的一种糖蛋白，本文重点研究了两种不同的免疫检测系统测定 CA125 结果的一致性，以评估磁微粒化学发光法检测 CA125 是否能够满足临床需求。

方法:选取 311 例临床血清样本，以罗氏 Cobas e601 电化学发光法（ECLIA）为参考方法，安图 Auto Lumo A2000Plus 磁微粒化学发光法（CMIA）为待评价方法，进行检测，根据美国临床和实验室标准协会（CLSI）新指南 EP9-A3 文件的要求，对两种方法学检测 CA125 的结果进行方法学比对和偏移评估。

结果:在 5.85-860.9U/mL 范围内，两种方法学的 CA125 检测结果具有高度相关性，相关系数 r=0.9946，截距 1.29。

结论: 安图 Auto Lumo A2000plus 磁微粒化学发光法和罗氏 Cobas e601 电化学发光法检测 CA125 结果具有一致性，

关键词:糖类抗原 125；CA125；EP9-A3；卵巢癌；方法学比对

417. Comparison of prognostic value of nutrition-based parameters of biliary tract cancer after surgical resection

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Background. Cancer patients are often complicated with nutritional disturbance, which is known to influence tumor progression. Although biliary tract cancer (BTC) is generally a rare disease, it has high clinical significance due to its dismal outcome and limited therapeutic options. Therefore, there is an unmet need for a more accurate nutrition-based patient stratification system to evaluate the nutrition status and to predict the prognosis of cancer patients. Multiple nutrition-based parameters (NBIs) have shown potential prognostic value in the evaluation of neoplasms. But the prognostic value of NBIs for BTC remains unclear. Thus, we aimed to compare and elucidate the clinical value of different NBIs for BTC.

Methods. Analysis involved 575 patients with BTC, diagnosed at Peking Union Medical College Hospital between January 2003 and December 2017, were retrospectively reviewed. A total of 401 patients met the necessary criteria and were included in the data analysis. Optimal cutoff values for

NBIs were established using X-tile or defined according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for patient nutrition status. The parameters' predictive abilities were evaluated using Cox regression. The Kaplan-Meier method (K-M) was used to evaluate and compare the relationship between NBIs and long-term overall survival (OS). The prognostic abilities of the NBIs were compared using the areas under the receiver operating characteristic curve (AUROC), C-index, and time-dependent receiver operating characteristic curve (ROC) curves. Subgroup analysis was also carried out by K-M analysis.

Results. The Prognostic nutritional index (PNI) was superior to other NBIs. Univariate Cox analysis showed that OS was significantly associated with carbohydrate antigen 19-9 (CA 19-9), tumor number, tumor differentiation, lymph node metastasis, distant metastasis, Tumor Node Metastasis (TNM), non-radical resection, albumin (ALB), Nutritional Risk Index (NRI), Geriatric Nutritional Risk Index (GNRI), PNI, and Malnutrition Universal Screening Tool (MUST). Multivariate analysis confirmed PNI, CA 19-9, tumor differentiation, TNM, and operative outcome as independent predictors of poor OS. Both C-index and AUROC showed the superiority of PNI on predicting the overall survival of BTC patients. Patients with a low PNI had a high risk of worse OS. Patients in the low-PNI group also had older age, higher frequency of jaundice, higher CA 19-9, longer hospitalization days (HOD), and higher frequency of postoperative complications. Subgroup analysis of PNI based on disease type stratification showed a significant relationship with OS in the gallbladder carcinoma (GBC), extra-hepatic cholangiocarcinoma (ECC) and intra-hepatic cholangiocarcinoma (ICC) subgroups.

Conclusions. PNI is an independent predictor of BTC prognosis, and is superior to other NBIs in terms of prognostic ability.

418. 肾透明细胞癌中 ceRNA 网络基因和肿瘤浸润免疫细胞的相关性及其生物标志物筛选

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目的：以肾透明细胞癌（Kidney renal clear cell carcinoma，KIRC）为模型，采用生物信息学工具对 ceRNA 网络与免疫细胞间进行综合性分析，拟在找出可能与 KIRC 早期诊断和预后相关的因素。

方法：下载癌症基因组图谱（the cancer genome atlas，TCGA）数据库中 KTRC 相关数据，以 perl 语言分析 lncRNA、miRNA、mRNA 表达谱数据，并根据这三种差异表达基因之间的相互作用关系构建 ceRNA 调控网络，以 Kaplan-Meier 生存和 COX 回归分析与 KIRC 临床相关性及预后预测相关的 ceRNA 网络基因；以 CIBERSORT 去卷积分析法分析 22 种免疫细胞的差异分

布，以 Kaplan-Meier 生存和 COX 回归分析筛选与 KIRC 临床及预后预测相关的免疫细胞亚型，最后对筛选的 ceRNA 网络基因和浸润性免疫细胞进行相关性分析和共表达分析。

结果：构建的 ceRNA 调控网络以生存分析和单因素 COX、lasso 回归分析筛选到共有的 8 个基因；浸润性免疫细胞以单因素 COX、lasso 回归分析、生存分析和临床相关性分析筛选到共有的 2 株免疫细胞亚型；共表达分析显示 LINC01426、CCNA2、L1CAM 与 T cells follicular helper，LINC00894 与 Mast cells resting、T cells follicular helper 这 2 种基因与免疫细胞亚型的阵列组合具有早期诊断和预后评价价值。

结论：本研究依托生物信息学工具开发的两种 LncRNA、mRNA 与免疫细胞亚型组合阵列，可能作为 KIRC 的早期诊断和预后评价的生物标志物。

419. 大肠癌 LoVo 细胞源外泌体对肿瘤血管生成促进作用的研究

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目的：大肠癌是一种常见的消化道恶性肿瘤，促血管生成是其生长的关键。在大肠癌中 EGFR 靶向治疗和血管生成靶向治疗的发展已经在患者治疗中取得了重大进展，但其中仍存在大量问题未被解决。外泌体是细胞分泌的大小 30~100nm 的小囊泡，能够携带生物活性物质（miRNA、mRNA、蛋白质）转移到其他细胞，介导细胞间通讯。多项研究表明肿瘤细胞分泌的外泌体能够以独特的方式促进血管生成，但其中的确切机制仍不明确，还有待进一步探讨。本研究拟以大肠癌 LoVo 细胞分泌的外泌体为研究对象，体内外研究其对肿瘤血管生成的影响，并探讨其通过传递 EGFR 促血管生成的可能分子机制。

方法：提取大肠癌 LoVo 外泌体，将其内化进入受体 HUVEC 细胞，体外分析 LoVo 外泌体对血管生成的影响；进一步采用小鼠体内基质胶塞实验，体内分析 LoVo 外泌体对血管生成的影响。为探讨外泌体促血管生成的分子机制，对外泌体中 EGFR 进行敲减，观察其对血管生成的影响，并分析其对下游血管生成核心分子表达的影响。

结果：共聚焦显微镜观察到 LoVo 外泌体成功内化进入 HUVEC 内皮细胞，血管生成实验显示，LoVo 外泌体能够显著促进 HUVEC 细胞管状结构的形成，且加入外泌体分泌抑制剂后该促进能力减退。小鼠皮下注射混有 LoVo 外泌体的基质胶，取出后，HE 染色发现 LoVo 外泌体基质胶塞中存在血细胞，且免疫组化实验显示胶塞中存在有 CD31 表达阳性的内皮细胞。表明 LoVo 外泌体能够在体内外促进血管生成。Western blot 实验发现 LoVo 外泌体能够携带磷酸化 EGFR 进入 HUVEC 细胞，将 EGFR 敲减后，LoVo 外泌体对 HUVEC 细胞管状结构生成的促进

作用减弱，表明 LoVo 外泌体通过 EGFR 促进血管生成。进一步分析 LoVo 外泌体对下游血管生成核心分子表达的影响，发现 LoVo 外泌体不能改变 HUVEC 细胞中 VEGF 的表达，却能促进 HUVEC 细胞中 IL-8 的表达，表明 LoVo 细胞分泌的外泌体有可能通过水平传递磷酸化 EGFR，调控 HUVEC 细胞中 IL-8 的表达分泌，进而促进管状结构的形成。

结论：LoVo 外泌体能够在体内外促进血管生成，其可能机制为通过水平传递 EGFR，调控 HUVEC 细胞中 IL-8 的表达分泌，为癌症的转移提供新机制。

420. 三阴性乳腺癌新型治疗靶点的研究现状

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目的：探究近五年来三阴性乳腺癌的新型治疗靶点及相应的分子机制，为相关靶向治疗的研究提供参考，并对其未来的发展及临床转化做出展望。**方法：**“三阴性乳腺癌”和“治疗靶点”为关键词在 PubMed、CNKI 期刊全文数据库和万方数据知识服务平台，检索 2010-2020 的相关文献，共得到 798 条结果，其中英文文献 554 条，中文文献 244 条，对其中的 50 篇进行分析并进行综述。**结果：**乳腺癌是一种侵袭性强，易复发，预后不佳的恶性肿瘤，最新统计数据显示其发病率及死亡率高居女性恶性肿瘤的榜首，然而乳腺癌的发病率呈逐年增长的趋势，因此乳腺癌的治疗成为当下全球的研究热点。三阴性乳腺癌由于肿瘤细胞表面雌激素受体（estrogen receptor，ER）、孕激素受体（progestogen receptor, PR）和人表皮生长因子受体 2（Her-2)均为阴性，故而缺少特异性靶点，成为乳腺癌中恶性程度最高，死亡率最高的一个亚型。由此可见，探索三阴性乳腺癌的特异性治疗靶点成为解决其治疗难题的关键。过去几十年里，研究人员经过不断地探寻，发现了一系列对于三阴性乳腺癌具有积极作用的治疗靶点，例如聚二磷酸腺苷核糖聚合酶(poly ADP-ribose polymerase, PARP)，血管内皮生长因子(vascular endothelial growth factor，VEGF)，表皮生长因子受体(epidermal growth factor receptor，EGFR)，雄激素受体(androgen receptor，AR)，PI3K-AKT-mTOR 信号通路，PD-1/PD-L1。三阴性乳腺癌靶向治疗的发展取得了极大进步。此外，诸如 PROCR (protein C receptor)等新型三阴性乳腺癌靶点也不断被发现，为三阴性乳腺癌的靶向治疗提供了新的理论依据。**结论：**三阴性乳腺癌细胞表面 ER、PR 和 Her-2 免疫组化显示均为阴性，因此常规的乳腺癌治疗方法对该亚型治疗效果不佳。探究三阴性乳腺癌的特异性治疗靶点成为解决其治疗困境的有效方式。研究人员在不懈的努力下，探索出一系列可用于靶向治疗三阴性乳腺癌的靶点，为这种死亡率极高的恶性肿瘤的治愈奠定了基础。

421. Whole transcriptome sequencing-based construction and integrated analysis of differentially expressed lncRNA mediated ceRNA network in non-small cell lung cancer

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Abstract

Background: Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death globally, and non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Long non-coding RNAs (lncRNAs) have emerged as novel master regulators of initiation, progression, and response to therapy in a wide variety of solid tumors and hematological malignancies. Some lncRNAs may act as microRNA (miRNA) sponge to affect miRNA activities by regulating messenger RNA (mRNA) expression. Our study aimed to describe the regulatory mechanisms in NSCLC by constructing a regulatory lncRNA-miRNA-mRNA network.

Methods: Whole transcriptome sequence was performed in five NSCLC tissues and paired adjacent normal tissues to obtain the differentially expressed lncRNAs (DELs) of NSCLC. After that, the interactions between lncRNA and the targeted miRNAs were predicted by RegRna 2.0, miRcode, starBase, and PITA databases. MiRNAs and mRNAs expression profiles were obtained from TCGA database. Then, miRDB, miRTarBase and miRWalk datasets were used to search for the mRNAs targeted by the miRNA. Then, we draw a Venn diagram by R (Venn Diagram package) to find overlapped target genes of mRNA. Survival analysis of overlapped mRNAs were performed by GEPIA and LOGpc in NSCLC. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway revealed the functions and signaling pathways associated with the target genes. Furthermore, a lncRNA-miRNA-mRNA regulatory network was constructed by Cytoscape.

Results: A total of 559 lncRNAs (FC>2, P<0.05) were dysregulated in whole transcriptome sequence, of which 235 were up-regulated and 324 were down-regulated in NSCLC tissues compared with the adjacent normal tissues. We selected the most one up-regulated lncRNA NONHSAG002962.2 in whole transcriptome sequence. Through bioinformatics prediction, we gained 2 target miRNAs (hsa-miR-501-3p, hsa-miR-502-3p) of lncRNA NONHSAG002962.2. Combining with TCGA database, we found that the expression of hsa-miR-502-3p was up-regulated whereas hsa-miR-501-3p was down-regulated, hsa-miR-502-3p then be chosen for the next analysis. After that, we found 11 mRNAs associated with hsa-miR-502-3p. GO and KEGG pathway analysis revealed that differentially

expressed genes were mainly linked to Cell cycle, p53 signaling pathway, FoxO signaling pathway and Cellular senescence. Furthermore, the lncRNA-miRNA-mRNA regulatory network were constructed based on lncRNA NONHSAG002962.2, hsa-miR-502-3p and 11 mRNAs, allowing us to better understand its underlying mechanisms in NSCLC.

Conclusion: The study constructed a lncRNA-miRNA-mRNA ceRNA regulatory network associated with NSCLC. This network demonstrates a new mechanism based on whole transcriptome sequence, which is of great significance for the study of the tumorigenesis and progression of NSCLC.

Keywords: NSCLC, lncRNA, miRNA, bioinformatics, ceRNA

422. 灵芝孢子粉对 CA72-4 检测结果的影响研究

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目的：糖类抗原 CA72-4 (carbohydrate antigen 72-4, CA72-4)是一种由 CC49 和 B72.3 两株单抗识别的粘蛋白样的高分子量糖蛋白，分子量为 220-400KD。其在正常人血清中含量较低，在胃癌患者中有较高的阳性率 ,对胃癌的复发监测也有一定的应用价值；另外多种恶性肿瘤疾病如卵巢癌、结直肠癌、胰腺癌等发现 CA72-4 的血清水平有升高，且胰腺炎、肝硬化、肺病、风湿病、妇科病、卵巢良性疾病、卵巢囊肿、乳腺病和胃肠道良性功能紊乱等一些良性病血清 CA72-4 也会存在升高。美国临床生化学会推荐，CA72-4 用于联检胃癌、结直肠癌、卵巢癌，灵敏度大大提高，而且特异性几乎不变。通过文献查阅口服灵芝孢子粉会导致 CA72-4 一定层度升高，本文旨在探讨该一临床现象。

方法：选取 74 例正常人（影像学检查均无 CA72-4 相关良性及恶性病）， 采用糖类抗原 CA72-4 检测试剂盒（磁微粒化学发光法）在安图 AutoLumo A2000 全自动化学发光测定仪上进行检测，并动态监测其服用灵芝孢子粉前后血清 CA72-4 的变化。

结果：74 例患者在未口服该补品前血清 CA72-4 结果均为阴性（参考值范围为 10U/ml）；但是在服用灵芝孢子粉一个月以后有 15 人的 CA72-4 的结果大于 10U/ml，停服一个月后又降低至参考值范围内。

结论：单个肿瘤标志物升高并不代表着身患癌症，血清学检测也会存在一定的干扰，单个肿瘤标志物的升高也不必过于恐慌；肿瘤标志物的最主要的用途应该是肿瘤治疗的疗效检测和预后判断，而不是直接用于癌症的筛查和诊断。

423. 术前血浆外泌体 PD-1 在可切除II/III期胃癌患者中的预后预测

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目的：探索术前血浆可溶性 PD-1 及外泌体 PD-1 在可切除II/III期胃癌患者中的预后价值。方法：收集 2009 年 4 月至 2013 年 5 月在中国医科大学附属第一医院行胃癌根治术治疗的 84 例患者术前血浆和 36 例健康者的血浆。通过外泌体提取试剂盒提取血浆中的外泌体，ELISA 检测血浆中外泌体 PD-1 和可溶性 PD1 的表达水平。采用 Kaplan-Meier 和 Log-rank 检验法进行生存分析。通过 $\chi 2$ 检验和 Fisher's 确切概率法分析可溶性 PD-1 和外泌体 PD-1 的表达与临床病理参数间的相关性。利用 Cox 回归分析外泌体 PD-1 表达水平是否为胃癌预后的独立危险因素。此外，通过曼-惠特尼 U 检验分析胃癌患者与健康志愿者外泌体 PD-1 表达的差异性。结果：Kaplan-Meier 生存分析的结果显示，外泌体 PD-1 高表达组总生存期明显短于低表达组（P=0.040），而可溶性 PD-1 的表达与总生存期无相关性。二者与临床病理学参数未见明显相关性。单因素 Cox 风险回归模型分析结果表明外泌体 PD-1 表达水平、pTNM 分期、淋巴结转移、Lauren 分型与胃癌患者的预后相关。多变量 Cox 风险回归模型结果表明外泌体 PD-1 表达水平（P=0.013，HR=3.391，95%CI：1.288-8.924）是影响胃癌患者预后的独立危险因素。此外，与健康者相比，胃癌患者术前血浆中的外泌体 PD-1 水平偏高（P=0.029）。结论：术前血浆外泌体 PD-1 可作为可切除II/III期胃癌患者预后的潜在标志物。

424. Identification of hub genes and prognostic indicators for gastric cancer and correlation of indicators with tumor-infiltrating immune cell levels

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Abstract

Aims: To identify the hub genes and prognostic indicators of gastric cancer (GC) and analyze the correlation between the prognostic indicators and the tumor-infiltrating immune cell levels to provide useful information for GC diagnosis and treatment.

Methods: The TCGA stomach adenocarcinoma (STAD) dataset and two microarray datasets (GES13911, GSE79973) were used to screen overlapping differentially expressed genes (DEGs) between gastric cancer (GC) and normal gastric tissue samples. Hub genes were screened by protein-protein interaction (PPI) networks and module analysis of the overlapping DEGs. Their expression of mRNA at tissue was validated by using the ONCOMINE database. Meanwhile, we detected their level of mRNA in MGC-803, SGC-7901 and GES-1 cell lines through qRT-PCR. The prognostic indicators of overall survival (OS) was identified by Cox proportional hazards regression analysis and disease-free survival (DFS) was identified by survival package in R. Their expression of mRNA was validated in MGC-803 and GES-1 cell lines by qRT-PCR. The correlation of prognostic indicators with the tumor-infiltrating immune cell levels was analyzed by using Tumor IMmune Estimation Resource (TIMER).

Results: Ten hub genes, namely, CDC6, CDC20, BUB1B, TOP2A, CDK1, AURKA, CCNA2, CCNB1, MAD2L1, and KIF11, were screened. Based on the data from ONCOMINE database, they were overexpressed in GC tissues, compared to the normal tissues. Three prognostic factors, LUM, VCAN, and EFNA4, were identified, which were highly expressed in the GC cells than GES-1. LUM, VCAN, and EFNA4 were found to correlate with tumor-infiltrating immune cell levels in GC.

Conclusion: The identified hub genes and prognostic indicators of GC could be useful indicators for future GC diagnosis and treatment.

Keywords: Gastric cancer; Differentially expressed genes (DEGs); Hub gene; Prognostic indicator; Tumor-infiltrating immune cell

425. 颅咽管瘤测序数据管瘤和自动化分析平台及临床应用

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背景：近年来，越来越多的医院、实验室使用肿瘤测序相关技术，在基因组学的研究上取得了巨大的发展，但同时也产生、积累了大量大型的测序样本数据，不可避免地会产生复杂的数据管理方面、存储方面、安全方面和分析方面等问题。因此，我们迫切需要一个安全的测序信息管理和自动化数据分析系统，来正确处理、上传、存储和分析批量数据，管理不同用户的系统访问权限，统一上传的数据格式，以及快速的将患者临床信息与基因组测序数据相关联。

方法：我们开发的颅咽管瘤测序信息管理系统是一个基于 Web 界面，旨在用户管理、批量数据上传、存储和管理，并调用自动化分析流程进行生物信息分析的平台，结合了简洁的用户操作界面和独立的服务器端自动化数据分析流程。本系统基于 Django 框架在 Windows 环境下进行搭建，主要采用 Python 语言进行编写，也用于编写数据处理和分析脚本，数据库使用 SQLite 进行数据存储，在 uWSGI 服务器基础架构上运行。将本系统应用于多维组学测序数据集上进行测试，并与其他类似工具进行比较，从而验证本系统的性能。

结果：本系统允许用户通过邮箱注册验证，使用已审核通过的用户名和密码登陆系统。已登录的用户根据不同权限能够从数据库服务器检索有限的数据信息，通过直观的操作界面进行信息上传、管理和数据下载，以确保数据安全性。本系统通过友好的表单提示数据信息的输入规则，以实现数据的标准化统一管理。用户导入原始测序数据后，本系统以自动化和可重复的方式进行质量控制、序列比对和测序数据分析等完整过程，在数据分析过程中可显示测序任务进度状态和错误提示等详细信息。整个分析过程无需人工干预。分析完成后自动向用户发送电子邮件，告知用户登录并查看分析结果，将原始数据、已处理数据和输出结果文件以图形、表格或链接的形式在页面上显示，对数据进行可视化，并且可以查询原始数据、输出数据等其它信息和相关分析脚本的文件夹路径。

结论：本系统是一个集成了用户管理、样本信息上传、肿瘤测序信息管理、工作流管理系统，能够管理多维组学测序数据并调用相关数据分析流程进行生物信息分析。安全高效的信息管理和自动化工作流程能够使生物信息学家节约时间用于结果分析，而不是数据处理。特别是将本系统应用于临床研究，不仅需要更快、更便捷的数据管理和操作界面，还需要提升数据的准确性和安全性。

关键词：二代测序，用户管理，信息管理，自动化分析平台

426. Screening novel tumor-associated autoantibodies based on HuProt Protein microarray and combined with imaging indicators to identify benign and malignant lung nodules

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Objectives:

The aim of this study is to screen tumor-associated autoantibodies (TAAbs) by Protein microarray and conduct a panel of TAAbs and for discriminating benign lung nodules (BLN) from malignant lung nodules (MLN).

Methods

HuProt Protein microarray was performed to discovery significantly expressed TAAbs between 10 mixed lung cancer and 10 paired mixed normal control serum. The indirect enzyme linked immunosorbent assay (ELISA) was used to detect the expression of the candidate TAAbs in test cohort which included 70 lung cancer (LC) patients and 70 normal control (NC), verification cohort which included 70 LC patients and 70 NC and validation cohort which included 105 BLN patients and 105 MLN patients. The nodular characteristic data of LDCT was obtained from LDCT report. The area under the curve (AUC) was used to evaluate the diagnostic ability of each TAAbs and nodular characteristic. The model used in identifying BLN from MLN was built by logistic forward regression.

Results

Thirteen LC-related TAAbs (UBQLN1, SARS, ISM2, ZPR1, FAM131A, GGA3, PRKCZ, GOLPH3, NSG1, CD84, EEA1) were selected by HuProt Protein microarray. The expression of autoantibodies to SARS, ISM2, ZPR1, FAM131A, GGA3, PRKCZ, GOLPH3, NSG1, CD84, EEA1, UBQLN1 in LC were obviously higher than NC in test cohort and verification cohort. Six TAAbs (CD84, EEA1, GOLPH3, NSG1, SARS, UBQLN1) and five nodular characteristic existed a difference between BLN and MLN. The AUC of six TAAbs and five nodular characteristic(vascular notch sign, lobulation sign, pleural indentation, mediastinal lymph node enlargement, calcification) ranged from 0.580 to 0.683. The AUC of the model with anti-EEA1 and five nodular characteristic was 0.823 (95%CI: 0.763-0.883). When combined with CEA, the AUC of the combination was up to 0.853 (95%CI: 0.792-0.920).

Conclusion

This study confirmed that six TAAbs (CD84, EEA1, GOLPH3, NSG1, SARS, UBQLN1) identified by protein microarray may become potential biomarkers for the diagnosis of LC, BLN and MLN. The

logistic forward regression model based on anti-EEA1 and five nodular characteristic has higher diagnostic ability for discriminating BLN from MLN

427.组蛋白甲基化 H3K27me3 相关修饰酶表达差异与肝细胞癌预后分析

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目的：H3K27me3，即组蛋白 H3 上的第 27 位赖氨酸的三甲基化，是与基因失活密切相关的一种表观遗传修饰，其状态的改变与多种癌症中的异常基因沉默相关。现已证实的 H3K27me3 相关修饰酶包括甲基转移酶 EZH2、NSD2、NSD3 和去甲基化酶 KDM6A、KDM6B，其中 EZH2 在肝细胞癌中的表达通常失调，并对肿瘤的发生、发展和转移至关重要。本研究旨在分析 H3K27me3 相关修饰酶在肝细胞癌患者中的表达水平及联合分析条件下对患者预后的影响。

方法：在 The Cancer Genome Atlas（TCGA）数据库中下载肝细胞癌患者的 RNA-seq 数据和病例临床信息，得到基因表达矩阵，分析上述 H3K27me3 相关修饰酶基因在肝细胞癌患者肿瘤和癌旁组织中的表达水平。利用 R 语言软件绘制生存曲线，探究上述酶的异常表达在独立及联合分析情况下对患者预后的影响。

结果：由 TCGA 数据库获得 371 例肝细胞癌患者临床数据，其中 H3K27me3 相关修饰酶 EZH2、NSD2、NSD3、KDM6A 在肿瘤组织中的表达水平高于癌旁组织，而 KDM6B 则相反。对前四种酶进行独立生存分析，发现 EZH2、NSD2 与患者预后相关，且高表达不利于患者生存。两两联合分析，发现 EZH2 与任意一种酶联合时，共同高表达的患者预后更不利。三者联合与四者联合分析表明，共同高表达均与患者预后相关，且不利于患者生存。此外，含 EZH2 的联合分析组相较于其他组对患者预后的影响更为不利。然而，对 EZH2 高表达病例组联合 KDM6B 分析或对 EZH2 低表达病例组联合 NSD2、NSD3 分析，表达水平对患者预后均无显著影响。

结论：H3K27me3 相关修饰酶 EZH2、NSD2、NSD3、KDM6A 四种酶在肝细胞癌组织中高表达。多种酶共同高表达的肝细胞癌患者的预后效果更差，且含 EZH2 的联合分析会产生更不利的预后影响。由于 EZH2 在肿瘤病理中发挥重要作用，其已成为肿瘤治疗的潜在靶点。目前已有多种针对不同癌症类型的 EZH2 靶向抑制药物应用于临床试验，如 Tazemetostat 已用于肝损伤、恶性实体瘤、淋巴瘤等临床试验。分析 EZH2 等 H3K27me3 相关修饰酶的表达和预后效果，将有助于探明酶之间的关联性，对肝细胞癌的标志物诊断和患者的预后分析具有重要的指导意义。

关键词：肝细胞癌，H3K27me3，组蛋白甲基化酶，组蛋白去甲基化酶，预后

428. 基于多组学的乳头状型颅咽管瘤的分子特征研究

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目的：颅咽管瘤是常见的儿童颅内肿瘤，根据组织形态学分成造釉型(ACP)和乳头状型(PCP)。乳头状型颅咽管瘤主要在成人中发生，而关于儿童 PCP 仅有零星的报道，临床上常被误诊。本研究旨在通过多组学数据分析 PCP 肿瘤分子特征，为临床诊断和治疗提供思路。

方法：本研究收集了 17 例 PCP 病人肿瘤和血液标本，进行全外显子和转录组二代基因测序，并使用 EPIC 芯片测定全基因组 DNA 甲基化。使用 Broad Institute 推荐的最佳实践流程分析体细胞突变，结构变异以及拷贝数变异。对 9 例样本进行 RNA-seq 分析，使用 edgeR 算法识别 PCP 相比正常垂体样本的差异表达基因，然后对差异基因进行功能富集，对关键基因进行蛋白质互作网络分析。采用 ssGSEA 算法分析特异性浸润免疫细胞的相对丰度。

结果：本研究分析了 17 例 PCP 的全外显子测序数据，发现其中的 16 例(94%)都有 BRAF 突变，并对儿童与成人 PCP 驱动突变基因的差异性进行分析，发现儿童与成人都有 MAPK 通路，成人主要集中在炎症通路，衰老通路，细胞黏附通路，儿童额外有钙结合相关通路基因发生变异。RNA-Seq 测序分析发现，与正常垂体样本比较得到的差异基因进行通路富集分析，在 PCP 中高表达的这部分基因显著富集在炎症相关的通路中，这表明，乳头状型颅咽管瘤存在炎症通路的特征，因此认为它可能是炎症驱动的肿瘤。结合临床数据，发现儿童乳头状型颅咽管瘤的样本通常更易出现钙化，常被误诊为脓肿，分子特征差异明显，因此儿童 PCP 有可能是颅咽管瘤一类新的亚型。

结论：本研究从转录组和全外显子水平分层次对乳头状型颅咽管瘤进行全面的分析，发现 PCP 存在炎症相关的通路特征，并表征了儿童 PCP 肿瘤的分子特征。

关键词：乳头状型颅咽管瘤，BRAF V600E 突变，多组学分析

429.运用生物信息学方法筛选乳腺癌差异表达及预后相关基因

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目的: 乳腺癌是全球最常见的妇科肿瘤，然而,乳腺癌预后相关因子并不完全清楚，本文利用生物信息学方法分析乳腺癌预后的分子标志物。**方法：**从 GEO 数据库中下载 5 个关于乳腺癌的基因表达谱（GSE7904、GSE10780、GSE10810、GSE29431、GSE42568），在 R 语言中利用 Affy 包对数据进行预处理并用 RMA 法进行归一化，利用平台数据对表达谱进行基因注释，用

limma 包对基因表达谱进行差异分析，分别挑选出 5 个表达谱的显著差异基因（|logFC|>1, p<0.05）取交集处理后得到最终的共有差异表达基因（differentially expressed genes, DEGs）。利用 DAVID 数据库对 DEGs 进行 GO 功能注释和 KEGG 通路分析，并在 STRING 数据库对 DEGs（综合分数≥0.8）构建蛋白互作网络图。在 Cytoscape 软件上利用其 Cytohubba 插件对蛋白互作网络进行模块分析选取蛋白互作网络中重要的核心蛋白。其核心基因用来自 TCGA 数据库中的乳腺癌 seq 数据验证其表达情况，在 Kaplan-Meier Plotter 数据库中探讨核心基因的表达及其与患者生存期的关系。**结果：**最终筛选出 DEGs 242 个，其中在乳腺癌中表达上调基因有 73 个，下调基因有 169 个。GO 功能注释及 KEGG 分析结果显示 DEGs 主要富集在 ECM-受体相互作用、细胞周期、PPAR 信号通路上。筛选出的核心蛋白包括 FOS、KIAA0101、MELK、BUB1B、CCNB1，这些核心蛋白用 STRING 数据库重新构建了蛋白互作网络图。核心基因在 TCGA 数据库的表达分析结果显示 KIAA0101、MELK、BUB1B、CCNB1 在乳腺癌中较正常乳腺组织 mRNA 表达上调，FOS 表达下调（p<0.05）。生存分析显示核心基因中 KIAA0101、MELK、BUB1B、CCNB1 基因 mRNA 高表达与乳腺癌患者的总生存率（OS）呈负相关（p<0.05），FOS 在乳腺癌中低表达且低表达乳腺癌患者的 OS 较低。**结论：**本研究发现在乳腺癌中有五个核心基因可能影响乳腺癌的发生发展，并且影响乳腺癌患者的预后，这些核心基因可能是乳腺癌诊断和治疗的潜在靶点。

430. A Novel Ferroptosis-related Gene Signature for Overall Survival Prediction in Patients with colon cancer.

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Colon cancer is one of most malignant cancers around worldwide. Nearly 20% patients were diagnosed at colon cancer with metastasis. However, the lack of understanding regarding its pathogenesis brings difficulties to study it. In this study, the mRNA expression profiles and corresponding clinical data of colon cancer patients were downloaded from public databases. The least absolute shrinkage and selection operator (LASSO) Cox regression model was utilized to construct a multigene signature in the TCGA cohort. colon cancer patients from the GEO cohort were used for validation. Our results showed that most of the ferroptosis-related genes (81.7%) were differentially expressed between colon cancer and adjacent normal tissues in the TCGA cohort. Twenty-six differentially expressed genes (DEGs) were correlated with overall survival (OS) in the univariate Cox regression analysis (all adjusted P< 0.05). A four-gene signature was constructed to stratify patients into two risk groups. Patients in the high-risk group showed significantly reduced OS compared with patients in the low-risk group (P < 0.001 in the TCGA cohort and P = 0.001 in the GEO cohort). The

risk score was an independent predictor for OS in multivariate Cox regression analyses (HR> 1, P< 0.01). Receiver operating characteristic (ROC) curve analysis confirmed the signature's predictive capacity. Functional analysis revealed that immune-related pathways were enriched, and immune status were different between two risk groups. Finally, we predicted the four most significant small molecule drugs that inhibit colon cancer. In conclusion, a novel ferroptosis-related gene signature can be used for prognostic prediction in colon cancer. Targeting ferroptosis may be a therapeutic alternative for colon cancer.

431. NRF2 通路及其调控分子在食管鳞癌中的功能研究及抑制剂开发

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目的：本课题组前期利用 508 对食管癌样本进行了全基因组测序，我们发现 NRF2 分子的编码基因 NFE2L2 的多种突变与患者的不良预后显著相关，结合既往研究，我们推测 NRF2 分子的基因突变可能造成 NRF2 分子的过度激活从而促进食管癌的发生发展。本课题拟以 NRF2 分子为研究对象，探究其在食管癌进展过程中的功能，特别是我们关注的几种突变类型的功能；寻找 NRF2 分子突变后促进食管癌发生发展的遗传背景及上游分子机制；并根据机制筛选特异和有效的 NRF2 抑制剂；以期揭示 NRF2 分子突变在食管癌中的重要作用机制，针对 NRF2 突变和过度激活的食管癌患者特异性应用 NRF2 靶向抑制剂，为食管癌患者的诊断分型和指导用药提供基础。

方法：本研究通过食管癌全基因组测序鉴定出 NRF2 分子的编码基因突变，并进一步分析 NRF2 的基因突变与食管癌患者临床特征的关系。通过体内外细胞功能实验确定 NRF2 突变在食管癌中具体的生物功能，同时利用生物信息学整合分析寻找与 NRF2 突变共同发生的重要分子改变，并验证在该分子改变的遗传背景下 NRF2 突变对食管癌进展的作用。最后利用 DEL 小分子化合物库筛选与 NRF2 特异性结合的小分子化合物，同时尝试解析 NRF2 蛋白结构从而研制出针对 NRF2 特异性蛋白靶点的抑制剂。

结果:课题组基于 508 个食管鳞癌和癌旁样本的全基因组数据， 在（31/508）病例中，确定了 10 个 NFE2L2 体细胞突变位点。进一步生存分析结果表明，NFE2L2 基因突变的病人较未突变的病人生存期显著性下降。在细胞水平，我们在食管癌细胞系 KYSE180、KYSE150、KYSE510 中由 shRNA 介导了 NFE2L2 基因表达的沉默，作为细胞模型研究 NRF2 蛋白的功能，随后发现 NRF2 的下调抑制了细胞增殖。另外在 KYSE150 细胞中，通过在 NFE2L2 基因编码区引入突变位点激活 NRF2 表达，发现 NRF2 的上调促进了体内外的细胞增殖。多组学整

合分析数据表明，NRF2 分子改变与 Sox2 和 TP63 的扩增存在明显相关性，ChIP-qPCR 结果显示，Sox2 和 TP63 与 NRF2 分子的启动子区存在结合。

结论：NRF2 分子的基因突变与食管鳞癌患者的不良预后显著相关，突变造成的 NRF2 过度激活在体内外促进食管癌进展，Sox2 和 TP63 的转录调控可能是食管鳞癌中 NRF2 过度激活的上游机制。

432. 基于 WGCNA 的肝细胞癌诊断标志物的筛选及模型构建

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肝细胞癌是一个值得全世界关注的公共卫生问题。肝细胞癌起病隐匿，而且手术之后易复发，是肝细胞癌预后差的主要原因。因此，肝细胞标志物用于肝细胞的早期诊断具有重要的意义。生物信息学是目前研究肝癌相关标志物的有效的方法。加权基因共表达网络(WGCNA)作为生物信息学的一种方法，其巧妙的将基因的表达和临床表型联系。本文的研究目的是获取在肝细胞癌发生过程中的枢纽蛋白，并确定其诊断价值。我们从 GEO 获取 GSE14520, GSE101068, GSE107170, GSE121248, GSE112790, GSE40873, GSE45436, GSE62232, GSE9843, GSE36376 数据，并对其进行标准化处理。我们用 GSE14520 进行了基因共表达网络分析(WGCNA)，选择与临床表型高度相关的模块。并且用 Limma 包分析差异表达基因(DEGs)，最后取交集作为 hub 基因。最后，利用 837 个基因构建蛋白-蛋白相互作用(PPI)网络，寻找中心蛋白。最终获得 15 个蛋白质。利用人蛋白质组芯片数据对蛋白进行二次筛选，发现 CCNB1、CDK1 和 MELK 与肝癌组织高度相关。GSE101068, GSE107170, GSE121248, GSE112790, GSE40873, GSE45436, GSE62232, GSE9843, GSE36376 的数据标准化处理之后进行批次校正。其中 70%作为训练集，30%作为验证集。运用 logistic 回归分析方法评估三种基因对于肝细胞癌的诊断能力。结果表明在训练集中曲线下面积(AUC)为 0.85 (95%CI 0.82-0.87)，灵敏度为 71.4%，特异度为 91.2%。在验证集中,AUC 为 0.87 (95%CI 0.83-0.90)。敏感性和特异性分别为 77.2%和 90.1%。此外，这三种蛋白的面板也显示出很大的能力来区分肝癌与肝硬化和胆管癌(CCA)。我们通过绘制受试者工作特征(ROC)来评估三种蛋白区分胆管癌和肝细胞癌的能力，曲线下面积(AUC)、敏感性和特异性分别为 0.99、99.1%和 100%。我们同样评价这三种基因区分肝癌和肝硬化的能力，曲线下面积(AUC)为 0.95，敏感度为 87.3%，特异性为 91.7%。以上研究表明 CCNB1、CDK1 和 MELK 联合具有诊断肝细胞癌的能力。而且其还能很好的区分肝细胞癌和胆管癌以及肝硬化。

433. Effect and safety analysis of olanzapine combined with morphine hydrochloride sustained release tablets in the treatment of cancerous pain

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Objective:To observe the curative effect of olanzapine and morphine hydrochloride sustained release tablets in the treatment tumors with cancerous pain.

Methods:62 cases were treated with olanzapine and morphine hydrochloride sustained-release tablets, 63 cases were treated with morphine hydrochloride sustained-release tablets alone.Both were initially treated with morphine hydrochloride mild release tablets 10-30mg for pain relief, The observation group took 5-10 mg of olanzapine daily besides morphine hydrochloride sustained release tablets.

esults: the pain scores of patients，anxiety and depression in the combined group were significantly lower than the control group（P< 0.05）

Conclusion:the combined group are effective in the treatment of moderate and severe cancerous pain and pain relief, and also can improve the patient's anxiety and depression status and quality of life.

434. 基于高梯度磁场三维立体芯片捕获肿瘤源性外泌体检测早期原发性醛固酮增多症

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摘要：

目的: 原发性醛固酮增多症（Primary aldosteronism，PA）是最常见的继发性高血压之一。传统上，术前诊断 PA 亚型方式主要依赖 CT 和肾上腺静脉取血（adrenal vein blood sampling，AVS），前者诊断准确率低，后者具有侵入性、手术风险高。液体活检已经成为肿瘤早期诊断的重要研究方向。外泌体（exosomes）作为液体活检的“三驾马车”之一，包含丰富的遗传物质；其所携带的基因信息在某种程度上与肿瘤细胞 DNA 具有一致性。本课题组前期发现 PA 的单侧肾上腺腺瘤（aldosterone-producing adenoma，APA）亚型患者血浆外泌体中具有 KCNJ5 基因突变，因此，外泌体可能具有作为诊断 PA 亚型无创生物标志物的潜力。然而，传统的外泌体分离方法存在诸多问题，如超离，捕获效率低；沉淀法，纯度低等，大大限制的外泌体无创生物标志物的研究和应用，亟需开发一种具有高捕获效率和纯度的捕获外泌体方法，为 PA 亚型诊断提供有力的支撑。

方法：本研究开发一种基于高梯度磁场三维立体芯片捕获患者血浆外泌体，检测 PA 患者的 KCNJ5 基因突变，诊断 APA 亚型的方法。首先，构建了高梯度磁场三维立体芯片捕获装置，并捕获血浆外泌体；然后，通过 XNA-qPCR 法检测了靶向捕获的 KCNJ5 基因；最后，评估了 PA 患者血浆外泌体 KCNJ5 基因突变水平，确定 APA 患者的诊断性能。

结果：共聚焦显微镜结果显示该装置镍网上分布的 CD9/CD63 免疫磁珠成功捕获 PKH26 标记血浆外泌体。电镜结果显示经过 DTT 处理磁珠上的外泌体具有典型的“茶托状”双层膜小囊泡形态结构。优化该装置捕获血浆外泌体条件，通过外泌体 KCNJ5 基因 qPCR 检测发现，该装置捕获效率优于超离法。此外， XNA-qPCR 法检测了 PA 患者血浆外泌体 KCNJ5 基因突变，表明该方法可以对 PA 患者血浆外泌体 KCNJ5 基因突变进行有效的特异性识别，血浆外泌体 KCNJ5 基因突变有可能成为 PA 患者液体活检的生物标志物。

结论 ：成功构建了针对复杂样本体系，大体积样本量的血浆样本高效捕获外泌体，并检测 PA 患者的血浆中 KCNJ5 基因突变的方法。这种 PA 亚型诊断方法，为外泌体临床转化提供新的视野，为临床生物标志物的无创性检测提供新的方法。

435. NOL6, a new prognostic biomarker in breast cancer, which is related to tumor-infiltrating immunocytes

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Background: The roles of NOL6 in tumors and its relationship with immune infiltration remain unclear. Therefore, in this study, we aimed to investigate the expression level of NOL6 in tumors and its prognostic value, as well as the interaction between its expression and immune infiltration in breast cancer.

Methods: The expression level of NOL6 was evaluated by Oncomine, TIMER, and GEPIA databases. We conducted a survival analysis via Kaplan-Meier Plotter and GEPIA databases. The TIMER database was utilized to estimate the correlation of NOL6 expression level and immune infiltration.

Results: After screening a variety of tumors, it was found that comparing with normal tissue, the expression level of NOL6 in breast cancer tissue was significantly higher (P-value<0.05). Also, the higher expression level of NOL6 was demonstrated to contribute to better clinical outcomes of breast cancer patients (P-value<0.05). In addition, we found that the expression of NOL6 was associated with the infiltration of diverse immune cells in breast cancer, including M2 macrophages (ρ=-0.025, P-value<0.05) and CAFs (ρ=-0.179, P-value<0.05). Notably, survival analysis showed that patients with high NOL6 expression + low M2 macrophages/CAFs infiltration had high cumulative survival rates (HR=1.63, P-value<0.05; HR=1.53, P-value<0.05).

Conclusion: NOL6 plays a crucial role in the development of breast cancer and be a valuable prognostic biomarker. A therapeutic strategy that focuses on NOL6 and immune cells, like M2 macrophages or CAFs, may provide a new way for the treatment of breast cancer.

436. C2orf40 inhibits Hepatocellular cancer by reducing UBR5 ubiquitination and upregulation of P21

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Although the treatment of hepatocellular carcinoma (HCC) made great progress in recent years, there is still not satisfactory. Targeted therapy has become a new direction in the treatment of HCC, and seeking for new therapeutic targets is the current research hotspot. C2orf40 has been reported as a tumor suppressor gene (TSG) in many cancers, however, the role and regulatory mechanism of C2orf40 in HCC remains to be studied.

Firstly, the down-regulation of C2orf40 in hepatocellular carcinoma cell lines and liver cancer tissue samples are often related to the methylation status of its promoter CpG from online data and clinical tissue samples. Then， in order to understand the role of C2orf40 in HCC, we constructed a hepatocellular cell lines stably expressing C2orf40 by transfecting C2orf40 plasmid into Hep3B and HepG2 HCC cell lines. We found that: overexpression of C20rf40 in HCC cell lines could effectively inhibit the proliferation via CCK8 and Colony formation assay；recovery of C2orf40 expression can induce G0 / G1 phase arrest and apoptosis by flow cytometry; overexpression C2orf40 could significantly inhibit cell migration and invasion through wounding healing assay, and Transwell. The above experiments proved the inhibitory effect of ECRG4 on tumor in vitro. Next, the xenograft tumor model in nude mice was used to prove the anti-tumor effect of C2orf40 in vivo. By injecting C2orf40 overexpression cells and vector control cells, after 25 days of observation, and recording the growth every 3 days, the following results were obtained: the tumor growth rate of C2orf40 group was much lower than that of the control group, and the average tumor volume and tumor volume were significantly lower than those of the control group. HE staining, immunohistochemistry and TUNEL staining also proved that C2orf40 can reduce cancer cell proliferation and promote cancer cell apoptosis. Finally, we confirmed the protein co-localization between C2orf40 and UBR5 by immunofluorescence, and proved that C2orf40 may up-regulate p53 and 21 by reducing the ubiquitination of UBR5 by Western blot assay.

In conclusion, in our study, the low expression of C2orf40 in HCC was reported for the first time to be

related with promoter CpG methylation and the recovery of C2orf40 can inhibit the tumorigenesis. Furthermore, we found that C2or40 may play as a tumor suppressor and inhibit the ubiquitination of UBR5, thereby promoting the expression of P53/P21. Our findings also support the possibility of C2orf40 as a prognostic biomarker and a potential therapeutic target in HCC.

437. Integrating multi-omics data to identify subtypes and prognostic biomarkers in acute myeloid leukemia

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Motivation: The subtypes of Acute myeloid leukemia (AML) are usually defined by morphology and genetic mutations, which are inadequate in clinical diagnosis and prognosis. Integration analysis of multi-omics data has great potential to discover new biomarkers of AML, which may contribute to a comprehensive understanding of the biological mechanisms of disease development.

Results: Two subtypes, C1 (N = 82) and C2 (N = 51), were identified from 133 TCGA-LAML samples containing RNA expression, miRNA expression, DNA methylation and DNA copy number data by an unsupervised clustering algorithm, and the overall survival of C1 was significantly worse than C2 ($P = 0.0037$). These two subtypes are less correlated with main clinical features (FAB morphology, Cytogenetics risk category, Neoadjuvant treatment), suggesting that they are typing strategies independent of traditional subtypes. The immune scores ($P = 0.0009$), stromal scores ($P = 0.0421$) and immune cytolytic activity scores ($P = 0.0014$) estimated from C1 were significantly higher than C2. The estimated proportion of infiltrating regulatory T cells in C1 was significantly higher than C2 ($P < 0.05$), proportion of infiltrating memory B cells was in the opposite ($P < 0.01$). The mutation frequency of TP53 ($P < 0.05$) in C2 was lower than C1, and IDH2 ($P < 0.01$) and WT1 ($P < 0.05$) was in the opposite. There was no significant difference in DNA copy number between these subtypes. Therefore, C1 is considered to be a more dangerous and severe subtype. A total of 80 hypomethylated up-regulated genes were identified, the expression of 29 genes and the methylation level of 32 CpG sites were significantly correlated with the overall survival. There were 16 genes associated with prognosis at both expression level and methylation level of relevant CpG sites, which are enriched in AML-related biological processes and signaling pathways, such as cytokine-cytokine receptor interaction and glycosaminoglycan degradation. 10 differentially expressed miRNAs were associated with the prognosis. After feature screening, a logistic regression model consisting of three genes (GALM, PLA2G16, ROBO3), two methylation CpG sites (cg09436502, cg12043428) and one miRNA (hsa-mir-181d) , which are considered as prognostic biomarkers, was basically able to distinguish two subtypes (Accuracy = 0.7407, AUC of ROC = 0.8882). The analysis found that downregulated hsa-mir-181d was significantly associated with poor prognosis, its expression was

negatively correlated with the expression levels of GALM (r = -0.4959, P <1e-09) and PLA2G16 (r = -0.4368, P < 1e-07), while there was a possible binding site between hsa-mir-181d and PDK4, a related gene of cg09436502. In addition, upregulated PLA2G16, GALM and ROBO3 were also associated with poor prognosis, and there was a weak protein interaction between PDK4 and GALM, PLA2G16.

Conclusions: Integrating multi-omics data using machine learning algorithms identified two subtypes of AML that differ from traditional subtypes, several related protein-coding genes, miRNA, and methylated CpG sites were found to affect the prognosis as biomarkers between these two AML subtypes. This work revealed some insights into the disease progression of AML, and the mechanism of these biomarkers needs to be further studied in vivo.

438. Comprehensive analysis of key genes associated with ceRNA networks in nasopharyngeal carcinoma based on bioinformatics analysis

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Background: Nasopharyngeal carcinoma (NPC) is an epithelial malignancy with high morbidity rates in the east and southeast Asia. The molecular mechanisms of NPC remain largely unknown. We explored the pathogenesis, potential biomarkers, and prognostic indicators of NPC.

Methods: We analyzed mRNAs, long non-coding RNAs (lncRNAs), and microRNAs (miRNAs) in the whole transcriptome sequencing dataset of our hospital (five normal tissues vs. five NPC tissues) and six microarray datasets (62 normal tissues vs. 334 NPC tissues) downloaded from the Gene Expression Omnibus (GSE12452, GSE13597, GSE95166, GSE126683, and GSE70970, GSE43039). Diferential expression analyses, gene ontology (GO) enrichment, kyoto encyclopedia of genes and genomes (KEGG) analysis, and gene set enrichment analysis (GSEA) were conducted. The lncRNA-miRNA-mRNA competing endogenous RNA (ceRNA) networks were constructed using the miRanda and TargetScan database, and a protein–protein interaction (PPI) network of diferentially expressed genes (DEGs) was built using Search Tool for the Retrieval of Interacting Genes (STRING) software. Hub genes were identifed using Molecular Complex Detection (MCODE), NetworkAnalyzer, and CytoHubba.

Results: We identifed 61 mRNAs, 14miRNAs, and 10 lncRNAs as shared DEGs related to NPC in seven datasets. Changes in NPC were enriched in the chromosomal region, sister chromatid segregation, and nuclear chromosome segregation. GSEA indicated that the mitogen-activated protein

kinase (MAPK) pathway, phosphatidylinositol-3 OH kinase/protein kinase B (PI3K-Akt) pathway, apoptotic pathway, and tumor necrosis factor (TNF) were involved in the initiation and development of NPC. Finally, 20 hub genes were screened out via the PPI network.

Conclusions: Several DEGs and their biological processes, pathways, and interrelations were found in our current study by bioinformatics analyses. Our fndings may ofer insights into the biological mechanisms underlying NPC and identify potential therapeutic targets for NPC.

439. Exploring the heterogeneity of luminal B in breast cancer based on DNA methylation

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Breast cancer is a heterogeneous disease that affects people's health. Although current treatments have reduced the mortality rate of breast cancer, the estimated number of deaths due to breast cancer worldwide is expected to increase significantly each year. Therefore, the diagnosis and treatment of breast cancer are very important. Because of the high heterogeneity of breast cancer, the most important step is to classify breast cancer. Perou and Sorlie et al. divided breast cancer into five subtypes: luminal epithelial A (Luminal A), luminal epithelial B (Luminal B), HER2 overexpression type, basal-like type (BLBC), and normal like type. Among them, Luminal B subtype has aggressive clinical and biological characteristics . In contrast to luminal A tumors that usually receive endocrine therapy, Luminal B should be used more aggressive treatments. Due to the molecular and clinical heterogeneity of this Breast cancer subtype, this treatment is not always effective , so the application of molecular data to its classification is important for its diagnosis and prognosis. We are concerned about the luminal B of breast cancer that a common breast cancer subtype, which shows differences in treatment prognosis. We applied TCGA DNA methylation data and cBioPortal clinical data for breast cancer luminal B subtype to divide it into three subgroups and compared the differences between the three groups. In summary, we explained that DNA methylation can group a single subtype of breast cancer, described the subgroups of breast cancerLuminal B to achieve accurate diagnosis and effective treatment, and explained the differences in three subgroups of luminal B.

440. Long non-coding RNA NEAT1 Regulate the Self-renewal of Liver Cancer Stem Cells via the Hippo Signal Pathway

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lncRNAs play an important role in regulating the function of cancer stem cells (CSCs), and lncRNA NEAT1(The nuclear paraspeckle assembly transcript 1) has been reported to promote cancer progression, but the regulatory role of NEAT1 in liver cancer stem cells (LCSCs) remains to be elucidated. Herein, we observed for the first time that NEAT1 was transactivated by stemness-associated factor SOX9 (SRY box-containing gene 9) and up-regulated in LCSCs. Moreover, our data suggest that NEAT1 interference inhibited the expansion and self-renewal ability of LCSCs, while overexpression of NEAT1 promoted the expansion and self-renewal ability of LCSCs. Mechanistically, NEAT1 physically interacts with AKAP8 protein, a chaperone of PKA (cAMP dependent protein kinase), to decrease the cytoplasmic distribution of PKA, thus attenuating the phosphorylation of LATS (large tumor suppressor kinase) and YAP (yes-associated protein). The nuclear translocation of YAP activated the Hippo signal pathway, affecting LCSCs expansion and self-renewal. Clinical investigation showed that high expression of NEAT1 was associated with chemotherapy resistance but sorafenib sensitivity, implying its role in individualized therapy. In conclusion, our data suggest that NEAT1 might be a promising therapeutic target against LCSCs and a potential predictor of patients benefit from chemotherapy.

441. FAM84B 通过 p53 通路促进食管鳞癌细胞增殖

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摘要

目的:研究食管鳞癌中 FAM84B 的表达情况及其对细胞生长的调控机制。**方法:**收集食管鳞癌病例并进行全基因组测序和外显子测序，筛选出拷贝数明显扩增的基因 FAM84B。在高表达 FAM84B 的食管鳞癌细胞系 KYSE150 中，应用小干扰感染法干扰 FAM84B 之后，采用 MTT 法和硬克隆形成实验观察 FAM84B 对细胞生长的影响。在低表达 FAM84B 食管鳞癌细胞系 KYSE450 中，应用质粒 pCMV-3×flag-FAM84B 过表达 FAM84B 之后，采用 MTT 法和硬克隆形成实验观察 FAM84B 对细胞生长的影响。采用 Western blot 检测敲低 FAM84B 的表达对细胞周期蛋白 CDK4、CDK6 和 CCND1 表达的影响。

结果:对 508 例 ESCC 石蜡切片进行全基因组测序，发现 FAM84B 基因在 508 例肿瘤组织中发现 109 例拷贝数扩增（21.45%）；FAM84B 存在于 8q24.21 附近，并且是一个显著放大的病灶峰；敲低 FAM84B 抑制食管鳞癌细胞增殖；过表达 FAM84B 促进食管鳞癌细胞增殖；

FAM84B 低表达促进 p53 介导的细胞周期进行。

结论:FAM84B 通过抑制食管鳞癌细胞 p53 通路蛋白的表达，促进细胞周期由 G1 期向 S 期转化，进而促进细胞增殖。

442. LINC00467 is up-regulated by TDG-mediated acetylation in non-small cell lung cancer and promotes tumor progression

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The long non-coding RNA (LncRNA) abnormally expresses in several cancers including non-small cell lung cancer (NSCLC). To better understand the role of key lncRNA involving cancer progress, we conduct a comprehensive data mining on LINC00467 and determine its molecular mechanisms. We identified LINC00467 was the up-regulated lncRNA that common significantly differentially expressed in NSCLC and CRC tissues from GEO database. LINC00467 highly expressed in NSCLC tissues and associated with advanced clinical stages and poor outcome. Knockdown of LINC00467 inhibited cell growth and metastasis via regulating the Akt signaling pathway. Finally, we demonstrated that TDG mediated acetylation is the key factor controlling LINC00467 expression. In conclusion, LINC00467 promotes NSCLC progression via Akt signal pathway. The identified LINC00467 may serve as a valuable diagnostic and prognostic biomarker as well as a therapeutic target for NSCLC.

443. MSIsensor-pro: fast, accurate and matched normal-sample-free detection of microsatellite instability(MSI)

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Background. Microsatellite instability (MSI), is a key biomarker in cancer therapy and prognosis. Traditional experimental assays are as laborious and time consuming. Due to the requirement of matched normal samples, NextGeneration Sequencing (NGS)-based computational methods would not work on Leukemia samples, paraffin stored samples as well as patient derived xenografts/organoids. Here, we introduce MSIsensor-pro, an ultrafast, accurate and versatile MSI detecting NGS-based computational method to directly handle tumor samples of various target sequencing regions, sequencing depths and tumor purities.

Methods. MSIsensor-pro introduces a multinomial distribution (MND) model to quantify polymerase

slippages of microsatellite for each tumor sample and a discriminative site (DMS) selection method to enable MSI detection without matched normal samples. The magnitudes of deletion slippages (hysteresis synthesis, denoted as p) and insertion slippages (presynthesis, denoted as q) in the MND model are estimated with sequencing data in a given sample. Then, the p and q values are used to evaluate the stability of microsatellites sites in the tumor sample. Finally, the proportion of the unstable sites is used to score MSI status.

Results. We noticed that even without matched normal samples, based on benchmark result on 1,532 TCGA samples, MSIsensor-pro’s AUC (0.994) value was much higher than mSINGS (0.594), which also not requires matched normal. It is slightly higher than those of MSIsensor (0.989) and mantis (0.986), requiring both normal and tumor samples. For samples with low sequencing depth (20x) and low tumor purity (20%), the AUCs of MSIsensor-pro (0.998 and 0.966), MSIsensor (0.968 and 0.960) and mantis (0.959 and 0.935) were much higher than those of mSINGS (0.658,0.517). Additionally, MSIsensor-pro requires much less computational resources and runs more efficiently than all the other methods. Finally, MSIsensor-pro achieves more than 0.98 AUC with just 50 random DMS sites, indicating its potential application of MSIsensor-pro in target sequencing.

Discussion. By eliminating the requirement of matched normal samples, MSIsensor-pro enables MSI detections in paraffin stored samples, Leukemia samples and patient derived xenografts/organoids. MSIsensor-pro is able to score MSI with as few as 50 microsatellite sites, indicating its potential applications on target sequencing panels, stool DNA and liquid biopsy samples such as circulating tumor DNA (ctDNA).

444. Proteomic profiles of urinary exosomes derived from children with community- acquired pneumonia caused by viral and M. pneumoniae infection

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Pneumonia is the leading cause of death in young children globally. Diagnostic uncertainty regarding the etiology of pneumonia in pediatric populations contributed to ineffective therapy and public problems such as antibiotic overuse. It has been shown that urinary exosomes facilitated the diagnosis of numerous diseases. Characteristics of urinary exosomes, however, from patients especially pediatric patients with pneumonia remain to be ill-defined. Herein, we identified urinary exosomal proteins from children with community-acquired pneumonia (CAP) caused by viruses and M. pneumoniae using liquid chromatography–tandem mass spectrometry (LC-MS/MS). A variety of differentially expressed proteins that reflect different body responses to viral or M.

pneumoniae infection may be considered as the potential diagnostic markers for distinguishing viral pneumonia and non-viral pneumonia. Furthermore, viruses and M. pneumoniae induced dysregulation of proteins related to many diseases. We inferred that urinary exosomal proteins may predict other complications in pediatric patients with pneumonia. In conclusion, our proteomic analysis of urinary exosomes offers receivable strategies to look for diagnostic biomarkers.

445. 乳腺癌微环境预后相关基因的组学分析

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目的：探讨乳腺癌（breast cancer，BC）微环境对患者预后的影响，分析预后相关基因的预后价值。方法：结合 TCGA（The cancer genome atlas）数据库中 BC 转录组数据和相应临床信息，采用 ESTIMATE 算法进行免疫评分和基质评分，采用 Kaplan-Meier 法分析 BC 微环境与患者预后的相关性；采用 R 语言程序包 limma 筛选差异表达基因（DEGs），通过 GO、KEGG 富集分析确定 DEGs 潜在功能，通过 COX 回归分析和蛋白质互作（PPI）网络分析筛选与预后相关的核心 DEGs；最后采用差异分析、生存分析和临床相关性分析以评价核心 DEGs 的潜在预后价值。结果：从 TCGA 数据库下载 1178 例 BC 患者的转录组数据和相应临床信息，Kaplan-Meier 生存曲线显示免疫评分高组患者的生存时间比低分组长，基质评分组无明显差异。差异表达基因分析得到 201 个上调基因和 25 个下调基因，富集分析显示 DEGs 主要与免疫细胞增殖和分化、免疫反应、细胞因子活性和膜的细胞成分等相关。COX 回归分析和 PPI 网络分析显示 CD2 为预后相关核心 DEG，进一步分析显示 CD2 在肿瘤样品中的表达水平高于正常样品，同一患者的肿瘤和正常样品中观察到类似结果；CD2 高表达与 BC 患者预后呈正相关，其表达水平随着分期的进展而下降。结论：BC 微环境免疫细胞含量与患者预后呈正相关，CD2 表达水平可能有助于 BC 患者预后预测。这一结论有必要通过进一步的临床研究加以验证。

446. 基于微滴式数字 PCR 的非小细胞肺癌 EGFR-T790M 突变检测方法的建立

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【摘要】 **目的** 基于微滴式数字 PCR（droplet digital PCR，ddRCR）技术建立 EGFR-T790M 突变检测方法，并对该方法进行系统性优化及评估。**方法** 针对 T790M 突变，设计相关的探针引物，建立 ddPCR 反应体系，确立最佳退火温度并进行基本的性能验证。在此基础上，对 72 例 NSCLC 患者 cfDNA 样本进行临床验证，分析与伯乐 ddPCR 产品的一致性。**结果** 建立并优化 ddPCR 反应体系，线性评估示 R2>0.99，空白检测限为突变微滴数目≥2，特异性为 100%，灵敏度分析示突变检测下限可达到 0.05%，重复性及批间精密度 CV＜20%，准确度相对偏差在±10%范围内。对 72 例 NSCLC 患者 cfDNA 样本进行验证，与伯乐 ddPCR 产品的一致性为 91.67%（k=0.749；P<0.001）。**结论** 应用 ddPCR，成功建立非小细胞肺癌 EGFR-T790M 突变检测方法。

447. Tumor educated platelet C/D box small nucleolar RNA 55 as a potential diagnostic biomarker in lung cancer

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Background: Recent evidence suggests that snoRNAs play an important role in the regulation of mRNA splicing. Tumor-educated platelet (TEP) present both pre-mRNA and splice factors might indicate that TEP snoRNAs mediate alternative splicing. Herein, we systematically estimated dysregulation of snoRNAs in lung cancer and clarified the biomarker potential of SNORD55 in platelets.

Methods: We compared expression levels of snoRNA between lung cancer and normal tissues using SNORic datasets. Platelet was collected from plasma by low speed centrifugation and subjected to total RNA isolation. We determined SNORD55 abundance in platelets of patients with treatment-naive lung cancer and healthy controls by quantitative PCR.

Results: SNORD55 expression was significantly upregulated in LUAD and LUSC tissues compared to corresponding non-tumor tissues. However, expression of SNORD55 was significantly decreased in platelets from lung cancer patients especially from early-stage patients compared with healthy controls. Then, depending on receiver operating characteristic (ROC) curve analysis we found platelet samples were superior indicators better than tissues. Furthermore, platelet counts were closely associated with the growth during the carcinogenesis of lung cancer.

Conclusions: We have shown that SNORD55 in platelets could potentially serve as a non-invasive biomarker for diagnosing lung cancer.

Keywords: TEP, snoRNA, SNORD55, diagnosis, biomarker.

448. 通过单细胞测序分析肿瘤相关成纤维细胞 CAFs 在三阴性乳腺癌中的研究

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乳腺癌疾病是女性最常见的恶性肿瘤之一，据资料统计，发病率占全身各种恶性肿瘤的 7-10%，在妇女仅次于子宫癌。三阴性乳腺癌指一组雌激素受体（ER）、孕激素受体（PR）和人表皮生长因子受体-2（HER-2）表达均阴性的乳腺癌，好发于小于 40 岁的年轻女性，约占所有乳腺癌的 10%~22%。随着人类对肿瘤研究的不断深入，越来越多的研究表明，恶性肿瘤的生物学行为不仅取决于肿瘤细胞本身，肿瘤微环境对肿瘤的发生发展也起着决定性的作用。肿瘤微环境由细胞外基质(extracellular matrix，ECM)和各种肿瘤间质细胞(包括成纤维细胞、免疫细胞等)组成。其中，肿瘤相关成纤维细胞(cancer-associated fibroblasts，CAFs)是最丰富的肿瘤间质细胞，研究表明，它可分泌多种成份，参与多种癌症的发生发展过程。 乳腺癌的进展受到多因素的作用，不仅是单个肿瘤细胞的克隆性增殖，亦受肿瘤间质成分的影响以及肿瘤微环境中多种信号通路的调控，其中肿瘤细胞以细胞因子、趋化因子、生长因子、黏附分子为传递信号与 CAFs 进行信息交流，共同搭建动态网 络肿瘤微环境，并共同调控肿瘤微环境中的免疫应答反应。CAFs 是肿瘤微环境最重要的细胞成份之一，它不仅参与微环境血管和淋巴管形成、细胞外基质(extracellular matrix，ECM)重塑，而且促进乳腺癌的发生，癌细胞增殖、侵袭和转移，其标志分子也可作为乳腺癌临床诊断、靶向治疗和预后的生物标志。基于 GEO 数据库中关于三阴性乳腺癌的样本数据进行单细胞测序分析。通过单细胞测序分析得出肿瘤相关成纤维细胞的标志基因，根据 logFC 值由大到小排序，将表达量高且免疫细胞浸润相关性高的基因作为目标基因进行后续分析，来了解 CAFs 通过哪些调控机制来影响乳腺癌的侵袭转移，为乳腺癌治疗提供新的靶点。

449. 肿瘤相关成纤维细胞对肿瘤免疫代谢的影响

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生物医学研究者越来越重视肿瘤微环境（tumor microenvironment，TME）在肿瘤进展及治疗中的作用，其中，肿瘤相关成纤维细胞（cancerassociated fibroblasts，CAF）居重要地位。 CAF 能够直接促进肿瘤细胞的增殖、转移，也可以通过重塑 TME 以调节肿瘤免疫代谢调控肿瘤的发生、发展。CAF 还可通过影响非肿瘤成分或非肿瘤细胞与肿瘤细胞之间的相互作用，为肿瘤治疗开辟新的治疗方式。CAF 的代谢与高度增殖的细胞（如肿瘤细胞）的代谢相同，依赖

有氧糖酵解。 CAF 代谢的改变可能与肿瘤细胞产生的 ROS 诱导低氧诱导因子 1α（hypoxia-inducible factor-1α，HIF1α）表达相关。另外，CAF 代谢的改变伴随着分解代谢和自噬活动的增强，提示可能通 过再利用营养物质为其他 TME 细胞提供能量。由于肿瘤细胞往往处于低氧和营养匮乏的环境中，因此肿瘤细胞以合成代谢为主，而 CAF 则以分解代谢为主；有研究进一步提示肿瘤细胞的合成代谢与 CAF 的分解代谢是耦合的，CAF 的分解代谢可为肿瘤细胞的生长提供重要的代谢物质。肿瘤细胞与其 CAF 相互促进代谢重编程，建立了一种共生关系。目前有越来越多的研究关注肿瘤代谢方向，其中 CAF 对肿瘤代谢重编程的调节是重要方向，并且具有研究价值。

450. E3 连接酶 RNF40 的 GST 融合蛋白载体构建、表达与纯化及与 TWIST1 之间相互作用的研究

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【目的】

乳腺癌是女性中发病率最高的恶性肿瘤，TWIST1 基因是癌基因。我们实验室为明确是否 E3 连接酶 RNF40 与 TWIST1 相互作用，影响 TWIST1 的功能。

【方法】

1.融合蛋白的构建：设计引物，通过 PCR 扩增 RNF40 各基因片段，EcoR I、Nhe I 酶双酶切目的片段及载体，目的片段与载体连接，连接产物转化阳性转化子的筛选鉴定；2、GST 融合蛋白表达、纯化：将测序正确的单克隆转化，摇菌至 OD 值约 0.6，加入 IPTG 诱导，SDS-PAGE 凝胶电泳检测；将培养的菌液离心收集菌体细胞后，用 Lysis Buffer 悬浮菌体细胞超声破碎后，加入 Glutathione Sepharose 4B 琼脂糖凝胶，于 4 度旋转机孵育 70min 后洗脱，SDS-PAGE 凝胶电泳鉴定；3、体外结合实验：TWIST1 真核表达后，GST 融合蛋白-TWIST1 蛋白孵育，形成复合物，Western Blot 检测复合物；4、IP/Co-IP 实验：TWIST1、RNF40 蛋白样品处理，TWIST1 抗体-agarose beads 孵育，复合物洗涤，Western Blot 鉴定复合物。

【结果】菌落 PCR 鉴定琼脂糖凝胶电泳显示：RNF40 各段分别为 690bp、900bp、600bp、570bp、246bp,相应位置具有条带，经重组质粒酶切鉴定，酶切后 RNF40 各段在相应位置、4960 位置（载体）具有条带，测序鉴定：RNF40 各段均符合克隆质粒大小；用 SDS-PAGE 凝胶电泳检测融合蛋白的表达，发现经诱导后，RNF40 各段在相应位置具有亮带。纯化后，SDS-PAGE 凝胶电泳也发现上述位置具有条带，其它杂带变少，RNF40 的 GST 融合蛋白得到表达与纯化。后续我们实验室可能将继续 IP/Co-IP 研究 RNF40 和 TWIST1 两蛋白的相互作用及泛素化调控机制。

【结论】成功构建 E3 连接酶 RNF40 的 GST 融合蛋白载体并表达与纯化，为下一步实验分析 E3 连接酶 RNF40 与 TWIST1 是否相互作用提供了实验物质基础，为乳腺癌的诊治提供新的候选靶标。

451. Bioinformatics Analysis Finds Immune Gene Markers Related to the Prognosis of Bladder Cancer

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Bladder cancer is one of the most common malignant tumors of the urinary system that seriously threatens the health of a population. In recent years, the application of immunotherapy has significantly changed the treatment of bladder cancer, but only some patients can benefit from the treatment with immune-checkpoint inhibitors. Many problems are unsolved in the field of bladder cancer immunotherapy, especially in the search for genes that are critical to the level of immune cell infiltration and new effective therapeutic targets. We attempted to use bioinformatics analysis to identify immune gene markers related to the prognosis of bladder cancer and to establish a prognostic signature for bladder cancer patients based on their immune gene expression profiles. We used univariate Cox proportional hazards regression analysis, the least absolute shrinkage and selection operator (LASSO) Cox regression, and multivariate Cox proportional hazards regression analysis from The Cancer Genome Atlas (TCGA) bladder cancer cohort (TCGA-BLCA). Fifteen genes related to prognosis were screened using the survival analysis, correlation analysis, cancer and adjacent cancer differential expression analysis, and mutation analysis. The potential biological role of these genes was determined using survival analysis and principal component analysis (PCA). The receiver operating characteristic (ROC) curve assesses the prognostic value of the predictive signature. The gene ontology (GO), Kyoto encyclopedia of gene and genome (KEGG), Gene set enrichment analysis (GSEA), and other methods were used to reveal the differential gene enrichment in the signaling pathways and cellular processes of high- and low-risk groups. The single-sample gene set enrichment analysis (ssGSEA) method was used to quantify the infiltration levels of 24 immune cells in the tumor immune microenvironment and these immune genes were found to be closely related to the tumor immune microenvironment. In summary, we screened 15 immune genes that were closely related to bladder cancer overall survival (OS) and may be potential prognostic indicators of bladder cancer. They may have research and clinical application value in bladder cancer immunotherapy. we used 15 immune genes to construct a new immune-related gene signature that was verified and could be helpful in improving individualized prognosis of patients with bladder cancer.

452. AMPK 激活在肿瘤细胞转移过程的转移适应的机制研究

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AMP 激活的蛋白激酶（AMPK）是细胞代谢的关键调节剂，也是生物能量代谢调节的关键分子、被称为“细胞能量调节器”,在糖尿病、癌症和血管疾病中发挥重要作用。肿瘤细胞的演进与能量代谢调节、自噬、细胞周期调控和死亡方式等密切相关，而 AMPK 在这些功能中均发挥重要作用。研究证实，AMPK 是否促进还是抑制肿瘤的生长，还取决于肿瘤的类型、阶段以及能量需求的微环境。针对乳腺癌的转移，已有研究表明 AMPK 的过表达与乳腺癌患者较短的无转移生存期相关，且在动物实验模型相关数据的支持下，发现了相对于原位肿瘤，转移灶中 AMPK 的活性明显增高，并且表明它通过使癌细胞适应代谢和氧化应激，驱动丙酮酸脱氢酶复合物（PDHc）的激活来维持三羧酸循环，促进癌细胞转移。干扰 AMPKa-1 可降低乳腺癌患者肺转移的几率，而原发肿瘤的生长并不受此影响，至此由 AMPK 介导的 PDHA 磷酸化驱动 PDHc 活化和 TCA 循环为癌细胞能够适应转移的微环境发挥了重要作用，这就提示 AMPK 激活在肿瘤细胞转移过程起至关重要，也为发生转移的肿瘤的靶向治疗提供了新思路。

453. TAMS 作为 TNBC 免疫治疗关键靶点的前瞻性研究

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通过对 TCGA 数据库中 1099 例乳腺癌样本的临床数据集合，筛选出 123 例三阴乳腺癌患者 mRNA 表达数据并整理删除正常组织样本数据,识别出免疫细胞表达数据集中所有 $p<0.01$、折叠改变≥1.5 或≤-1.5 的双向表达基因(DEGs),对 200 个上调基因和 11 个下调基因进行了基因本体(GO)和京都基因组百科全书(KEGG)富集分析,发现差异基因蛋白富集通路多集中在巨噬细胞表达。此外，亦有研究证明 TAMs 与肿瘤的发生和发展密切相关，分为与炎症反应相关的 M1 型和与肿瘤相关的 M2 型，参与了肿瘤的免疫调节，促进肿瘤的浸润和转移。与其他乳腺癌组织学相比，TNBC 分泌更多的粒细胞集落刺激因子，从而促进 M1 细胞向 M2 状态转化。大量 CD163 + M2 型巨噬细胞与肿瘤细胞增殖、分化不良、组织学导管类型密切相关，CD163 + 细胞直接与人表皮生长因子受体阴性和 TNBC 组织学相关，与 luminal a 亚型呈负相关。不同乳腺癌亚型对于不同分类巨噬细胞以及其余免疫细胞 T 细胞，B 细胞（CD5+、CD10+等），肿瘤相关成纤维细胞等又有不同的作用通路和临床意义，提示可以针对 TAMS 或免疫微环境中其他细胞对 TNBC 进行免疫治疗。在三阴乳腺癌生物信息的基础上，针对三阴乳腺癌和非三阴乳腺癌样本进行下一步细胞对比实验，以观察 TAMS 可以作为三阴乳腺癌切实有效的治疗靶点。

454. 利用生物信息学分析乳腺癌中免疫相关的 lncRNA

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近年来，随着分子生物学的快速发展，肿瘤的分子诊断已成为肿瘤研究的热点，探讨与乳腺癌相关的癌基因或抑癌基因为乳腺癌的临床诊疗提供了新的方向。长链非编码 RNA（long non－coding RNA，lncRNA） 是近年来恶性肿瘤研究中火热的领域，它因不编码蛋白，曾被称作“垃圾基因”。随着科研的发展， 越来越多的 lncRNA 被证实参与乳腺癌的发生发展，相对正常组织，某些 lncRNA 在乳腺癌组织中异常表达，并导致乳腺癌细胞增殖能力增强、具有侵袭能力、介导上皮－间质转化、导致耐药等。基于 TCGA 数据库中 1099 例乳腺癌患者的转录组数据和临床数据。通过整理转录组数据将 mRNA 和 lncRNA 区分开，后续在 GSEA 官网下载两个免疫相关的基因集分别为 IMMUNE_RESPONSE 和 IMMUNE_SYSTEM_PROCESS，将其和 mRNA 做共表达分析提取出和免疫相关的表达基因。再将所提出的免疫基因和 lncRNA 中的基因共表达，提取出免疫相关的 lncRNA 基因,继续将其和临床数据一起分析得到预后相关的基因。通过单因素和多因素 COX 模型构建得到一个风险基因相关基因集，根据这个基因集做后续相关的生存分析、风险曲线、独立于后分析、多指标 ROC 曲线、临床相关性分析、主成分分析、GSEA 富集分析。结果表明和预后相关的高风险的且和免疫相关的 lncRNA 有 LINC01235、OTUD6B-AS1。综上相关研究，将有利于我们在临床治疗中选择个体化精准治疗，减少患者复发风险，为乳腺癌新疗法的开发提供可能的靶点。

455. 4K 评分法在前列腺癌中的应用以及发展前景

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前列腺癌（Carcinoma of Prostate，CaP）是泌尿外科最常见的恶性肿瘤，也是男性发病率第二的恶性肿瘤，肿瘤标志物（Tumor Marker，TM）的应用可以对肿瘤的早期诊断，临床分期和治疗有着积极作用。现在血清前列腺特异性抗原（Prostate Specific Antigen，PSA）是应用最为广泛的前列腺肿瘤标志物，但因其特异性较弱的局限性，过分依赖该项指标很容易会导致过度医疗，目前研究的比较有发展前景的就是 4K 评分法（现已被美国 NCCN 指南纳入临床实践），将四激肽释放酶标志物组合（tPSA、fPSA、hK2、intact PSA）进行标记，开发为专业的评分系统，以激肽释放酶为依托，将 PSA 及其衍生物与直肠指检（DRE）作为补充，预测准确率比单纯筛查 PSA 更高，作为前列腺癌筛查方式的补充，对于指导前列腺癌主动监测、早期诊断前列腺癌及预测高风险前列腺癌，避免过度医疗有着重要的参考价值和巨大的潜力。

456. Specific analysis of pseudogenes mediated by DNA methylation during breast cancer progression.

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DNA methylation presents a random distribution on the genome, and some CpG position occur on fragments of pseudogenes. Although pseudogenes have long been widely regarded as non-functional gene copies in the genome, DNA methylation may make it possible for pseudogenes to undergo functional changes. During the occurrence and development of cancer, along with changes in various molecular mechanisms, in order to reveal the function of pseudogenes during breast cancer progression, we analyzes the role of DNA methylation of pseudogenes in the progression of breast cancer.

1019 Breast cancer samples from TCGA database were divided into five groups of samples that deteriorated according to pathological characteristics, and an orderly multiple logistic regression analysis was performed to screen out 1479 differential DNA methylation pseudogenes related to breast cancer development. The correlation of DNA methylation was calculated according to the methylation level of pseudogenes in each stage and an integrated pseudogene interaction network PMC (Pseudogene methylation correlation network) was constructed. PMC contains 1406 pairs of 243 pseudogene interactions. Combined with the parent gene corresponding to the pseudogene, a subtype network containing the parent gene was extracted from the protein interaction network to form a WTP (Wild type parent gene protein-protein network) of the parent gene. Develop algorithms based on PMC and WTP: Screening of specific pseudogenes based on double-layer neural network (SSDN), which defines the level of DNA methylation of pseudogenes involved in breast cancer development The MPMB (Methylation of Pseudogenes Mediates the index of Breast cancer development) identifies pseudogenes that play a key mediator role in breast cancer.In the end, 46 pseudogenes were obtained. Survival analysis was performed on their DNA methylation levels and the survival time of breast cancer patients. The pseudogenes ENSG00000235988 (AC245100.5) and ENSG00000226361 (TERF1P5) were significantly associated with patient survival.

The results indicate that DNA methylation-mediated pseudogenes can be used as important tumor markers related to breast cancer progression, and DNA methylation plays an important role in the function of pseudogenes, which is important in the field of oncology In-depth understanding and discovery of the function of pseudogenes provide a new perspective.

457. Saliva-derived cfDNA is Applicable for EGFR Mutations Detection but not for Quantitation Analysis in Non-Small Cell Lung Cancer

shanshan ding

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Background: Both quantitative and qualitative aspects of plasma cell-free DNA (plasma cfDNA, pcfDNA) have been well-studied as potential biomarkers in non-small cell lung cancer (NSCLC). Accumulating evidence has proven that saliva also has the potential for the detection and analysis of circulating free DNA (saliva cfDNA, scfDNA).

Methods: In the current study, we aimed to explore the potential application of scfDNA in NSCLC diagnostics and consistency of epidermal growth factor receptor (EGFR) mutations detection in paired pcfDNA and scfDNA using droplet digital PCR (ddPCR) and analyzed the relationship between EGFR mutations and clinical treatment response.

Results: In the quantitative cohort study, scfDNA concentration in NSCLC patients was not different from that in healthy donors, or in benign patients. ScfDNA concentration was significantly lower than pcfDNA concentration, yet they are not statistically significant in relevance (Spearman's rank correlation r=-0.123, P=0.269). In the qualitative cohort study , the overall concordance rate of EGFR mutations between pcfDNA and scfDNA was 83.78% (31 of 37; k=0.602; P< 0.001). EGFR mutations detection in paired pcfDNA and scfDNA was significantly correlated with the clinical treatments response (Spearman's rank correlation r=0.664, P=0.002).

Conclusions: Our results demonstrated that saliva might not be the idea material for cfDNA quantitative test, and scfDNA concentration is not applicable for NSCLC diagnostics. Conversely, scfDNA was capable of acting as the supplement for EGFR mutations due to the coincidence rate of EGFR mutations detection between scfDNA and pcfDNA.

458. The expressions of SIVA1 and UBE2A are associated with poor prognosis in nasopharyngeal carcinoma with chemoradiotherapy

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Purpose: The study aimed to illustrate the association of the expression of SIVA1 and UBE2A with the clinical prognosis in nasopharyngeal carcinoma (NPC) after chemoradiotherapy.

Methods: All patients were initially positive diagnosed with NPC between June 2016 and December 2018, the median follow-up period was 25 months. The expression of SIVA1 and UBE2A protein in 57 and 52 NPC patients' tissues pretherapy were detected by immunohistochemistry, respectively.

Results: NPC patients with a positive SIVA1 or high UBE2A expression had a shorter 2- year PFS or OS as compared with those with a negative SIVA1 or high UBE2A expression (all P<0.05, respectively). In the Cox model, 2-year PFS and OS was shorter in those patients with positive SIVA1 expression compared with negative SIVA1 expression (HR=3.971, P=0.008; HR=2.794, P=0.024). Comparison of 2-year PFS between high and low UBE2A expression demonstrated decreased outcome in high UBE2A expression NPC patients after radiotherapy (HR=3.048, P=0.028).
Conclusion: Positive SIVA1 and high UBE2A expression identified a poor prognosis in patients with NPC after chemoradiotherapy.

459.机器学习随机生存森林定义铁死亡相关标志物预测膀胱癌患者预后及免疫治疗响应性

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背景：铁死亡是一种铁依赖性的新型的细胞程序性死亡方式，之前的研究证明了其对预后和免疫微环境的重要作用。目前尚无对膀胱癌铁死亡特征系统分析及其对于免疫检查点抑制剂治疗影响的研究报道。

方法:我们通过机器学习非监督聚类——K 均值聚类（Kmeans）算法全面评估 1,889 例膀胱癌患者的铁死亡水平差异，并与肿瘤微环境细胞浸润特性进行了系统关联。以探索铁死亡对于膀胱癌微环境的异质性影响。使用随机生存森林构建了铁死亡评分，通过单因素及多因素比例风险回归模型(Proportional Hazards Model，Cox)、受试者工作特征曲线 (Receiver Operating Characteristic Curve，ROC)、肿瘤免疫功能障碍和排斥（Tumor immune dysfunction and exclusion,TIDE）评分、路径对齐的子网映射（Subnetwork Mappings in Alignment of Pathways，SubMAP)等算法评估铁死亡评分预后意义及是否可以预测患者免疫检查点抑制剂获益。

结果:我们确定了膀胱癌存在四种不同的铁死亡水平，并展示了不同亚型之间的临床和病理特征、肿瘤干细胞指数、生物学信号通路、癌症免疫循环、拷贝数及体细胞突变差异，以探索影响铁死亡相关的潜在生物学途径，另外我们的结果表明铁死亡评分是可靠的、独立的预后标志物，铁死亡评分也可以预测免疫检查点抑制剂响应性，评分较高的患者表现出较高的免疫检查点分子表达，较低的肿瘤干细胞指数，对免疫治疗表现出显著的治疗优势。

总结:本研究证实铁死亡在肿瘤免疫微环境多样性和复杂性的形成中起着不可忽略的作用，增加了我们对膀胱癌铁死亡特征的认识，并提供指导更有效的个性化免疫治疗策略。

460. The model combined CEA and LDCT to identify BPNs from MPNs

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Abstract

Background

Lung cancer causes million deaths annually, with early diagnosis being urgent to effective treatment. LDCT could effectively detect early lung cancer and reduce lung cancer-related mortality. However, the high false positive rate limits its clinical application. Carcinoembryonic antigen (CEA), a common tumor biomarker, is involved in the early diagnosis of multiple tumors. Here we present a diagnostic prediction model for distinguishing benign pulmonary nodules (BPNs) from malignant pulmonary nodules (MPNs), which combined LDCT and CEA via machine learning.

Methods

We performed univariate analysis of 13 candidate LDCT characteristics in 363 participants (MPNs, n=271; BPNs, n=92). Eventually, we chose 5 significant predictors finally to construct the prediction model by using six machine learning algorithms. The six models were validated in an independent dataset of 129 patients, in which 92 lung cancers had been diagnosed in clinic. The diagnosis effect of the six models were evaluated by AUC, sensitivity, specificity.

Results

Our final diagnostic prediction model, established by logistic regression, which included CEA, nodule number, mediastinal lymph node enlargement, vessel convergence sign (VCS), spicule sign, lobulation sign owned a highest diagnostic efficiency, and the AUC, sensitivity, specificity were 0.914 (95%CI: 0.883-0.945), 79.3%, and 89.1%, respectively. External validation showed area AUC was 0.908 (95%CI: 0.858-0.957). Aim to early stage of lung cancer and benign nodules, the model had the favourable diagnostic effect as well, the AUC, sensitivity, specificity were 0.913 (95%CI: 0.881-0.945), 89.1%, and 79.2%. Especially for the pulmonary nodules which diameters were less than 3 cm, the model still own a benign differential diagnosis performance (AUC=0.865, 95%CI: 0.814-0.916, sensitivity=73.1, specificity=86.1).

Conclusion

We constructed a favourable model, combined with five LDCT characteristics and CEA, which may be useful for screening BPNs from MPNs in clinic.

Key words

CEA, LDCT, model, machine learning, lung cancer, MPNs, BPNs

461. Tumor-derived exosomal miRNA as diagnostic biomarkers in non-small cell lung cancer

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Background: Delayed diagnosis is the main obstacle to improve prognosis of non-small cell lung cancer (NSCLC). Novel biomarkers for the diagnosis of NSCLC are urgently needed. This study aimed to identify the specific exosomal miRNAs with diagnostic and prognostic potential in NSCLC patients.

Materials and Methods: Transmission electron microscopy (TEM), qNano and western blots were used to characterize the exosomes isolated from the serum of NSCLC patients (n=330) and healthy donors (n=312) by ultracentrifugation. Exosomal miRNAs were profiled by miRNA microarrays and verified by quantitative PCR (qPCR). The diagnostic accuracy was determined by receiver operating characteristic (ROC) analysis.

Results: A total of differential 22 miRNAs were screened out based on $P < 0.05$ and fold difference>2.0 by miRNA microarrays, among which, exosomal miR-5684 and miR-125b-5p were significantly down-regulated in NSCLC patients compared to healthy donors, processing favorable diagnostic efficiency for (early) NSCLC. Importantly, the exosomal miR-125b-5p were associated with metastasis ($P < 0.0001$), chemotherapeutic effect ($P=0.007$) and survival ($P=0.008$).

Conclusion: Exosomal miR-5684 and miR-125b-5p levels are significantly down-regulated in NSCLC patients, and serve as the promising diagnostic and prognostic biomarkers for NSCLC.

Keywords: non-small cell lung cancer, serum, exosome, MiR-5684, MiR-125b-5p, biomarker, diagnosis.

462. Tumor-derived exosomal miR-620 as a diagnostic biomarker in non-small cell lung cancer

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Background: Accumulating evidence support the role for exosomal miRNA in diagnosis. The purpose of this study was to identify the tumor- derived exosomal biomarkers in the serum to improve the diagnostic value of patients with non- small cell lung cancer (NSCLC).

Materials and Methods: Exosomes isolated from the serum of NSCLC patients (n = 235) and healthy donors (n=231) by ultracentrifugation were characterized using transmission electron microscopy, qNano, and Western blot. Differential serum exosomal miRNAs were validated by qPCR.

Results: After GO and KEGG analysis showed that miR-620 were associated with vascular wound healing and PARP signaling pathway. Our results showed that exosomal miR-620 was significantly down-regulated in NSCLC patients ($P<0.0001$) as well as in early-stage NSCLC patients ($P<0.0001$) compared with those from healthy controls, the area under the curve (AUC) was 0.728, 0.707, respectively. Exosomal miR-620 was associated with drinking ($P=0.008$) and distant metastasis ($P=0.037$). Additionally, the down-regulated exosomal miR-620 was associated with chemotherapeutic effect ($P=0.005$). Cell proliferation and apoptosis experiments illustrated that overexpression of miR-620 inhibited cell proliferation and promoted apoptosis, while down-expression of miR-620 promoted cell proliferation and inhibited apoptosis.

Conclusion: Serum exosomal miR-620 was a promising diagnostic and prognostic non-invasive biomarker in NSCLC patients.

Keywords: Non-small cell lung cancer, Serum, Exosomes, MiR-620, Biomarker, Diagnosis

463. An injectable nano-platform based on GSH-responsive PLGA for dual-delivery of doxorubicin and curcumin to overcome multidrug resistance in cancer therapy

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Background: Multidrug resistance (MDR) is the main restriction on the effectiveness of cancer chemotherapy. The rapid development of nanotechnology opens up a new avenue to overcome tumor MDR.

Methods: In this study, a drug delivery nano-platform based on PEGylated PLGA with glutathione (GSH) response (DCNP) for the co-delivery of doxorubicin (DOX) and curcumin (CUR) was

prepared. The GSH-triggered drug release profile and cellular uptake efficiency of DCNPs were studied in vitro. MDR tumor cells were subsequently introduced to investigate the p-glycoprotein suppression efficiency and cytotoxicity of DCNPs. Finally, the DCNPs were injected into MDR tumor-bearing mouse model to explore the systemic toxicity, pharmacokinetics and anti-tumor efficiency.

Results: The DCNPs showed stable drug encapsulation capability in normal physiological environment and rapid drug release under high concentration of GSH. In vitro results revealed that the DCNPs could significantly improve the cellular uptake and cytotoxicity of DOX in MDR cells, which was attributed to the encapsulation of drug bypassing the protein pump on one hand, and the inhibition of p-gp expression by CUR on the other hand. Moreover, the DCNPs showed better biocompatibility, more prolonged blood circulation and enhanced anti-tumor efficiency compared to free drugs.

Conclusion: The GSH-responsive drug delivery nano-platform DCNPs had controllable drug delivery capability with p-gp suppression and enhanced anti-tumor efficiency in MDR tumors, providing a promising candidate for overcoming tumor MDR.

464. The effects of non-thermal plasma on NSCLC - a study based on a 3D cell culture system

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Lung adenocarcinoma is one of the leading mortality cancer endangering human, the existing of cancer stem cells (CSCs) is one of the main reason for failure of chemotherapy and radiotherapy. Non-thermal atmospheric pressure plasma (plasma for short) has been shown to have promising anticancer activity by modulating intracellular reactive oxygen species (ROS). However, very less studies reported the effects of plasma on cancer using 3D culture model, which is an ideal model to study CSCs. In this study we used a 3D cell culture model to investigate the role of plasma-jet activated medium (PAM) on lung denocarcinoma stem cells (LASCs). Stemness marker expression, tumorigenic ability, etc. were examined after PAM treatment. Our results reveal that PAM could inhibit proliferation and tumorigenesis of lung adenocarcinoma stem cells, furthermore, we found that the inhibition effects was conducted by PAM-induced cell autophagy of lung adenocarcinoma stem cells. The therapeutic efficacy of PAM was further demonstrated in mice bearing 3D cultured A549 multiple cellular spheroid lung adenocarcinoma xenografts. Our study suggests that the novel ROS-modulating method by PAM has promising anticancer activity with an advantage of elimination of stem-like cancer cells. This novel device merits further study to evaluate its potential for use in cancer treatment.

465. 基于 3D 模型探索癌相关成纤维细胞分泌的 CXCL14 在非小细胞肺癌铂类耐药中的作用及机制

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非小细胞肺癌(NSCLC)治疗中以铂类为基础的化疗方案发挥着举足轻重的作用，然而肿瘤细胞对化疗药物产生耐药影响患者疗效和预后，因而对肺癌晚期耐药等进展相关机制的探索有较大临床意义。肿瘤作为一个整体其微环境（microenviroment）的重要性近年来被越来越多研究证实。癌相关成纤维细胞（cancer associated fibroblasts，CAFs）是肿瘤微环境中占比最高的基质细胞型，研究表明 CAFs 的不同分泌蛋白可促进结直肠癌、肺癌、乳腺癌及胰腺癌等的进展和耐药，而其导致耐药的机制有待进一步探索。我们前期成功培养原代非小细胞肺癌患者的肿瘤相关成纤维细胞及癌旁成纤维细胞；通过筛选表达发现 CAFs 高表达 CXCL14 等分泌蛋白。体外试验发现尽管在增殖方面无明显作用，CXCL14 可促进肿瘤细胞迁移和侵袭，同时可以增强肿瘤细胞对顺铂的耐药能力。为了进一步验证该结果我们利用 3D 培养模型（细胞系及患者来源的类器官模型）结合高内涵拍摄观察细胞对药物的反应。在细胞系 3D 模型中 CXCL14 的添加降低了使用化疗药后 PI/Calcein-AM 的细胞比例，同时 Cleaved-Caspase3 染色比例降低。接下来我们在细胞系和高表达 CXCL14 的 CAFs 的共培养体系中添加 CXCL14 的中和抗体，发现 80ng/ml 中和抗体可以逆转 CAFs 的部分功能。在类器官培养模型中，我们也观察到 CXCL14 添加组在化疗药处理后较对照组活力更强。在机制上我们发现 CXCL14 处理可以增强 ALDH1A1 细胞比例，侧群细胞比例亦增高，我们检测了干性及耐药相关指标发现 ABCG2、CD133、CXCR4 等升高，接下来我们将通过动物实验进一步证实我们的相关猜想。本研究为肿瘤耐药逆转提供新的靶点和策略，有助于我们更深入了解肿瘤进展中的分子事件，为综合治疗提供新思路。

466. Nasopharyngeal carcinoma diagnosis based on a single-cell Raman-based platform

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Nasopharyngeal carcinoma is a kind of head and neck cancer with high degree of malignancy, which is easy to relapse and metastasize. Traditional testing relying on immunofluorescence or fluorescent in situ hybridization were proved to be tedious and expensive. Accurate, quick and intact diagnose is important for improving survival rate of those patients with nasopharyngeal carcinoma. Raman-based cell assay provided abundant varied compound fingerprints of cancer cells in comparison with normal

cells, is a promising tool for evaluation the cancer progress. Herein, we developed an efficient and accurate method on a label-free and noninvasive single-cell Raman microspectroscopy (SCRM) platform, to distinguish NPC cell lines 5-8F, 6-10B, SUNE1, CNE1, CNE2, C666-1, HK1 from nasopharyngeal normal cell line NPEC1-BMI1. NPC cancer cells and non-cancer cells can be differentiated by analyzing their intrinsic phenotypic Raman spectra at a large scale (5337 cm-1 Raman spectra in total). The Raman spectra of glycogen, nucleic acids and tyrosine in NPC cancer cells were significant higher than those in non-cancer cells. However, the Raman spectra of lipids in NPC cancer cells were significantly lower than those in non-cancer cells. Those results are consistent with the high expressions of glycogen, nucleic acids and tyrosine and low expression of lipid in NPC cancer cell. Support Vector Machine (SVM) analysis distinctly differentiate NPC cancer cells from non-cancer cells with 97.85% accuracy. Nasopharyngeal tissues were also clearly distinguished from control tissues with 93.95% accuracy. Together, our study developed an efficient SCRM-based method to evaluate the cells canceration of nasal tissue in advance which shed light on established quick and accurate diagnose during surgery of Nasopharyngeal carcinoma. As a complementary tool, the platform was expected to view the real-time dynamic cancerization status and contributed to improve the diagnosis and operation effects.

467. Effecting of prognostic factors without pathological complete response after neoadjuvant therapy for breast cancer

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Objective: Pathological complete response (pCR) after neoadjuvant therapy (NAT) for breast cancer is significantly associated with long-term survival. However, most patients do not achieve pCR after NAT, and the prognostic factors are not yet clear. Therefore, this study aimed to explore the factors that influence the prognosis of patients who do not achieve pCR after NAT. **Methods:** We performed a retrospective study of the clinical data between 2010 and 2017. 1048 patients with breast cancer did not achieve pCR after evaluation of the residual cancer burden (RCB) post-NAT. In this study, clinicopathological factors were investigated for associations with disease-free survival (DFS) and overall survival (OS). SPSS21.00 was used for statistical analysis, and Kaplan-Meier and Cox regression for survival analysis. $P<0.05$ was considered statistically significant. **Results**: In this study, all patients with non-pCR after NAT for breast cancer were females, with an average age of 50±10.3 years (range, 24-77 years). Clinical stage and PR expression before NAT were found to influence DFS in non-pCR patients, while clinical stage before NAT was an independent influencing factor of DFS in non-pCR patients ($P<0.05$). Clinical stage before NAT, postoperative histological grade, tumor-

infiltrating lymphocytes (TILs), lymph node metastasis, and Ki67 expression were found to influence OS in non-pCR patients, while clinical stage before NAT, postoperative TILs and Ki67 expression were independent influencing factors of OS in non-pCR patients (P<0.05). According to the molecular classification of breast cancer patients, the clinical stage before NAT was independent influencing factors of DFS in non-pCR patients with luminal A breast cancer (P<0.05). The clinical stage before NAT was an independent influencing factor of OS in non-pCR patients with luminal B and triple negative breast cancer (P<0.05). Clinical stage before NAT and postoperative TILs were independent influencing factors of DFS and OS in non-pCR patients with HER2-overexpressing tumors (P<0.05). **Conclusion:** Non-pCR patients with an advanced clinical stage before NAT have a short overall survival and a high risk of recurrence and metastasis, and HER2 overexpressing non-pCR patients with high TILs have a long OS and a low risk of recurrence and metastasis.

468. FGF13 suppresses tumor proliferation and invasion by regulating Wnt in breast cancer

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Objective: Invasion and metastasis is the main cause of Breast cancer（BC） poor prognosis, but its molecular mechanism is still unknown. Studies have shown that FGF13 is expressed in a variety of tumors and is related to tumor progress. The purpose of this study is to analyze the effect of FGF13 on the proliferation and migration of Breast cancer, and to preliminary explore the possible molecular mechanism of FGF13 in breast cancer.

Methods: 22 ductal invasive carcinoma tissues and 19 ductal carcinoma in situ tissues were collected between 2016 and 2019 in the Fourth Hospital of Hebei Medical University .The expression of FGF13 was compared by real-time quantitative polymerase chain reaction （ RT-qPCR ） and immunohistochemical.Then we analyzed the role of FGF13 in breast cancers based on database. Overexpression of FGF13 in two BC cell lines, MDA-MB-231 and MCF-7 , MTS assays and clone formation assays were used to detect breast proliferation, wound healing Assay and transwell test were used for observing breast cancer migration. Next, we used RT-qPCR and Western blot to detect the expression of EMT (epithelial-mesenchymal transition) and Wnt markers mRNA and protein levels.

Results: Bioinformatics database analysisindicated that the high expression of FGF13 was closely associated with good survival in BC.Clinical results showed that FGF13 expression was higher in ductal carcinoma in situ than that in invasive carcinoma (P<0.05). Then we found that FGF13 inhibited the proliferation of BC cells in MTS and clone formation experiments(P<0.05). wound healing Assay and Transwell assay demonstrated that FGF13 diminished cell migration of BC cells(P<0.05). Additionally,The EMT epithelial marker CDH1 mRNA level increased in the

FGF13 overexpression group, while the mRNA and protein of mmp2，zeb1 and Snail1 decreased. And Wnt pathway related genes mRNA and protein levels were down-regulated in the FGF13 overexpression group.

Conclusion: Taken together, our results suggest that FGF13 acts as a tumor suppressor that negatively regulates BC cell proliferation and migration , and the effect of FGF13 on breast cancer migration ability may be related to regulating the Wnt signal pathway and inhibiting the EMT process.

469. Relationship between HER2 expression and tumor interstitial angiogenesis in primary gastric cancer and its effect on prognosis

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Abstract: Her2-positive gastric cancer is a unique subtype of disease, requiring different diagnosis and treatment strategies and methods. Neoplasms are significantly correlated with the occurrence, invasion and metastasis of tumors. The purpose of this study was to explore the correlation between HER2 amplification and tumor interstitial angiogenesis in patients with gastric cancer. **Methods:** The data of 1,121 patients with gastric cancer were retrospectively analyzed, and the amplification of HER2 was detected by immunohistochemistry (IHC) and FISH. CD34 IHC was used to label MVD. We analyzed the factors affecting HER2 amplification, the difference in MVD under different HER2 states, the factors related to 5-year survival rate of patients, and predicted the independent factors affecting 5-year survival rate of gastric cancer patients. **Results:** We found 115 cases with HER2 positive rate of 10.26%. HER2 amplification was more likely in gastric cancer patients with more than 5.2cm tumor diameter, Lauren intestinal type, tubular adenocarcinoma, and the depth of infiltration at stage T2, ($P < 0.05$). Gender, age, tumor location, number of lymph node metastasis, distant metastasis, clinical stage, nerve invasion and vascular tumor thrombi were not the factors affecting HER2 amplification of gastric cancer ($P > 0.05$). MVD count of HER2-positive gastric cancer was significantly higher than that of HER2-negative gastric cancer, ($P<0.05$). The 5-year overall survival rate of 1121 patients with gastric cancer was 51.92%. HER2 amplification, high MVD count, large tumor size, tubular adenocarcinoma, Lauren intestinal type, deep tumor infiltration, numerous lymph node metastases and late clinical stage are all associated with low 5-year survival rate, indicating poor prognosis in gastric cancer patients, ($P<0.05$). The 5-year survival rate of gastric cancer patients was not correlated with gender, age, tumor location, distant metastasis, nerve invasion and vascular cancer plug, ($P > 0.05$). Multivariate analysis showed that Lauren classification, Infiltrating depth, Nodal status, Clinical stage, HER2 expression, MVD count were independent factors affecting the prognosis of gastric cancer patients, ($P<0.05$). **Conclusion:** By analyzing the clinicopathological features and

prognostic factors of gastric cancer, we found that HER2 overexpression was not only closely related to gastric cancer neovascularization, but also an independent predictor of prognosis of gastric cancer. In clinical treatment, anti-HER2 targeted therapy and anti-angiogenesis drugs can be adopted to achieve effective treatment.

470. Pulmonary Peripheral Mixed Squamous Cell and Glandular Papilloma and and Show Mutations in BRAF and EGFR

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Mixed squamous cell and glandular papilloma of the lung is an extremely rare neoplasm, with only 30 cases reported in the English literature. As they can lead to diagnostic confusion with mucinous adenocarcinoma and has no clear signs, clinical symptoms, or imaging features, leading it necessary to recognize this disease We analysed four cases from our hospital through the image of computed tomography, morphologic, immunohistochemistry. Most lesions composed of a mixture of stratified squamous cells, ciliated or non-ciliated cuboidal to columnar cells, mucous cells, and scattered goblet cells in a variety of architectural patterns. The nuclear atypia was mild. Among the 4 patients, 1 was males and 3 were females, with a mean age of 62years (55-72years). All of them have no history of smoking. The squamous component was positive for p40 and CK5/6, and the glandular cells were positive for TTF-1. Both components were diffusely positive for CK7. Then we performed a next-generation sequencing (NGS) study of 4 cases with identification of BRAF V600E and EGFR mutation . Above all , Mixed squamous cell and glandular papilloma of the lung is an indolent pulmonary tumour with a Higher frequency of BRAF V600E and EGFR mutation .It can have a very good prognosis after wedge resection and tends to occur in asymptomatic elderly patient.

471. An unusual “null” pattern of four MMRs proteins and rare gene expression of gastric cancer and literature review

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PURPOSE: Gastric cancer is one of the most common cancers and a main cause of cancer deaths worldwide. Its molecular and clinical characteristics have been complicated by histological and etiological heterogeneity. The maintenance of the mismatch repair (MMR) pathway is essential for accurate DNA replication and genome stability. Different IHC staining patterns reflect the complex

biological phenomena underlying MMR deficiency. Therefore, it is greatly important to improve our understanding of abnormal IHC findings and their biological significance.

METHODS: We analyzed an abnormal expression of IHC in four MMR-related proteins by an unusual “null” IHC staining pattern , including MLH1, PMS2, MSH2, and MSH6, and analyzed the expression of gene level.

RESULTS: MLH1 promoter hypermethylation of the tumor was positive. Moreover, next-generation sequencing was performed and showed that the four genes exhibited changes. One of these was the mutation of the clipping region in exon 12 of MLH1 (c.1039-13_1039-8del), missense mutation in exon 11 of PMS2 (c.1799T>C, p.Met600Thr) , missing copy number in exon 14 of MSH2 , and missense mutation in exon 4 of MSH6 (c.2693C>A, p.Pro898His).

CONCLUSIONS: This observation highlights a rare but potential phenomenon in this strategy in assessing MMR proteins, and reports the rare changes of MMR genes.

472. Machine learning techniques for monitoring postoperative breast cancer patients based on routine blood indexes

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Background

Breast cancer (BC) continues to be a leading cause of cancer death among women worldwide. Reliable noninvasive biomarkers for monitoring postoperative BC patients are urgently needed. This study used machine learning techniques to build monitoring models for quantifying the risk of BC.

Methods

In this study, 781 serial blood samples from 136 BC patients and 788 normal blood samples from 788 female individuals were included. Samples were processed and analyzed using Sysmex XN-1000 and Mindray BC-6800 device. The dataset contained 23 routine blood indices and one dependent variable, which referred to the patient status (health or illness). Random Forest and Lasso regression model were used for feature selection and model building.

Results

The selected indices by Lasso regression are composed of six routine blood indices (LYMPH#, MPV, MCHC, PLT, RDW-SD, EO%) and five of them showed significant differences between different groups. BC patients could be identified from normal group with sensitivity, specificity, and area under the curve of 84.51%, 90.28%, and 90.96%, respectively. We created a HTML file with logistic equation to evaluate the BC risk score in real time. The most important variable identified by Random Forest was LYMPH#. In terms of model accuracy, two algorithms produced close outcomes.

Conclusions

Machine learning approaches to routine blood indices is a cost-efficiency noninvasive tool to monitor cancer treatment. It is also evident that LYMPH# has the remote correlation with BC development and progression.

473. SCARA5 inhibits proliferation of NSCLC through HSP70/FOXM1/CCNB1 axis

qi peng

CQMU

Background:Scavenger Receptor Class A Member 5(SCARA5),also known as TESR, is expressed in various tissues and organs participating in host defense. Recent studies have reported that it plays an anti-tumor role in various tumors,but the mechanism of SCARA5 in lung cancer are still unclear.**Methods:**Bioinformatics,methylation-specific PCR, Quantitative Real-time PCR and Immunohistochemistry were used to detect expression and methylation of SCARA5 in lung cancer tissues and cell lines.The biological effects of SCARA5 on lung cancer were confirmed by CCK8, clone formation test and flow cytometry.Western Blot,R-seq,luciferase assay were applied to explore the mechanism of SCARA5.Chemosensitivity assay was used to explore the effect of scara5 to chemotherapeutic drugs.**Results**:We found SCARA5 is frequently downregulated in lung cancer cell lines and tissues and negatively correlated with promoter methylation.Ectopic expression of SCARA5 can suppress proliferation of lung cancer both in vitro and in vivo through upregulating HSPA5 expression, which inhibiting FoxM1 expression and resulting in G2 / M arrest.SCARA5 also improve susceptibility of lung cancer cells to DNA damage related chemotherapeutic drugs.**Conclusion:**Hypermethylation of promoter leads to decrease of SCARA5 expression, which is related to prognosis in lung cancer.It inhibits lung cancer cell proliferation through HSPA5/FOXM1/CCNB1 axis.SCARA5 promoter methylation status may be a potential marker of prognosis and chemotherapy guidance in lung cancer.

Keywords: SCARA5, Methylation,HSPA5,FOXM1,Cisplatin

474. SNORD54 作为诊断肺癌的新型肿瘤标记物

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研究背景

在临床实践中，活检对于确定肺肿瘤的组织学及其分期至关重要。目前，组织活检是一种侵入性的、耗时的检查，通常依赖于肺癌的确诊，但由于肿瘤的解剖位置，获取组织样本的途径往往受到限制。此外，为了了解肿瘤的进展而对治疗的初步反应，往往需要再次活检；考虑到使

用组织活检的局限性，可在液体活检中检测到无细胞 microRNAs(cf-miRNAs)、无细胞 DNA(CfDNA)、无细胞长非编码 RNA(cf-lncRNAs)、和循环肿瘤细胞(CTC)可能提供具有成本效益的程序，有可能改善整体疾病管理。因此，液体活检在当前的肿瘤学研究中得到了极大的探索，因为它是一种微创的方法，可以用于癌症的早期检测和对癌症治疗的反应。小核仁 RNA(SnoRNAs)是一类聚集在核仁中的非编码小 RNA。主要有两类 snoRNA。C/D 盒 snoRNA 含有进化上保守的盒 C(RUGAUGA)和 D(CUGA)基序，它们分别位于远离 5'端和 3'端的几个核苷酸处。H/ACA 盒 snoRNA 有两个大的发夹结构域，它们通过保守的 H 盒基序(Ananna)和 3'端的短 ACA 尾巴相连。最近的几项研究独立地表明，snoRNAs 参与了人类疾病的发展。SNORD115 调节 5-羟色胺受体 2C 的选择性剪接，SNORD115 缺乏导致 PWS 表型的关键特征。SNORD50A 和 SNORD50B 在人类癌症中经常缺失。它们与 K-RAS 结合并抑制其活性。SNORA42、SNORD33、SNORD66 和 SNORD76 是癌基因，与健康人相比，它们在非小细胞肺癌(NSCLC)患者中高表达。最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法

1. 数据库筛选差异 SnoRNA，FC>2。2.肺癌石蜡组织与癌旁组织验证筛选的 SnoRNAs。3.150 例肺癌患者血浆与 150 例健康人血浆验证筛选的 SnoRNAs。

研究结果

1. SNORD54 为筛选的差异基因。2.30 例肺癌石蜡组织与癌旁组织中 SNORD54 的表达量具有统计学差异，P<0.0001。3.150 例肺癌血浆与 150 例健康人血浆中 SNORD54 表达具有显著的统计学差异，P<0.0001。

关键词：肺癌、SnoRNA、血浆、循环肿瘤标志物、诊断

475. EphA7 基因高甲基化应用于宫颈癌筛查的验证评价

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目的：Eph 基因在很多肿瘤的发生、发展及预后中有着重要意义。为了发现新型生物标志物以改善宫颈癌的预防预后监测，我们鉴定并验证了 EphA7 在宫颈癌和癌前病变中的 DNA 甲基化。

方法：采用甲基化特异性聚合酶链反应（MSP）方法检测宫颈癌细胞系（Siha，Caski，Hela）和正常细胞系（293t）及 42 例石蜡切片组织样本的 EphA7 基因的甲基化水平；并进一步采用荧光定量甲基化特异性聚合酶链反应（QMSP）检测了 70 例宫颈液基细胞样本（TCT），利用

ROC 曲线分析其 DNA 甲基化检测对宫颈癌的临床价值；同期,采用 CRISPR-Tet 干扰技术证实了 DNA 甲基化对 EphA7 基因的转录表达具有直接调控作用。

结果：EphA7 基因在宫颈癌细胞系（Siha，Caski，Hela）呈现甲基化，在正常细胞系（293t）显示非甲基化；在组织样本中 EphA7 DNA 甲基化的阳性率分别是宫颈正常组织样本为 0%（0/17）、宫颈上皮内瘤变期 CIN II 为 45.83%（8/17）、癌症组织为 100%（8/8）；在临床液基细胞样本（TCT）中 EphA7 基因甲基化水平随着癌症进展逐渐升高（P<0.05），取 ROC^{AUC} 为 0.816。采用 CRISPR-Tet 干扰技术可以逆转 EphA7 基因的转录表达，本实验中单一有效的 gRNA 可提高其 mRNA 表达水平达 8 倍。

结论：EphA7 基因甲基化可能是宫颈癌筛查和预防的新型潜在生物标志物。 CRISPR-Tet 是有效的甲基化基因干扰工具，可以为下一步机制的深入研究及后续的宫颈癌预后的监测奠定良好的基础。

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476. SNORD45A 作为诊断非小细胞肺癌的新型肿瘤标记物

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研究背景：在发达国家和发展中国家，肺癌是导致男性和女性癌症死亡的最重要的主要原因之一。据报道，每年有超过 150 万人死于肺癌。非小细胞肺癌(NSCLC)是最常见的肺癌类型。尽管癌症治疗取得了进展，但非小细胞肺癌的预后仍然很差，因为患者的 5 年存活率不到 18%，部分原因是大多数非小细胞肺癌患者被诊断为晚期。SnoRNAs 是一类保守的调控 RNA 分子，在结构和功能上主要分为 C/D 盒 snoRNA 和 H/ACA 盒 snoRNAs。它们作为小核仁核糖核蛋白在核仁中组装的支架，主要参与指导核糖体和短链 RNA 的转录后修饰，这是 rRNA 控制的蛋白质生物发生所必需的。其他功能包括调节选择性剪接。许多 snoRNA 与 Cajal 小体区相关，聚集成染色体内和染色体间簇。大多数 snoRNAs 定位于蛋白质和非蛋白质编码基因的内含子。最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法：1.数据库筛选 snoRNAs。2.肺癌与癌旁石蜡组织验证筛选的 snoRNAs。3.120 例肺癌患者与 120 例健康人血浆验证筛选的 snoRNAs。

研究结果：1.数据库筛选出 SNORD45A，在肺癌组织与癌旁组织表达量的差异倍数 FC>2。2.SNORD45A 在 24 例肺癌 FFPE 与癌旁 FFPE 表达量具有统计学差异，P<0.0001。3.SNORD45A 在 120 例肺癌血浆与健康人血浆表达量具有统计学差异，P<0.0001。

关键词：SnoRNA、非小细胞肺癌、血浆、循环肿瘤

477. SNORD51 作为诊断小细胞肺癌的新型肿瘤标记物

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研究背景

虽然小细胞肺癌(SCLC)仅占肺癌的 15%，但它的高死亡率与侵袭性密切相关，后者的特点是生长迅速、转移快、缺乏早期发现的种生物标志物，可诊断为晚期肺癌。由于目前常用的非侵入性检查方法如电子计算机、X-射线断层扫描技术、痰癌细胞等均为非侵入性检查认为仅对晚期肺癌的诊断有用，探索早期诊断方法是一项相当艰巨的任务，研究无创、方便、高效的检测方法具有重要意义。尽管吸烟仍然是所有肺癌(ES-15，特别是小细胞和鳞状细胞癌)的主要危险因素，但值得注意的是，只有 10%的吸烟者最终会患上肺癌。需要预测性生物标记物来辅助诊断小细胞肺癌。

SnoRNAs 属于一组长度在 60-300 个核苷酸范围内的 ncRNA 分子。功能是对核糖体 RNA 和一些剪接体 RNA 进行转录后修饰。最近的研究表明，功能不正常的 snoRNA 可能在人类恶性肿瘤的发生和发展中发挥作用。例如，SNORA42 已被证明是肺肿瘤发生的癌基因，SNORD33、SNORD66 和 SNORD76 是非小细胞肺癌的潜在标记物，HBII-239 snoRNA 可能对外周 T 细胞淋巴瘤有诊断和预后意义。越来越多的证据表明，snoRNAs 可能积极参与肿瘤的发生，并在肿瘤生物学中发挥不同的作用。最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法：1.数据库筛选具有差异表达的 snoRNAs。2.小细胞肺癌石蜡组织与癌旁组织验证筛选的 snoRNAs。3.100 例小细胞肺癌血浆与 100 例健康人血浆验证筛选的 snoRNAs。

研究结果：1.SNORD51 差异倍数大于 2，为筛选到的基因。2.24 例小细胞肺癌石蜡组织与癌旁组织中 SNORD51 表达量具有统计学差异，$P<0.0001$。3.100 例肺癌血浆与 100 例健康人血浆中 SNORD51 表达量具有统计学差异，$P<0.0001$。

关键词：小细胞肺癌、SnoRNA、血浆、循环肿瘤标记物

478. SNORD55 作为诊断肺癌的新型肿瘤标记物

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研究背景

肺癌是最常见的恶性肿瘤之一，也是全球癌症相关死亡的主要原因。尽管采用了先进的成像和细胞学筛查策略来早期发现肿瘤，但大多数肺癌病例是在晚期被诊断出来的，这是肺癌死亡率高的一个决定因素。因此，迫切需要开发一种有效的肺癌筛查试验。许多有前途的非侵入性生

物标志物已经被观察到，然而，由于目前可获得的验证性研究的缺乏，它们的临床应用仍然有限。

SnoRNA 的大小从 60 到 300 个核苷酸不等。在哺乳动物中已经发现了至少 200 个 snoRNA，但还有更多的 snoRNA 有待发现。有两种类型的 snoRNA：C/D 框或 H/ACA 框 snoRNA。在脊椎动物中，大多数 snoRNAs 位于蛋白质编码基因的内含子内，并通过 RNA 聚合酶 II 转录。然而，snoRNA 也可以由长的非蛋白质编码 RNA(LncRNAs)的内含子加工而成。例如，LncRNA 的 Gas5 编码 9C/D 盒 snoRNA(snoRNDs74-81)。最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法

1.TCGA 数据库筛选 snoRNAs。2.肺癌石蜡组织与癌旁组织验证筛选的基因。3.肺癌患者血浆与健康人血浆验证筛选的 SnoRNAs。

研究结果

1.SNROD55 为筛选的基因。2.30 例肺癌石蜡组织与癌旁组织中 SNORD55 表达具有统计学差异，P<0.0001。3.150 例肺癌患者血浆与健康人血浆 SNORD55 表达具有显著的统计学差异，P<0.0001。

关键词：肺癌、SNORNA、诊断、血浆

479. SNORD62 作为诊断非小细胞肺癌的新型肿瘤标记物

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研究背景

肺癌是世界范围内癌症死亡的主要原因，分为两种亚型：小细胞肺癌(SCLC)和非小细胞肺癌(NSCLC)。后者是最常见的肺癌类型，占所有肺癌病例的近 85%。非小细胞肺癌是一种多因素的恶性肿瘤，有几个危险因素，如吸烟史、接触石棉和营养不良，这些都会增加非小细胞肺癌的发病率。尽管非小细胞肺癌患者有多种治疗方法，如手术、化疗和放疗，但由于诊断较晚、对细胞毒药耐药以及缺乏可行和令人信服的预后生物标记物，5 年总存活率(OS)仍然很低，仅为 15%。因此，迫切需要新的、可靠的生物标志物来预测非小细胞肺癌的预后。小的 ncRNA 正在成为癌症范例中的新参与者，并在肿瘤发生中变得越来越重要。人类肿瘤的 miRNA 表达图谱已经确定了可能用于癌症诊断、预后和治疗的信号[10-17]。此外，由于 miRNAs 的主要功能是转录后调节因此一些 miRNAs 可以作为肿瘤抑制基因或癌基因发挥作用。然而，其他类型的小核糖核酸也可能在调节不同的细胞过程中发挥关键作用因此，研究肿瘤中其他类 ncRNAs 的异常表达及其诊断和治疗价值具有重要意义。尤其是小核仁

RNA(SnoRNAs)或 snoRNA 失调在肿瘤发生中发挥了重要作用。例如，最近的研究显示，一些迹象表明 snoRNA 作为癌症相关基因发挥了意想不到的作用。随着人们对 snoRNAs 在肿瘤发生中作用的认识不断加深，snoRNAs 有望成为癌症的新生物标记物和治疗靶点。因此，在这篇综述文章中，我们将主要讨论 snoRNAs 在肿瘤发生中的新功能，以及小 ncRNAs 在未来癌症诊断和治疗中的可能应用。最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法：1.SNORNA 数据库筛选基因。2.NSCLC 石蜡组织与癌旁组织验证筛选到的差异基因。3.肺癌患者血浆与健康人血浆验证筛选到的差异基因。

研究结果：1.SNROD62 在数据库中差异倍数显著。2.30 例肺癌 FFPE 与癌旁 FFPE 中 SNORD62 具有统计学差异，P<0.0001。3.160 例肺癌患者血浆与 160 例健康人血浆中 SNORD62 表达量具有显著的统计学差异，P<0.0001。

关键词：NSCLC、SNORD62、循环肿瘤标志物、血浆

480. LINC00152 和 NCL 在 TEP 的异常表达与相互作用模式及其作为 NSCLC 生物标志物的研究

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目的 血小板是外周血中第二丰富的细胞类型,虽无细胞核,但包含丰富的 RNA。研究表明,健康个体与多种癌症患者之间存在差异血小板 RNA 谱。在肿瘤及其微环境的潜在影响下,血小板内 pre-mRNA 发生剪接；应激的巨核细胞 RNA 库改变；除此之外,血小板还能通过例如囊泡介导的运输机制连续地将核酸和蛋白质与其他血小板、免疫细胞、内皮细胞以及肿瘤细胞进行生理交换。因此 TEP RNA 分析将揭示最新的、增强的和动态反应的肿瘤活性。血小板是肿瘤微环境的重要组成部分,被认为是介导肿瘤进展和癌症全身扩散的关键步骤。其在癌症中差异表达的 RNAs 除可用作诊断外,还可能影响血小板在癌症进展中发挥的功能。除了存在 pre-mRNA 外,血小板还含有其他种类的 RNA,包括 microRNA（miRNA）、长链非编码 RNA（lncRNA）等。其中 lncRNA 可在表观遗传学、转录以及转录后等多种层面上调控靶基因的表达。本研究拟通过血小板 lncRNA 芯片分析,发现差异 lncRNA 表达谱及其与病理类型、分期之间的关系,探讨其在非小细胞肺癌诊断及转移预测等方面的应用价值。并在前期研究基础上,进一步探索 TEP 中 LINC00152 和 NCL 的相互作用模式和功能机制。 **方法** 通过血小板 lncRNA 表达谱的芯片分析，筛选出差异基因 LINC00152。随后采集山东省肿瘤医院诊断为肺癌初治病人以及健康志愿者各 200 名的血浆样本，分离富集血小板并获得血小板 RNA。用 qPCR 的方法大样本验

证 LINC00152 的表达模式，统计分析其在肺癌初治病人与健康志愿者血小板中的表达差异，同时分析其对于肺癌的诊断效能。利用 AGO2 RIP、pull down 等方法探究血小板 LINC00152 对 NCL 的调控模式，并基于血小板功能试验进一步探究 LINC00152 对血小板生物学功能的调控机制。 **结果** （1）采用 qPCR 的方法对肺癌患者和健康供体的血小板中 LINC00152、NCL 水平进行定量，结果显示二者在肺癌患者血小板中表达显著下调（p<0.0001），且与组织表达趋势相反。另外，LINC00152 与 NCL 在 48 例肺癌初治患者和 48 例健康志愿者血小板中的表达水平高度相关（p=0.0005/p<0.0001）； （2）利用 ROC 曲线分析，检测 LINC00152、NCL，两者联合对肺癌的诊断效能，结果显示，分别为 AUC=0.666/0.677/0.697。

481. SNORD69 作为诊断非小细胞肺癌的新型肿瘤标记物

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研究目的：肺癌是人类最常见的癌症类型之一，也是全球癌症相关死亡的主要原因。在中国，每年新诊断的肺癌病例超过 70 万例。肺癌包括小细胞肺癌(SCLC)和非小细胞肺癌(NSCLC)，非小细胞肺癌约占肺癌诊断的 80%-85%。尽管手术、放疗和化疗在过去几十年中取得了很大的进步，但这种恶性肿瘤的存活率仍然很低。因此，需要更多地努力寻找无创、可靠的生物标志物来早期发现非小细胞肺癌并预测其预后。小核仁 RNA(SnoRNAs)是一个保守的核 RNA 家族(70-200nt)，通常集中在 Cajal 小体或核仁中，它们要么参与小核 RNA(SnRNAs)或核糖体 RNA 的修饰，要么参与核糖体亚单位成熟过程中的 rRNA 加工在人类中存在绝大多数 snoRNA 编码在内含子中。SnoRNAs 是从切除的和去分支的内含子中通过核酸外切修剪来的，并通过形成小核仁核糖核蛋白(SnoRNPs)在具有特定蛋白质组分的复合体中发挥功能最近的研究表明，snoRNAs 在外周血浆中稳定存在且易检测，使其作为新型循环肿瘤标志物早期诊断肺癌成为可能。

研究方法：1.数据库筛选具有显著差异倍数的 SNORNAs。2.肺癌 FFPE 与癌旁 FFPE 验证筛选的 SNORNAs。3.肺癌患者血浆与正常人血浆验证筛选到的 SNORNAs。

研究结果：1.SNROD69 的差异倍数大于 2,为筛选到的基因。2.30 例肺癌 FFPE 与癌旁 FFPE 中 SNORD69 的表达量具有显着的统计学差异，P<0.0001。3.160 例肺癌患者血浆与 150 例正常人血浆中 SNORD69 的表达量具有显著的统计学差异，P<0.0001。

关键词：肺癌、SNORNA、诊断、血浆

482. 肿瘤标志物 CA724 的中国人群参考范围研究

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目的：探讨消化系统肿瘤标志物 CA724 在健康人群的参考范围。

方法：依托 2016 年全国常见消化系统疾病流行病学调查，采用随机分层抽样的方法，从北京平谷区、北京石景山区、黑龙江省哈尔滨市道里区、江西省南昌市东湖区、江西省宜春市上高县、贵州省贵阳市观山湖区纳入 2904 例受试者，收集患者相关临床症状和体征信息，分别进行胃镜检查、超声检查、血常规、C13 呼吸实验、CA724 检测等，SPSS 软件对结果进行统计分析。CA724 浓度分布表示为单侧 95%。

结果：根据患者的临床表现和检查结果进行综合评价，人群中幽门螺杆菌感染、胆囊炎、胆结石、病毒性肝炎、胃溃疡、胃癌发生率分别为 5%，2.6%，4.2%，1.2%，5.5%，1.0%。排除以上常见消化系统疾病患者，CA724 单侧 95%浓度分布为 18.6U/mL。按性别分组，男性、女性浓度分布分别为 18.1，19.9，女性浓度稍高。按年龄分布，小于 20 岁、20 岁、30 岁、40 岁、50 岁、大于 60 岁，CA724 浓度分布分别为 16.9、18.3、20.3、19.4、19.2、24.4U/mL，随年龄增长 CA724 浓度有增长的趋势。按照地区分布，北京石景山区、北京平谷区、黑龙江省哈尔滨市道里区、江西省南昌市东湖区、江西省宜春市上高县、贵州省贵阳市观山湖区

CA724 浓度分布分别为 17.5、15.9、20.7、17.4、16.1、23.4U/mL。结论：CA724 在我国健康人群中参考范围为 18.6U/mL，明显高于国外数据 6.9U/mL。女性、高龄、贵州等地区 CA724 浓度会稍高。肿瘤标志物参考范围设定对于临床诊疗和健康管理意义重大，应根据我国各地区情况分别建立参考范围。

483. Study on commonalities and specificities between cancer and metastatic cancers from other origins

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Motivation: Metastasis is the ultimate challenge against cancer and has increasingly received significant attention. Although much knowledge has been accessed, mechanisms underlying its progression remain incompletely understood. Especially for the cancer and metastatic cancers from other origins, deep explorations on their commonalities and specificities in molecular levels are of pressing needs, which may provide helpful information for the effective treatments for the cancer

patients.

Methods and materials: We use several optimization models and algorithms to identify multiple kinds of driver gene sets to deeply investigate this problem. In this study we mainly focus on three kinds of representative cancers: 1) glioma and the brain metastases from breast carcinoma, non-small-cell lung cancer and melanoma; 2) hepatocellular carcinoma and the liver metastases from breast carcinoma, colorectal cancer, non-small-cell lung cancer, melanoma, pancreatic cancer and prostate cancer; 3) non-small-cell lung cancer and the lung metastases from breast carcinoma, colorectal cancer, head and neck carcinoma and melanoma.

Results: There are many interesting results obtained. For example, three is no common driver gene set between glioma and the corresponding three brain metastases, but there exist some ones between the brain metastases from breast carcinoma and melanoma. On the other hand, we have found some glioma specific driver gene sets relative to the corresponding brain metastases, and vice versa. Furthermore, we identified some common and specific driver gene sets between hepatocellular carcinoma and liver metastasis from colorectal cancer, as well as some common driver gene sets between the lung metastases from breast carcinoma and head and neck carcinoma, and non-small-cell lung cancer specific driver gene sets relative to lung metastasis from colorectal cancer, and so on.

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484. Prognosis difference based on gender in patients with hepatocellular carcinoma

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Objective Although men have a higher risk of hepatocellular carcinoma (HCC) than women, whether there is a different prognosis based on gender is still controversial. The study was aimed to investigate if there was a difference in gender-based outcomes among HCC patients who underwent transcatheter arterial chemoembolization (TACE) combined with locoregional ablation therapy.

Methods A retrospective analysis was conducted on 806 patients with HCC who were treated with TACE combined with local ablation in Beijing You'an Hospital affiliated to Capital Medical University from January 1, 2012 to December 31, 2016. Standard propensity score matching was performed to create two highly comparable groups. Forest plot was used to display the results of a subgroup analysis. The cumulative recurrence-free survival(RFS) and overall survival (OS) rates were calculated by Kaplan-Meier method, and the Cox proportion hazard model was conducted to screen for independent predictive factors for indicating recurrence and long-term prognosis of HCC patients.

Results Women had a higher average age at diagnosis than men. At baseline, men had high levels of

indicators than women, such as white blood cells, lymphocytes, blood urea nitrogen, prealbumin, alkaline phosphatase, gamma-glutamyltransferase (GGT), as well as activated partial thromboplastin time. Women had better 1-, 3-, and 5-year RFS rates (79.0%, 54.6%, 49.6% vs 68.4%, 40.4%, 33.4%, P<0.001), and had slightly better OS rates without a significant difference when compared to men (100%, 95.0%, 85.7% vs 98.6%, 88.0%, 81.2%, P=0.092), which was consistent with the consequences of data processed by PSM method. There were different risk factor spectrums for recurrence between men and women. Age, tumor number, tumor size, neutrophils, globulin, GGT, together with alpha fetoprotein (AFP) could influence recurrence for men, however for women, only age and globulin were independent risk predictors.

Conclusions Women have a better prognosis than men. Prognosis difference with respect to gender may indicate the significance of gender-based stratification in preoperative evaluation and prognostic management of HCC patients.

485. Epidemiology and oncological outcomes of patients with young-onset Colorectal Cancers

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Objective Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer-related death all over the word. Although the overall incidence of CRC has decreased owing to the implementation of population-based screening, the incidence of CRC in patients younger than 50 years is increasing. This young-onset CRC now accounts for 10-12% of all new CRC diagnoses. little is known about the mechanisms of and factors that contribute to development of young-onset CRC.

Methods A retrospective review was performed using the Surveillance, Epidemiology, and End Results (SEER) database from 2006 to 2016. Inclusion criteria consisted of positive histology and active follow-up CRC. Patients with missing AJCC stage and satge 0 (Ca in situ) were excluded. We collected data on age, sex, race, origin, site, AJCC stage, grade, surgery, survival months and vital status. Patients were cohorted by age (< or ≥50 years). Outcomes and overall survival for patients younger than 50 years and patients 50 years old or older were compared.

Results A total of 31,021 patients were analyzed in this study. 3,534 patients were younger than 50 years and 27,487 were aged 50 years or more. There were differences in race, origin, site, stage, grade and surgery between the two age groups. The younger patients had a significantly higher proportion of Black and Spanish-Hispanic -Latino. Oncologically, the younger patients were more likely to rectum and sigmoid colon site. The young-onset were more likely to be diagnosed at advanced stage (III-IV stage, 58.4 versus 47.1 per cent; P < 0.001) and receive surgery (87.1 versus 85.5 per cent; P = 0.013). 3-year overall survival was better in those under 50 years old (P < 0.001). Univariate and

multivariate analysis using the Cox regression model showed that M stage, AJCC stage were independent risk factors in youg-onset.

Conclusions Epidemiology and oncological outcomes of patients younger than 50 years were different from patients 50 years old or more. M stage and AJCC stage might be indicative of a prognostically unfavorable biological tumor profile in youg-onset.

486.广西地区乙肝病毒/华支睾吸虫感染双暴露与肝细胞癌发病风险及预后的相关性研究

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目的 本研究分析和评价肝吸虫合并 HBV 感染的协同作用对肝细胞癌（简称肝癌）发病风险和预后的影响，为今后广西地区肝癌的个体化防治提供重要的科学依据。

方法 本研究采用以医院为基础的病例对照研究方法。病例组为 14-18 年期间在广西医科大学附属肿瘤医院经术后病理诊断确诊的肝癌患者，排除合并严重心脏、肺脏、肾脏以及脑血管疾病的患者。对照组则来自同医院同一时期非肿瘤、无肝胆类疾病患者，以性别，年龄 ±3 与病例组按照 1:1 匹配。最终纳入 1138 例病例组和 1138 例对照组。

结果 病例组和对照组在 BMI、吸烟史、饮酒史、肝硬化史、肝癌家族史和 HBV 合并肝吸虫感染情况之间的差异具有统计学意义（P<0.05）。多因素 logistics 回归分析结果显示，相比于 HBV 和肝吸虫感染双阴性的患者，HBV 感染而无肝吸虫感染患者（OR=25.331，95%CI=18.977-33.812， P<0.001 ）、肝吸虫感染而无 HBV 感染患者（OR=4.489，95%CI=1.946-10.356, P<0.001)、肝吸虫和 HBV 感染双暴露患者（OR=73.69，95%CI=31.753-171.015, P<0.001）发生肝癌的风险显著增加。我们进一步分析病例组中 HBV 和肝吸虫感染双阴性患者，HBV 感染而无肝吸虫感染患者，肝吸虫感染而无 HBV 感染患者和肝吸虫和 HBV 感染双暴露患者之间临床病理特征的分布差异。结果发现，年龄、吸烟史、饮酒史、肝硬化史、AFP 值、凝血酶原时间、丙氨酸转氨酶、天冬氨酸转氨酶在四组患者中的分布存在显著差异（P<0.05）。多因素 Cox 回归分析显示，HBV 感染而无肝吸虫感染（HR=1.96，95%=1.25-3.07，P=0.003）和肝吸虫和 HBV 感染双暴露（HR=2.36，95%=1.31-4.26，P=0.004）是肝癌患者术后发现预后不良的独立危险因素。

结论 肝吸虫和 HBV 感染双暴露可能影响肝癌发生，并可能导致患者术后预后不良。肝吸虫和 HBV 感染人群应作为广西肝癌发生和预后不良的高危人群提供个体化防治。

487. Metformin and endometrial cancer risk: A Meta-analysis

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Objective To assess the association between metformin and endometrial cancer risk by conducting a meta-analysis.

Methods A comprehensive search of electronic databases, conference abstracts, and clinical trial registers was performed to identify available evidence. No language restrictions were applied in our search strategy. Studies that evaluated the association between metformin use and endometrial cancer risk were considered. The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or non-randomized studies; (2) evaluated exposure to metformin and endometrial cancer risk; (3) reported risk ratio (RR) and a 95% confidence interval (CI) or provided data for their calculation. Articles were excluded if they were: (1) editorials, letters, reviews, and case reports; (2) studies without appropriate data for determining an estimate of RR and a 95% CI. The risk of bias in RCTs was evaluated according to the Cochrane Collaboration's tool [23]. The methodological quality of non-randomized studies was assessed according to the Newcastle–Ottawa scale [24]. Studies with a score of 7 or higher were considered as high quality studies. Heterogeneity among study results was explored using the Chi-square (χ^2, or Chi^2) and I^2 test. If substantial heterogeneity (p value < 0.10 or I^2 > 50 %) was found, a random-effects model was used to calculate the pooled effect with appropriate cautious interpretation; otherwise, a fixed-effects model was applied. Heterogeneity was explored in subgroup analyses by study design, reference therapy, and adjustment for age and BMI or obesity. We pooled relative risk (RR) estimates with 95% confidence intervals (CIs) by using either a fixed-effects or a random-effects model. The analyses were performed using Stata version 12.0 software (Stata Corporation, College Station, TX).

Results A total of 744 records were screened of which 13 articles were assessed for eligibility. Of these, 4 studies were excluded for the following reasons: 1 used overlapping data, and 3 did not have available data. Nine studies (1 randomized controlled trial, 5 cohort studies, and 3 case-control studies) involving more than 1.20 million participants and 7,762 cases of endometrial cancer met eligibility criteria. The included RCT was considered at low risk of selection bias, attrition bias, and other bias, but unclear risk of detection bias, high risk of performance bias and reporting bias. Five of the included non-randomized studies were considered as high-quality studies (scores of 7 or higher) .

In meta-analysis of all studies involving 7,762 cases of endometrial cancer, no evidence for an association between metformin use and endometrial cancer risk was observed (RR, 0.96; 95% CI, 0.80 to 1.16). The results showed significant heterogeneity among the studies (p = 0.000; I^2 = 75.5%) .Similarly, the pooled data showed that metformin use was not significantly associated with

endometrial cancer risk in patients with diabetes (RR, 0.93; 95% CI, 0.78 to 1.11). There was significant heterogeneity among the studies (p = 0.001; I^2 = 68.7%). In subgroup analyses, the results were stable across different study designs and comparisons, and remained unchanged after adjusting for age and BMI or obesity.

Conclusions The current meta-analysis suggests that metformin has no chemopreventive effect against endometrial cancer.

488. FoxQ1 与 Wnt/β-Catenin 信号通路在蒿甲醚逆转大肠癌细胞同期放化疗抵抗中的作用研究

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目的 1.建立大肠癌 HT-29 同期放化疗抵抗细胞模型;2.阐明大肠癌细胞同期放化疗共同抵抗的关键基因 FoxQ1 对 WnT/β-Catenin 信号通路的调控作用；3.阐明蒿甲醚通过 FoxQ1 调控 WnT/β-Catenin 信号通路，逆转大肠癌细胞同期放化疗共同抵抗。

方法 1. 采用 10μmol/l 5-Fu 及 4Gy 6MV X-ray 对人结直肠癌细胞 HT29 进行体外同期放化疗，建立放化疗抵抗细胞株;2.MTT 实验、平板克隆实验、Transwell 迁移及侵袭实验检测同期放化疗后 HT29 细胞株的同期放化疗抵抗性；3.设立对照组、实验组，采用 qRT-PCR 、Western blot 实验分析在 mRNA 和蛋白水平上 β-Catenin 表达是否与 FoxQ1 表达相一致；4.采用 MTT 检测蒿甲醚对 HT29CRR/HCT116CRR 细胞株的半数抑制率（IC50），采用 qRT-PCR 和 Western blot 实验分析经蒿甲醚作用后的放化疗抵抗大肠癌细胞中 FoxQ1 及 β-catenin 的 mRNA 和蛋白量的变化；5.数据统计和分析采用 SPSS19.0 软件包进行，数据以均数±标准差（±s）表示，组间资料应用 t 检验。

结果 1.经过 12 次体外同期放化疗后，成功建立同期放化疗后 HT29 残癌细胞株；2 在 mRNA 和蛋白水平，HT29CRR/HCT116CRR 中抑制 FoxQ1 致使 β-Catenin 的表达水平降低；过表达 FoxQ1 致使 β-Catenin 的表达量增加，且具有统计学意义;3. 在 mRNA 和蛋白水平，HT29CRR/HCT116CRR 蒿甲醚处理组 FoxQ1 和 β-Catenin 的表达水平均低于未加药组，且具有统计学意义。

结论 1.在 mRNA 和蛋白水平上，FoxQ1 可以影响 β-catenin 的表达，证实 FoxQ1 对 WnT/β-Catenin 信号通路的调控作用，为后续的研究提供了研究的方向和依据。2.蒿甲醚可以在 mRNA 和蛋白水平上通过 FoxQ1 调控 Wnt/β-catenin 信号通路逆转大肠癌同期放化疗抵抗作用。

489. 线粒体转录因子 A 在食管鳞癌发生发展中的作用研究

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目的 以食管癌临床组织样本、线粒体转录因子 A(mitochondrial transcription factor A, TFAM)干涉/过表达食管癌细胞株及皮下荷瘤小鼠动物模型为基础，在多水平上系统地研究 TFAM 表达对食管癌细胞生长的作用，并进一步探讨其分子机制，研究结果将为深入研究食管癌发生发展的分子机制和建立新的防治策略奠定理论基础。

方法 使用公共数据库及免疫组化实验方法分析 TFAM 在食管癌组织样本中的表达以及分析其与食管癌病人预后相关性。为检测 TFAM 对食管癌细胞生长的影响，使用 MTS 实验、克隆形成实验和 EDU 实验等检测细胞增殖活力的实验方法；为检测 TFAM 对肿瘤形成的影响，使用荷瘤小鼠皮下成瘤实验。使用划痕实验和 Transwell 实验检测 TFAM 对食管癌细胞转移作用的影响。

结果 1）利用公共数据库以及 Western blot、qPCR、IHC 等实验方法检测食管癌病人组织样本中 TFAM 的表达，结果显示 TFAM 在 ESCC 组织中 mRNA、蛋白水平显著上调；随后使用统计学方法进行分析：结果显示肿瘤病人中 TFAM 的高表达与食管癌的发展及食管癌病人的不良预后存在着重要的相关性。

2）筛选高表达以及低表达 TFAM 的食管癌细胞系，构建 TFAM 稳定干涉和过表达的食管癌细胞模型。

3）MTS 实验、克隆形成实验以及 EDU 实验的检测结果提示 TFAM 能显著促进食管癌细胞的增殖；裸鼠皮下成瘤实验的结果提示 TFAM 能显著促进食管癌的增殖。4）划痕实验和 Transwell 实验的结果提示 TFAM 能显著促进食管癌细胞的转移。

结论 本研究表明 TFAM 在食管癌发生发展中起着重要作用，对设计有效治疗药物有着重要的理论指导意义。

490. DJ-1 Promotes Epithelial-to-Mesenchymal Transition via Enhancing FGF9 expression in Colorectal Cancer

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Objective Tumor metastasis is mainly contributed to high recurrence and mortality in colorectal cancer (CRC). In previous study, we found that DJ-1 plays an important role in CRC metastasis, and is the main target in Ciclopirox olamine (CPX)-treating CRC. However, the mechanism underlying DJ-1 inducing CRC metastasis remains elusive.

Methods Western blot, Immunofluorescence and real-time PCR assays were used to detect the expression of DJ-1, Wnt signaling, FGF9, E-cadherin and Vimentin in CRC cancer cell line SW480 and RKO. In vitro, the ability of cell migration and invasion were measured by transwell and wound healing assays. Immunohistochemistry (IHC) was used to examine the expression profile of FGF9, and the correlation between FGF9 and epithelial–mesenchymal transition (EMT) in CRC patients.

Results In present study, our results showed that DJ-1 could activate Wnt signaling resulting in enhanced invasive potential and epithelial-to-mesenchymal transition (EMT) in CRC cells. RNA-seq and bioinformatics analysis reveals that DJ-1/WNT signaling pathway may promote CRC cells EMT by regulating FGF9 expression. Molecular validation showed that expression of FGF9 was positive regulated by DJ-1/WNT signaling pathway and decreasing FGF9 expression impeded DJ-1-induced CRC invasive ability and EMT, suggesting FGF9 is involved in DJ-1-enhanced CRC metastasis. In addition, we also showed that FGF9 was overexpressed in CRC human specimens and was significantly associated with tumor differentiation. High FGF9 expression was correlated with worse overall survival, and a correlation exhibited between FGF9 and EMT markers (E-cadherin and Vimentin) in CRC samples.

Conclusions Together, our results determined that FGF9 was involved in DJ-1-induced invasion and EMT in CRC cells and may represent a promising therapeutic candidate for CRC anti-metastatic strategies.

491. Exosomal microRNAs derived from prostate cancer cells promote osteogenesis and correlate to PCa bone metastasis

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Objective Prostate cancer (PCa) is the most common malignant tumor in male urinary system and osteoblastic bone metastasis is the most observed metastasis in prostate cancer patients. It has been demonstrated that circulating microRNAs contained in extracellular vesicles are potential early biomarkers and therapy targets for many diseases. However, the potential role of exosomal microRNAs in prostate cancer bone metastasis, is not yet to be fully explored.

Methods After isolation and purification EVs using ultracentrifugation from conditioned media of bone metastatic co-opting prostate cancer cells and normal cells , total RNA was extracted. Subsequent to library preparation and small RNA-Seq, differential gene expression analysis was performed. Data were filtered by mean miRNA expression of ≥ 50 reads, two fold up or down regulation between 2.5 -7.5 and adjusted p-value ≤ 0.05. The uptake of PCa-sEVs was performed. Three candidate miRNAs (has-miR-200c-3p; has-miR-1275; has-miR-383-5p) were internalized and

osteoblast differentiation were detected by qPCR , histochemical staining and protein activity detection. Meanwhile, the correlation of exosomal miRNAs expression and bone metastases was examined by qRT-PCR.

Results Total reads of miRNAs in bone metastatic co-opting PCa-EVs exceeded significantly than that in normal EVs ($p<0.001$), indicating that miRNAs delivered by PCa cells play critical role in PCa bone metastasis. PCa-conditioned media enhanced osteoblast differentiation and can be reversed by GW4869. The uptake of PCa-EVs by MC3T3-E1 was efficient. The high expression of the three candidate miRNAs in PCa-EVs was verified by qPCR. All the three candidate miRNAs promoted osteogenesis, verified by mRNA expression of osteoblastic markers (ALP, OCN, RUNX2, OSX), ALP activity, ALP staining and Aliza Red S staining. In addition, all the three candidate exosomal miRNAs derived from patient serum were demonstrated to be associated with tumor progression and bone metastasis ($P<0.05$).

Conclusions These findings suggest that miRNA cargos in PCa-EVs play a pivotal role in the development of osteoblastic bone metastasis of PCa , which can be potential early biomarkers and therapy targets for prostate cancer bone metastasis.

492. S1P lyase 在肝癌中的表达及对其预后的影响

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目的 探讨 S1P lyase 在肝癌中的表达情况，及其对肝癌预后的影响。

方法 选取桂林医学院附属医院 54 例肝细胞癌患者，real-time PCR 分析 S1P lyase 在 54 对肝细胞癌癌组织及癌旁组织中的表达，运用统计学方法探讨 S1Plyase 表达与肝癌临床病理特征的关系；利用 Kaplan-Meier 分析网站分析 S1P lyase 对肝癌预后的影响；应用 STRING 数据库初步探讨神经鞘脂信号通路中可能与 S1P lyase 相互作用的信号分子。

结果 S1P lyase 在肝癌组织中的表达明显低于癌旁组织（P＜0.05）。S1P lyase 在最大径≥10cm 的肝癌病例中的表达量低于 5cm≤最大径≤10cm 及最大径≤5cm 的肝癌病例（P＜0.05），AJCC 分期（III+IV）期肝癌患者中 S1P lyase 的表达低于（I+II）期患者（P＜0.05）。Kaplan-Meier 分析显示 S1P lyase 表达量越低，肝癌病人预后越差(HR=0.65, P=0.017)。而 STRING 数据库数据表明 S1P lyase 可能与神经鞘脂代谢通路中 CERS2、CERS4、CERS5、CERS6、SGPP1、SGPP2、ORMDL1、ORMDL2 及 ORMDL3 存在潜在相互作用的可能。

结论 S1P lyase 在肝癌中低表达，S1P lyase 低表达预示着肝癌患者的不良预后。

493. PTPRO Suppresses Esophageal Cancer Metastasis by Dephosphorylating and Inhibiting MET-mediated Glutaminolysis

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Objective Objective Epigenetic silencing of tumor suppressors is a universal early event driving oncogenesis. PTPRO (protein tyrosine phosphatase receptor-type O), a member of the R3 subfamily of receptor protein tyrosine phosphatases, is hypermethylated in its promoter region in many malignancies. The objective of this study is to identify how a membrane-bound tyrosine phosphatase PTPRO regulates MET-mediated metastasis and glutaminolysis in esophageal squamous cell carcinoma (ESCC).

Methods Methods Immunoblotting and immunochemistry were used to determine PTPRO expression in ESCC cell lines and a cohort of in ESCC patients. Gain of function and loss of function experiments were executed in cellular and genetic mouse and xenograft models. The role of PTPRO in cancer metastasis were examined by a popliteal lymph node metastasis model in vivo, transwell migration and matrigel invasion assays in vitro. The effect of PTPRO in cancer metabolism was evaluated by glutamine consumption assay kit and glutamate production assay kit. Metabolic enzyme activity was analyzed by Glutaminase (GLS) Activity Assay Kit and Glutamine Synthetase (GS) Activity Assay Kit. The molecular mechanism by which PTPRO directly interacted with MET was explored using bimolecular fluorescence complementation, proximity ligation assay, co-immunoprecipitation, and in vitro substrate-trapping assay.

Results Results Analysis of the PTPRO expression in a tissue microarray (TMA) showed that PTPRO levels were remarkably reduced in ESCC patient sample, and it was negatively associated with prognosis and metastasis. Using knockout mice and xenograft models, we showed that PTPRO robustly suppresses metastasis in ESCC. Using a cell model, we found that PTPRO inhibits ESCC metastasis by regulating glutamine catabolism. We identify PTPRO as an upstream regulator of c-MET; PTPRO directly dephosphorylates MET at Y1234/1235, thereby suppresses metastasis and glutaminolysis. Moreover, combine low PTPRO and high phospho-MET strongly associated with poor prognosis and was an independent prognostic factor of ESCC patients.

Conclusions Conclusion These findings demonstrate that PTPRO suppresses metastasis and glutaminolysis by directly dephosphorylating MET. PTPRO-MET axis implicates a potential prognostic indicator and therapeutic target.

494. 过表达 microRNA-934 促进人宫颈癌 SiHa 细胞侵袭、迁移与上皮间质转化

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目的 研究 microRNA-934 对宫颈癌细胞侵袭转移能力的影响及作用机制。

方法 采用茎环法实时荧光定量 PCR 检测 microRNA-934 在 23 例配对的宫颈癌与癌旁组织中的表达；构建稳定过表达 microRNA-934 的 SiHa 宫颈癌细胞株，划痕愈合实验、transwell 实验检测细胞的迁移、侵袭能力；预测 microRNA-934 靶基因，蛋白印迹检测 SiHa-LV-miR-934 细胞中 DKK1 的表达，萤光素酶报告实验分析 microRNA-934 与靶基因 DKK1 mRNA 3'UTR 的结合；蛋白印迹检测上皮间质转化（EMT）相关蛋白的表达变化。

结果 相对于癌旁组织，microRNA-934 在宫颈癌组织中显著高表达；在 SiHa 细胞中上调 microRNA-934，可显著促进宫颈癌细胞的侵袭和迁移能力，DKK1 蛋白表达受到明显的抑制且 microRNA-934 能够显著抑制萤光素酶报告基因的活性；与对照组比较，SiHa-LV-miR-934 细胞 EMT 相关蛋白 E-cadherin 表达降低，而 N-cadherin、β-Catenin、Vimentin 表达增加，且 Wnt/β-Catenin 信号通路下游分子 Axin-2 表达升高。

结论 microRNA-934 在宫颈癌组织中呈高表达，microRNA-934 可能通过抑制靶基因 DKK1 的表达，诱导宫颈癌 SiHa 细胞发生 EMT，促进宫颈癌细胞的侵袭和迁移能力。

495. MTA3 represses esophageal cancer metastasis by inhibting glutamine synthetase-mediated glutaminolysis

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Objective Aims: Metastasis-associated protein 3 (MTA3), a component of the nucleosome remodelling and histone deacetylase (NuRD) complex and multi-effect coregulator, can serve as a tumor suppressor in many cancer types. However, the role of MTA3 in esophageal squamous cell cancer (ESCC) remains far from complete. We thus investigated the function of MTA3 in ESCC, one of the most common digestive cancers and a leading death cause by cancers.

Methods: The transwell assay and mouse lung metastasis model were performed to investigate the effect of MTA3 on metastasis in ESCC. Glutamine consumption assay kit and glutamate production assay kit were used to assess the glutaminolysis. Glutaminase (GLS) Activity Assay Kit and Glutamine Synthetase (GS) Activity Assay Kit were used to analyse the activity of specific metabolic enzymes dominate glutaminolysis. The regulatory mechanism of glutaminolysis by MTA3 was confirmed using Chromatin immunoprecipitation assay and Gaussia luciferase assay. The expression levels of MTA3 and GS in ESCC primary tissues were evaluated using immunohistochemistry. A semi-quantitative manner was employed to grade each specimen with a composite histoscore. Survival curves were plotted with the Kaplan-Meier method and compared by log-rank test. In addition, survival data were assessed by univariate and multivariate Cox regression analyses.

Results: The transwell assays showed that more MTA3-depleted cells migrated through the membrane. In contrast, MTA3 overexpression suppressed both ESCC cell invasion and migration. When these cells were injected into the tail vein of nude mice, more ESCC cells in the MTA3 knockdown group were found in the lungs. These findings suggest that MTA3 can repress ESCC metastasis in vitro and in vivo. Meanwhile, overexpressed and knockdown MTA3 can repress and expedite glutamine consumption and glutamate production uniformly, respectively. To determine how MTA3 acts on glutaminolysis, the activity of two specific metabolic enzymes dominate this metabolism, GS and GLS, were evaluated and found that overexpressed and knockdown MTA3 can restrain and enhance the activity of GS, respectively, but have less effect on GLS. Moreover, MTA3-deception-mediated increased metastatic properties is significantly reduced when treated with GS inhibitor suggesting GS plays a crucial role in MTA3-mediated metastasis repression. Mechanistically, Chromatin immunoprecipitation assay and Gaussia luciferase assay showed that MTA3 was recruited to the promoter of GS and supressed GS transcription. Howerver, knockdown of GATA3 abolished MTA3's repressive effect on GS and inhibited the MTA3's occupation on the promoter region of GS. These results collectively demonstrated that, in ESCC cells, MTA3 is recruited by GATA3 to inhibit GS expression, then ultimately represses glutaminolysis and metastasis. Furthermore, Kaplan-Meier analyses found that the overall survival of the low-MTA3/high-GS group is significantly worse than

that of the high MTA3/low GS group and the rest which include high MTA3/low GS, high MTA3/high GS, low MTA3/low GS. Finally, multivariate Cox regression analyses found that low MTA3/high GS can be used as independent prognostic indicators in ESCC patient prognosis.

Conclusion: MTA3 is capable of repressing ESCC metastatic properties through downregulating GS and low MTA3/high GS might be a potential prognostic factor for ESCC patients.

496. OCT1 /ALDOA signaling axis promotes colon cancer growth and progression by driving metabolic reprogramming

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Objective Metabolic reprogramming is considered to be the root of cancer growth and progression, which involved a multi-step and multi-gene. Aberrant expression of POU domain class 2 transcription factor 1 (POU2F1, also called OCT1) plays vital roles in carcinogenesis. However, the function of the OCT1 in maintenance of colon cancer malignancy is unknown. So this study aimed to investigate the effects of OCT1-mediated metabolic reprogramming on the growth and progression in colon cancer cells, and its possible mechanisms.

Methods OCT1 expression in colon cancer specimens was analyzed by immunohistochemistry. The effect of OCT1 expression on growth and metabolic reprogramming in colon cancer cells was assessed by altering its expression in vitro and in vivo. Mechanistic investigation was carried out using cell and molecular biological approaches.

Results Compared with non-tumorous tissues, OCT1 was highly expressed in colon cancer tissue specimens; Patients who displayed high expression of OCT1 may achieve a poorer progression free survival (PFS) and overall survival (OS), compared to those with low expression of OCT1 ($P<0.001$); Univariate and multivariate further showed that OCT1 expression was significantly associated with PFS and OS. Subsequently, we detected the effect of OCT1 expression on growth and metabolic reprogramming in colon cancer cells by altering its expression in vitro and in vivo. We found that the OCT1 overexpression obviously induced colon cancer cell proliferation and colony formation, markedly increased glucose consumption and lactate production, significantly activated the pentose phosphate pathway, and attenuated the DNA damage. In contrast, OCT1 silencing had the opposite effect, which significantly suppressed the colon cancer cell proliferation and colony formation, markedly decreased glucose consumption and lactate production, obviously inactivated the pentose phosphate pathway (PPP) and enhanced the DNA damage. Furthermore, we found that increased the expression of OCT1 could obviously up-regulate that of a key glycolytic enzyme, aldolase A

(ALDOA), also markedly upregulated the expression of hexokinase 2 (HK-2), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (PFKFB-2), pyruvate kinase isozyme type M2 (PKM2), glucose-6-phosphate dehydrogenase (G6PD), and ribose 5-Phosphate Isomerase A (RPIA). Mechanistically, OCT1 bound directly to the promoter regions of the ALDOA gene and positively regulated its transcriptional activity. Collectively, we found that aberrant ALDOA expression contributed to colon cancer tumorigenicity, ALDOA overexpression obviously induced colon cancer cell proliferation and colony formation, markedly increased glucose consumption and lactate production, activated the PPP, and attenuated the DNA damage, while silencing ALDOA had the opposite effect, significantly suppressed the colon cancer cell proliferation and colony formation, decreased glucose consumption and lactate production, obviously inactivated the PPP and enhanced the DNA damage. Addition to, we found that compared with non-tumorous tissues, ALDOA was highly expressed in colon cancer tissue specimens, the high expression of ALDOA in colon cancer tissue specimens was positively associated with poor prognosis; Interestingly, correlation analysis suggested OCT1 expression was positively correlated with ALDOA in colon cancer tissues, and the expression of ALDOA coupled with OCT1 expression provided better prognostic information than did OCT1 expression alone.

Conclusions Our findings reveal that the OCT1/ALDOA axis promotes the growth and progression of colon cancer via driving metabolic reprogramming, and constitutes potential prognostic predictors and therapeutic targets for colon cancer.

497.远处转移鼻咽癌患者血清外泌体差异表达 lncRNA 的筛选

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目的 提取转移和未转移的鼻咽癌患者血清来源的外泌体，对两组外泌体中 lncRNA 进行高通量测序，探究 lncRNA 表达谱，并筛选其差异表达。

方法 （1）采集鼻咽癌患者血清，根据临床分期以及是否发生转移分为转移组和非转移组，每组 6 例。采用超速离心法，分离血清来源的外泌体；（2） 采用 Western blotting、 透射电镜对所获得的外泌体进行鉴定；（3）利用高通量测序技术分析两组外泌体 lncRNA 的表达谱；（4）筛选显著差异表达的 lncRNA。

结果 （1） Western blotting 结果显示外泌体的标志蛋白 TSG101 呈阳性表达；透射电镜结果显示外泌体为圆形或者扁圆形，直径为 30-150nm 不等；（2）高通量测序及生物信息学分析结果显示，转移组与非转移组比较共有 17 个差异表达的 lncRNA， 其中包括 6 个上调表达，11 个下调表达；（3）差异 lncRNA 靶基因的 GO 功能富集分析结果表明，17 个差异 lncRNA 的靶基因主要参与血管生成、细胞增殖、细胞凋亡、细胞周期、DNA 损伤等生物学过程。

结论 来源于转移组和非转移组鼻咽癌患者血清的外泌体 lncRNA 存在差异表达，为进一步探讨外泌体来源的目标 lncRNA 在鼻咽癌发展、转移的机制提供研究基础。

498. 心肌相关转录因子 A 通过调控基质金属蛋白酶影响肺癌细胞的迁移和侵袭

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目的 由于缺少有效和敏感的早期检测手段，肺癌一直是世界范围内致死率较高的一种癌症，但可供选择的有效干预有限，因此对于肺癌的发生机制和病理的研究越来越引起人们的重视。近年来发现表观遗传的改变与肿瘤的发生密切相关，为肺癌的治疗提供了多种动态和可逆的治疗靶点。心肌相关转录因子 A（MKL1）通过小 RNA 干扰 MKL1 能够在乳腺癌中抑制肿瘤的生成，影响肿瘤细胞的迁移和侵袭能力。MMP9 是研究较为透彻的一族基质金属蛋白酶，有研究表明在巨噬细胞中 MMP9 能够受到 MKL1 的调控。并且有文献报道指出缺氧和细胞转化因子两种外界刺激能够激活 MMP9 的表达。据此，我们推测 MKL1 的抑制能够降低肺癌的形成，并且 MKL1 可能是通过影响 MMP9 启动子上表观遗传学的改变来促进肿瘤的迁移和侵袭。**方法** 我们使用三气培养箱设置 1%氧气来模拟缺氧的环境以及给予细胞转化因子来处理人的肺癌细胞系 H1299。通过荧光素酶试验和染色质免疫共沉淀试验研究 MKL1 在 MMP9 启动子上的结合序列以及结合序列上甲基化水平的改变。通过小 RNA 干扰 MKL1，ASH2 以及在 LLC 细胞中构建稳定缺失 MKL1，ASH2 的细胞，使用 RT-qPCR 和免疫印迹检测 MMP9 mRNA 和蛋白质水平观察 MKL1 和 ASH2 的抑制对 MMP9 mRNA 和蛋白的影响。通过 Transwell 迁移和侵袭实验检测 MKL1 和 ASH2 的缺失对 H1299 细胞迁移能力的影响。使用皮下荷瘤及肺迁移模型观察缺失 MKL1 和 ASH2 对细胞体内成瘤及迁移能力的影响。**结果** MKL1 的敲除能够抑制小鼠肺癌细胞的肿瘤生成能力，并且降低肿瘤在肺上形成结节的能力。MMP9 mRNA 和蛋白水平都随着 MKL1 的缺失而下降。干扰 MKL1 的表达以后，被缺氧和转化因子诱导升高的 MMP9 的表达受到影响。并且 MKL1 的缺失影响 MMP9 启动子上 H3K4 二甲基化和三甲基化的水平。ASH2 是 COMPASS 家族的成员，能够被 MKL1 招募至目的基因上影响转录的发生。干扰 ASH2 以后，同样能够影响应激诱导的 MMP9 的表达，并且 ASH2 的敲除能够影响小鼠体内肿瘤的生成和迁移能力。**结论** MKL1 促进肺癌的发生和迁移。MKL1 招募甲基转移酶 ASH2 至 MMP9 的启动子上，影响 MMP9 H3K4 二甲基化和三甲基化水平。MKL1 与 ASH2 均参与缺氧和细胞转化因子刺激下 MMP9 的上调，并且两者的缺失都会影响肿瘤的迁移和侵袭。

499. MCD differentially regulates renal cell carcinoma progression

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Objective Metastasis accounts for approximately 20 percent of renal cell carcinoma (RCC)-associated mortality. Recently, escalating epidemiology studies reveal that obesity, a complex disorder involving deregulated lipid metabolism, is one of the major risk factors in multiple cancers including RCC. Therefore, a better understanding of the relationship between lipid metabolism and metastasis may shed light on the development of precision medicines targeting to metabolic network for the treatment of metastatic cancer.

Methods Malonyl-CoA decarboxylase (MCD) catalyzes the conversion of malonyl-CoA to acetyl-CoA, thus prevents lipogenesis and meanwhile facilitates fatty acids oxidation (FAO). As an important switch between lipid biosynthesis and breakdown, the function of MCD in cancer is highly debatable. We therefore investigate the function of MCD in RCC development with cultured cells, xenograft tumor model, and clinical samples.

Results In this study, we found that MCD is required for RCC cell proliferation in vitro, and overexpression of wild type MCD instead of enzymatic dead mutant, accelerates xenograft tumor growth in vivo, which implies an oncogenic role of MCD. However surprisingly, our further study reveals that MCD inhibits RCC metastasis both in vitro and in vivo in an enzymatic activity-dependent manner, which suggests MCD as a tumor suppressor. The paradox of MCD function prompts us to further investigate the clinical correlation between MCD expression and RCC development. Indeed, MCD expression is significantly higher in the tumor sample compared to para-RCC kidney tissue from patients with stage I, II, and III RCC. Nonetheless, we found that MCD expression is clearly lower in patients with stage IV RCC, which correlates to much higher metastatic potential. The correlation between lower MCD expression and increased RCC metastasis is recapitulated by further analysis with a local cohort including 300 patients diagnosed with RCC.

Conclusions In general, our findings reveal that MCD differentially regulates RCC development in different stages, through catalyzing malonyl-coA conversion to acetyl-coA, which suggests the importance of lipid metabolism in RCC progression, and highlights the necessity to reconsider the function of other lipogenesis-associated genes such as ACC and FASN in cancer development.

500. Radiomics Combined with Semantic Features Nomogram for KRAS, NRAS, BRAF Status Prediction Using Contrast-enhanced CT in Colorectal Cancer

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Objective It is significant to improve the examination of RAS (KRAS and NRAS) and BRAF gene mutation status for advanced colorectal cancer(CRC) patients. Computerized tomography (CT) is a common inspection in cancer therapy. Radiomics can be used as a non-invasive and accurate method to judge patients' gene mutation status as well as guide clinical decisions.

Methods For this retrospective study, we enrolled 160 patients diagnosed with colorectal cancer with liver metastasis (CRLM) in two hospitals from January 2013 to October 2019. 149 patients from one hospital were allocated to the training cohort and 11 patients in another hospital to the external validation cohort. Patients were divided into the training cohort and external validation cohort according to their hospitals. All of the patients received lung and abdominal contrast-enhanced CT before chemical or radical therapy. A set of 888 radiomics features that reflected the characteristics of the metastatic liver lesions was extracted from the portal venous phase(PVP) of acquired abdominal CT for each patient. In the training set, we used 1,000 times punishment logistic regression together with 10-fold cross-validation to calculate the relationship between radiomics features and the gene mutation status of RAS and BRAF genes. We also evaluated the prediction accuracy of semantic features combined with radiomics features. Two radiologists used 3D-Slicer software to semi-automatically delineate and extract features of the region of interest(ROI). We used R (version 3.5.3) for statistical analysis.

Results 888 features were extracted using Pyradiomics. 9 features were effective for RAS and BRAF gene mutation status prediction in CRLM. In addition, our results suggested that two semantic features (presence of metastatic lesions other than the liver and the "micro-satellite" phenomenon) are related to gene mutation status. We constructed three scores, radiomics score, semantic score, and combined score. The combined score distinguished between wild and mutant type patients with AUC = 0.80 in the primary cohort and 0.67 in the validation cohort respectively. A nomogram was established based on radiomics together with semantic features.

Conclusions The semantic and radiomics features reflect the uniformity in the distribution of CT values and the morphology of the metastatic liver lesions. We find that liver lesions in patients with

mutant type are more heterogeneous, closer to a sphere in shape, and lower in gray-level values. Biopsies or surgeries were invasive and not able to monitor changes in gene mutation status dynamically. In the treatment of patients with advanced colorectal cancer, CT examination technology is a routine examination method and more acceptable to patients compared with Magnetic Resonance Imaging(MRI). This study proved that the application of radiomics features together with semantic features can improve noninvasive assessment of RAS (KRAS and NRAS) and BRAF gene mutation status in CRLM.

501. Metformin-Induced Killing of liver Initiating Cells via inhibition on PI3-K/Akt-dependent pathway

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Objective Liver tumor-initiating cells (T-ICs) are a subpopulation of tumor cells with the capacity of self-renew and differentiate into distinct cell types that comprise the bulk of the hepatoma. Liver T-ICs have been elucidated to render tumor recurrence and chemo-resistance and targeting T-ICs might be a novel strategy for HCC therapy. Metformin has been shown to selectively kill cancer cells, and HCC cell lines are sensitive to the effects of metformin. However, the mechanism underlying the enhanced susceptibility of HCC to metformin has not been elucidated.

Methods Spheroid assay and in vitro cell behavior assay were used to detect the influence of metformin on the self-renewal effect of HCC cells in vitro. Real-time PCR assay was used to detect the mRNA level of CD90, CD133 and Sox2 after SMMC-7721 cells were treated with metformin. Western blot assay was used to detect the change of p-Akt and p-mTOR protein expression after SMMC-7721 cells were treated with metformin. Animal models were conducted to explore the influence of metformin on SMMC-7721- injected NOD/SCID mice.

Results Metformin decreases the proportion of tumor stem cells in HCC cells. CD90, CD133 and Sox2 were significantly downregulated in HCC cells treated by metformin. The spheroid formation ability of HCC cells was attenuated obviously at the presence of metformin. What's more, PI3-K/Akt pathway was found downregulated in metformin-treated HCC cells and the inhibition ability was diminished by blockage of PI3-K/Akt pathway.

Conclusions Metformin plays an important role in HCC tumor-initiating cells through PI3-K/Akt signaling and may be a promising therapeutic drug for HCC patients.

502. Vasohibin 2 Promotes Lymphangiogenesis of Lung Squamous Cell Carcinoma through Snail-Dependent VEGF-D Signaling Pathway

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Objective Tumor metastasis is a process in which tumor cells enter the lymphatic vessels and blood vessels and then spread to the secondary site where they form secondary tumors. In vascular biology, angiogenesis and anti-angiogenesis therapy have been extensively studied, however, the molecular mechanisms involved in lymphangiogenesis and lymphatic metastasis remain unclear.

Methods We analyzed mRNA expression profiles of 937 primary lung squamous cell carcinoma (LUSC) samples from The Cancer Genome Atlas (TCGA) to explore the genes related to the poor prognosis of LUSC patients, and filtered out Vasohibin 2 (VASH2) as a significant predictive factor, which has been identified to promote angiogenesis in multiple kinds of tumors.

Results We demonstrated that high level of VASH2 was associated with poor prognosis and high potential of lymphatic metastasis in an independent Chinese LUSC cohort. VASH2 promoted the proliferation and invasion of LUSC cells both in vitro and vivo. Forced over-expression of VASH2 in LUSC cells promoted the amplification and tube-formation of HUVEC and HLEC cells via upregulating VEGF-D production which could be reserved by Snail inhibition. Furthermore, Blocking VASH2/VEGF-D signaling using specific antibodies dramatically inhibited tumor growth in mice by interfering proliferation of cancer cells and lymphangiogenesis in tumor tissues.

Conclusions In conclusion, VASH2 facilitated lymphangiogenesis and tumor growth in a Snail-dependent manner which might serve as a novel biomarker for early diagnosis and prognosis prediction, as well as a potential therapeutic target in LUSC.

503. ZBTB48 抑制靶基因 MGAT5 表达调控鼻咽癌的 EMT 和转移

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目的 放化疗后出现复发和远处转移是导致鼻咽癌(NPC)患者治疗失败和死亡的主要原因；上皮-间充质转化(EMT)在肿瘤早期侵袭和转移过程中扮演重要角色。目前，ZBTB48 在肿瘤发生发展中的功能还鲜有报道。

方法 体外实验探讨 ZBTB48 和靶基因 MGAT5 在 NPC 细胞 EMT 和迁移侵袭中的作用；ChIP-qPCR 和启动子荧光素酶报告基因实验确证 ZBTB48 调控 NPC 细胞 EMT 和迁移侵袭等的作用可否由其靶基因 MGAT5 介导；免疫组化方法揭示 ZBTB48 及其靶基因 MGAT5 等的表达相关性及与生存预后的关系。

结果 qRT-PCR 和免疫组化结果表明 ZBTB48 在 NPC 组织标本中表达显著下调，ZBTB48 表达与肿瘤 T 分期、颈部淋巴结转移、远处转移以及临床分期等呈负相关。Western blot 检测结果显示，在过表达 ZBTB48 的 HONE1-EBV 细胞中，E-cadherin 表达水平显著升高，N-cadherin 和 vimentin 表达水平均显著降低；Transwell 和划痕迁移实验结果显示，ZBTB48 过表达抑制 HONE1-EBV 细胞的体外迁移。Western blot 结果显示，ZBTB48 敲除的 5-8F 细胞中，上皮标志性基因 E-cadherin 和 bβ-catenin 表达水平显著降低，N-cadherin 和 vimentin 表达水平均显著升高；Transwell 和划痕迁移实验结果显示，ZBTB48 敲除极大促进 5-8F 细胞的体外迁移。ChIP-qPCR 和启动子荧光素酶报告基因实验证实 ZBTB48 负向调控 MGAT5 的表达。对 177 例 NPC 组织免疫组化检测发现，ZBTB48 表达和 MGAT5 表达水平呈负相关。qRT-PCR 和 Western blot 检测结果显示，在 MGAT5 敲除的 HONE1-EBV 细胞中，E-cadherin 和 β-catenin 表达显著升高，N-cadherin 和 vimentin 表达水平显著降低；Transwell 迁移实验结果显示，MGAT5 敲除明显抑制了 HONE1-EBV 细胞的体外迁移。Boyden 小室侵袭实验结果显示，siMGAT5 可大部分逆转 ZBTB48 敲除所致 5-8F 细胞增强的体外侵袭能力。

结论 鼻咽癌 ZBTB48 表达下调，将导致其靶基因 MGAT5 表达上调，进而引起 NPC 细胞发生 EMT，从而促进了 NPC 的侵袭转移。

504. 基于甲基化及临床病理数据的肠癌转移预测模型的建立和验证

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目的 肠癌患者死亡的首要原因是转移，建立肠癌转移的预测模型对改善预后起关键作用，本研究拟结合肠癌甲基化数据和临床病理资料，建立肠癌转移的预后模型并验证，筛选出与肠癌肝转移相关、能预测肠癌转移风险的分子标志物，从而为临床实行个体化治疗提供重要的依据。

方法 利用机器学习技术，对 276 例肠癌的 RNA-seq 数据进行分析，结合多因素 lasso 回归分析，对 392 例肠癌患者的临床病理数据进行分析。综合以上分析建立了肠癌转移的风险评估模型。

结果 构建了一个基于 2516 个 CpG 位点的分类器来识别肠癌的转移，能够通过原发肿瘤组织的甲基化特征直接识别患者的转移状态。此外，我们建立了一个基于 18 个 CpG 位点的分类器来区分肿瘤和正常组织。利用(LASSO) Cox 回归，建立了一个基于 22 个 CpG 位点的模型来预测肠癌患者的 OS。两种分类器的预测效能(ROC)曲线下面积(AUC)均接近于 1，说明了所得模型具有有效的预测价值。

结论 该预后模型有望促进基于肠癌 DNA 甲基化特征的未来治疗决策，还可以通过不同的机器学习方法对肠癌 DNA 甲基化模式的利用进行进一步的研究。

505. Circadian clock gene period 2 down-regulation is associated with poor prognosis of obese breast cancer patients

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Objective Obese breast cancer patients have poor prognosis, but the mechanism by which obesity affects breast cancer remains unclear. The aim of the study was to identify and validate new markers associated with the prognosis of obese breast cancer.

Methods We reanalyzed the gene expression profiles of normal weight, overweight, and obese breast cancer to identify candidate genes and further validated its protein level by immunohistochemistry. Lastly, we explored the association between candidate genes and the prognosis of breast cancer in Tongji Hospital based on data of an 8-year follow up by the Kaplan–Meier method and univariate and multivariate Cox regression models.

Results The fold change of circadian clock gene period 2 (PER2), which displays a declining trend with body mass index (BMI) increase, is 0.76 in obese patients compared to normal weight patients. The low expression rate of PER2 protein was 44.7%, 51.5%, and 61.3% in normal weight, overweight, and obese patients, respectively. The 8-year recurrence-free survival (RFS) rate was 75.9%, 69.6%, and 64.1%, and the 8-year overall survival (OS) rate was 86.8%, 83.0%, and 76.1% in normal weight, overweight, and obese patients ($p<0.05$), respectively. The 8-year RFS rate was 66.2% and 76.4%, and the 8-year OS rate was 79.9% and 86.3% in low or high PER2 expression groups ($p<0.05$), respectively. The unadjusted hazard ratio (HR) of PER2 was 1.550 (95% confidence interval (CI), 1.029-2.335) and the adjusted HR was 3.003 (95% CI, 1.838–4.907).

Conclusions Taken together, our results suggest that low expression of PER2 is an independent risk factor for breast cancer prognosis and may be a reason for poor prognosis in obese patients.

506. Dvl2 通过 DEP 结构域增强 Spats1 与 β-catenin/TCF4 复合物的结合

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目的 Wnt 信号通路在正常组织发育中发挥重要作用，其功能异常常会导致多种肿瘤的发生。前期我们发现与 Dvl2 结合的新蛋白 Spats1 能够通过促进 TCF4 降解抑制 Wnt 信号，但 Dvl2 在该过程中的作用尚不清楚。

方法 我们构建了 Dvl2、Spats1 不同结构域缺失的质粒，采用 GST-pull down 实验、免疫荧光技术、Western blot、质粒转染以及荧光素酶活性检测等实验来研究 Dvl2 在 Spats1 抑制 Wnt 信号通路中的作用。

结果 通过免疫沉淀实验发现，Dvl2 不仅在体外与 Spats1 存在相互作用，在细胞内也存在相互作用；免疫荧光实验证实在多种细胞内，Dvl2 与 Spats1 存在共定位，提示 Dvl2 与 Spats1 的相互作用存在空间基础，有意思的是在不存在 Dvl2 时，Spats1 主要分布在细胞核内，而在 Dvl2 存在的情况下，Spats1 进行重新分布,与 Dvl2 在细胞浆呈点状分布；Gene mapping 实验发现，Dvl2 的 PDZ 和 DEP 结构域对 Spats1 的结合起到重要作用，而 Spats1 任意部分的缺失都会导致相互作用的消失。进一步的试验结果证实，Dvl2 能够增强 Spats1 与 TCF4/β-catenin 复合物的相互作用，而且 Dvl2 的 DEP 结构域对这种增强作用是必须的。

结论 Dvl2 通过 DEP 结构域增强 Spats1 与 β-catenin/TCF4 复合物的结合，可能在 Spats1 发挥 Wnt 抑制功能中其重要作用。

507. 重庆地区非小细胞肺癌患者 EGFR 突变状态及其与临床病理类型和肿瘤标志物的相关性研究

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目的 探讨非小细胞肺癌患者 EGFR 突变与临床病理类型及肿瘤标志物的相关性，便于临床制定合适的治疗方案。

方法 以重庆大学附属肿瘤医院行肺癌根治性手术的 179 名非小细胞肺癌患者为研究对象，术前通过化学发光法定量检测试剂盒检测 CA125、CA19-9、AFP 和 CEA。用石蜡包埋组织 DNA 快速提取试剂盒提取肿瘤组织 DNA，用人类 EGFR 基因突变检测试剂盒(荧光 PCR 法)进行基因突变检测。统计与分析非小细胞肺癌患者 EGFR 突变状态与临床病理类型及各肿瘤标志物表达水平之间有无相关性。

结果 48.04%(86/179 例)的患者发生 EGFR 突变，其中 8.14%（7/86 例）为 18 外显子突变，62.79%(54/86 例)为 19 外显子突变，29.07%（25/86 例）为 21 外显子突变，20 外显子没有突变。在男性患者中的突变率为 24.62%（32/130 例），女性患者中的突变率为 78.26%(54/69 例)。男性和女性患者突变率之间相比较统计学差异显著(P<0.05)。腺癌 EGFE 基因突变的发生率为 49.24%（65/132 例），鳞癌为 9.52%（2/21 例），腺鳞癌则为 76%（19/25 例）。腺癌及腺鳞癌分别与鳞癌比较，P 值均小于 0.05 ，统计学差异显著。肿瘤标志物 CA199、CA125 及 AFP 表达情况与 EGFR 基因突变比较，P 值均大于 0.05；CEA 与 EGFR 基因突变比较，P<0.05。

结论 EGFR 基因突变主要见于女性、腺癌及腺鳞癌患者，由于中国女性吸烟者不多，因而肺癌 EGFR 基因突变主要是女性、腺癌(或腺鳞癌)和非吸烟者，此特征与临床吉非替尼有效患者的特征吻合。统计分析显示，术前血清 CEA 水平与 EGFR 突变存在明显相关性。因此，根据术前 CEA 的表达量可以预测 EGFR 的突变，从而指导临床选择适合的治疗方案。

508. MCU-induced mitochondrial calcium uptake promotes mitochondrial biogenesis and colorectal cancer growth

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Objective Mitochondrial calcium uniporter (MCU) has an important role in regulating mitochondrial calcium (Ca^{2+}) homeostasis. Dysregulation of mitochondrial Ca^{2+} homeostasis has been implicated in various cancers. However, it remains unclear whether MCU regulates mitochondrial Ca^{2+} uptake to

promote cell growth in colorectal cancer (CRC).

Methods Therefore, in the present study the expression of MCU in CRC tissues and its clinical significance were examined. Following which, the biological function of MCU-mediated mitochondrial Ca^{2+} uptake in CRC cell growth and the underlying mechanisms were systematically evaluated using in in vitro and in vivo assays, which included Western blotting, cell viability and apoptosis assays, as well as xenograft nude mice models.

Results Our results demonstrated that MCU was markedly upregulated in CRC tissues at both the mRNA and protein levels. Upregulated MCU was associated with poor prognosis in patients with CRC. Our data reported that up-regulation of MCU enhanced the mitochondrial Ca^{2+} uptake to promote mitochondrial biogenesis, which in turn facilitated CRC cell growth in vitro and in vivo. In terms of the underlying mechanism, it was identified that MCU-mediated mitochondrial Ca^{2+} uptake inhibited the phosphorylation of transcription factor A, mitochondrial (TFAM) and thus enhanced its stability to promote mitochondrial biogenesis. Furthermore, our data indicated that increased mitochondrial Ca^{2+} uptake led to increased mitochondrial production of ROS via the upregulation of mitochondrial biogenesis, which subsequently activated NF-κB signaling to accelerate CRC growth.

Conclusions In conclusion, the results indicated that MCU-induced mitochondrial Ca^{2+} uptake promotes mitochondrial biogenesis by suppressing phosphorylation of TFAM, thus contributing to CRC cell growth. Our findings reveal a novel mechanism underlying mitochondrial Ca^{2+}-mediated CRC cell growth and may provide a potential pharmacological target for CRC treatment.

509. IL-37 在原发性肝细胞癌中的表达及其临床意义

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目的 探讨原发性肝细胞癌患者血清和组织中 IL-37 的表达及临床意义

方法 选择右江民族医学院附属医院 2017 年 2 月至 2018 年 11 月期间收治的 52 例原发性肝细胞癌患者作为研究对象，同时选取同一时期来我院体检的 50 例健康者为对照组，应用酶联免疫吸附试验法检测两组血清中 IL-37。将接受手术治疗的 40 例肝癌患者肝组织分为癌组织组和癌旁组织组，应用免疫组织化学法检测肝癌组织组和癌旁组织组中 IL-37 的表达水平。分别对实验组及对照组血清 IL-37 水平和肝癌织组中及癌旁组织组中 IL-37 表达的表达水平进行比较，应用统计学分析肝癌组织中 IL-37 表达与肝细胞癌患者各项临床指标的关系。

结果 实验组与对照组之间血清 IL-37 含量差异无统计学意义（$P>0.05$）。IL-37 蛋白在癌组织组的表达明显低于癌旁组织组（$P<0.05$）。肝癌组织中 IL-37 表达水平与患者肿瘤大小有关

（P<0.05），但与患者性别、年龄、肿瘤大小、是否肝硬化、是否乙肝病毒感染及甲胎蛋白水平等均无明显关系（P>0.05）

结论 IL-37 在原发性肝细胞癌组织中表达明显降低，且与肿瘤大小有关，表明 IL-37 在原发性肝细胞癌的发生发展过程中可能发挥重要的作用。

510. The epigenetically downregulated ZDHHC1 suppresses cancer growth through metabolism inhibition and oxidative/ER stress involved pyroptosis

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Objective Epigenetic abnormity has been recognized as one crucial factor of tumorigenesis. Methylation of vital tumor suppressor genes (TSGs) often leads to silenced expression. Meanwhile, cancer metabolism is a critical feature of cancer cells. Alterations in cancer cell metabolism, including glucose uptake, the pentose phosphate pathway (PPP), and redox homeostasis, contribute to cancer development. Here, we introduced a novel TSG, Zinc Finger DHHC-Type Containing 1 (ZDHHC1, also known as ZNF377), though frequently silenced due to epigenetic modification among various cancers, exerts significant anti-tumor effects through metabolic regulation.

Methods Quantitative reversed-transcription PCR (qRT-PCR), reverse transcription PCR (RT-PCR) and Western blot were employed to demonstrate transcriptional and protein levels of indicated factors. Methylation of ZDHHC1 promoter was profiled by bisulfite conversion and methylation specific PCR (MSP). Proteomics were analyzed by gas chromatography-mass spectrometry (GC-MS), and isobaric tags for relative and absolute quantitation (iTRAQ) were included for metabolomics analysis. Cellular functions were examined via corresponding approaches. Nude mice were used for xenograft models. Indirect immunofluorescence staining was utilized to obtain precise location and expression of target proteins. Oxidative stress indicators were detected using specific kits.

Results We found that ZDHHC1 expression was frequently silenced in tumor due to methylation, and restoration of ZDHHC1 expression resulted in suppressing cancer cell proliferation. ZDHHC1's salient anti-tumor roles were validated through in vitro and in vivo methods. Metabolomic and proteomic analyses predicted inhibitory role of ZDHHC1 in glucose metabolism pathways and PPP, which as later validated by examining key factors in these pathways. Mechanistically, we unraveled that ZDHHC1-mediated tumor suppression involves oxidative stress-related factors and key indicators

of endoplasmic reticulum (ER) stress and pyroptosis

Conclusions Taken together, our study indicates ZDHHC1 is a potential tumor-suppressor that is frequently silenced due to promoter methylation. It bears the ability of undercutting glucose consumption and anabolism of tumor cells, meanwhile exaggerating oxidative stress and ER stress to expedite cell death through induction of pyroptosis. The ZDHHC1-mediated glucose metabolism inhibition and pyroptosis pathways could be exploited for development of new cancer prevention and therapies.

511. Hypoxia-induced NAD+ interventions promote tumor survival and metastasis by regulating mitochondrial dynamics

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Objective Hypoxia, an important feature of the tumor microenvironment, is responsible for the chemo-resistance and metastasis of malignant solid tumors. Recent studies indicated that mitochondria undergo morphological transitions as an adaptive response to maintain self-stability and connectivity under hypoxic conditions.

Methods NAD+ may not only provide reducing equivalents for biosynthetic reactions and in determining energy production, but also functions as a signaling molecule in mitochondrial dynamics regulation.

Results In this review, we describe the upregulated KDAC deacetylase expression in the mitochondria and cytoplasm of tumor cells that results from sensing the changes in NAD+ to control mitochondrial dynamics and distribution, which is responsible for survival and metastasis in hypoxia.

Conclusions Targeting key KDAC deacetylases may provide novel clues for developing anti-cancer therapy through mitochondrial dynamics regulation in hypoxia conditions.

512. 乳酸脱氢酶 C4 在乳腺癌中的表达及其对乳腺癌细胞生物学功能的影响

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目的 研究乳酸脱氢酶 C4（LDH-C4）在乳腺癌组织中的表达，探讨 LDH-C4 对乳腺癌预后判断的价值；探讨 LDH-C4 表达上调对 MCF-7 乳腺癌细胞中的生物学影响及分子机制。

方法 通过免疫组织化学分析 158 例乳腺癌石蜡组织中 LDH-C4 蛋白在的表达情况。分析乳腺

癌不同临床病理参数与 LDH-C4 蛋白表达的相关性。对随访资料进行 Cox 回归模型，研究 LDH-C4 蛋白在乳腺癌预后判断的临床价值。通过慢病毒载体将外源 LDHC 基因导入 MCF-7 乳腺癌细胞中，通过稀释法结合绿荧光蛋白表达筛选 LDH-C4 阳性表达的单克隆细胞系。通过平板克隆、CCK-8 细胞增殖、细胞划痕、Transwell 小室等细胞生物学实验，研究 LDH-C4 表达上调对 MCF-7 细胞生物学行为的影响；Western blot 法检测 PI3K/AKT/mTOR 信号通路相关分子，探讨 LDHC 基因上调对乳腺癌 MCF-7 细胞生物学影响的可能机制。

结果 158 例乳腺癌石蜡组织切片免疫组化染色，LDH-C4 蛋白染色集中在细胞质中，呈淡棕色到深棕色，阳性率为 91.8%（145/158），其中低表达（-/+）和高表达（++/+++）分别为 41.8%（66/158）、58.2%（92/158）。经卡方检验，乳腺癌临床分期晚、腋窝淋巴结转移率高，患病年龄低者 LDH-C4 呈高表达（P<0.05）；Kaplan-Meier 法进行生存分析并经 Log-rank 检验结果显示，乳腺癌 LDH-C4 高表达者预后差（P=0.035）；Cox 回归分析显示临床分期（P=0.000）和 LDH-C4 表达水平（P=0.002）是乳腺癌预后的独立因素。2. 通过慢病毒感染成功筛选 LDH-C4 过表达的单克隆化的乳腺癌 MCF-7 细胞系；细胞学实验结果显示，LDH-C4 蛋白过表达可增强乳腺癌 MCF-7 侵袭和迁移能力，而对细胞生长增殖无显著影响；免疫印迹法初步显示，过表达 LDH-C4 蛋白可上调乳腺癌 MCF-7 细胞中 AKT 和 mTOR 蛋白的表达。

结论 LDH-C4 在乳腺癌组织中具有很高的表达阳性率，其表达与临床分期、腋窝淋巴结转移相关；高 LDH-C4 蛋白水平预示乳腺癌不良预后。过表达 LDH-C4 可增强 MCF-7 细胞增殖、侵袭和迁移能力，其机制可能与 AKT/mTOR 细胞信号通路的激活有关。

513. 乳酸脱氢酶 C4 在肝细胞癌中的表达及其生物学功能研究

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目的 通过分析乳酸脱氢酶 C4(LDH-C4)在(HCC)中的表达及其与 HCC 患者的临床病理特征及其预后的关系,明确 LDH-C4 过表达对 HCC 细胞 Bel-7402 的细胞生物学行为能力的影响，并探讨相关分子机制。

方法 基于高通量肝癌组织芯片，采用免疫组化染色技术检测 HCC 癌组织中 LDH-C4 蛋白的表达水平，分析 LDH-C4 表达情况与肝癌患者临床病理特征的关系。荧光显微镜观察 GV492-LDHC 病毒感染后的 Bel-7402HCC 细胞中 EGFP 表达情况，筛选 LDH-C4 表达呈阳性的细胞系。通过 RT-qPCR 鉴定 LDH-C4 mRNA 过表达的效果。通过 CCK-8 实验、划痕修复实验及 Transwell 小室等实验分别检测 LDH-C4 对 HCC 细胞 Bel-7402 在体外的增殖、迁移及侵袭能力的影响。基于建立的 LDH-C4 稳定过表达的 Bel-7402 细胞系基础上，对各组细胞中乳酸、丙酮酸等细胞能量代谢产物含量进行检测，同时检测各组肿瘤细胞中葡萄糖消耗水平，探究

LDH-C4 过表达对 Bel-7402HCC 细胞能量代谢的影响；通过 Western blot 实验检测 AKT/mTOR 信号通路中相关蛋白表达水平受 LDH-C4 过表达的影响。

结果 HCC 中的 LDH-C4 呈现高表达状态，主要表达于 HCC 细胞的细胞质中，且 LDH-C4 的表达水平与 HCC 患者的 T 分期、临床分期及瘤体大小明显相关（P<0.05）；生存分析结果提示：LDH-C4 高表达患者的预后较低表达者更差（P<0.05）。CCK-8 实验、划痕修复实验及 Transwell 小室实验检测结果提示：LDH-C4 过表达可提升 Bel-7402HCC 细胞在体外的迁移侵袭能力，但对生长增殖无明显影响。3.能量代谢实验结果显示：Bel-7402 细胞中 LDH-C4 过表达可提高乳酸产生含量，降低丙酮酸含量，提高细胞对葡萄糖的利用；Western blot 结果提示：过表达 LDH-C4 可上调 AKT/mTOR 信号通路中 AKT 蛋白及 mTOR 蛋白的表达。

结论 HCC 组织中 LDH-C4 呈现较高表达状态，与 HCC 患者的肿瘤大小、T 分期以及临床分期呈现明显正相关；LDH-C4 可作为 HCC 患者预后监测的一项重要参考指标。Bel-7402HCC 细胞中 LDH-C4 过表达可促进该细胞在体外的迁移和侵袭能力,促进 Bel-7402HCC 细胞的能量代谢水平，可能与 AKT/mTOR 信号通路的激活有关。

514. SARI 过表达对 CNE2 鼻咽癌细胞生物学活性的影响及其机制研究

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目的 构建 SARI 基因过表达真核表达载体并完成鉴定。研究 SARI 基因过表达对 CNE2 鼻咽癌细胞的生物学特性的影响并初步探讨相关分子机制。

方法 钓取并克隆 SARI 基因的全长 cDNA 序列，纯化后用 Bgl II 和 Xba I 进行双酶切消化，经 T4 DNA 连接酶作用，连接至 pDsRed2-C-RFP 真核表达载体，连接产物经转化、挑取克隆、扩增培养后，提取小量质粒，进行 DNA 测序鉴定，并用 Bgl II 和 Xba I 内切酶消化酶消化连接产物，琼脂糖凝胶电泳鉴定。重组质粒转染 SARI 阴性表达的 CNE2 细胞，荧光显微镜观察 SARI-RFP 融合蛋白的表达。Western blot 检测转染后 SARI-RFP 融合蛋白的表达。pDsRed2-SARI-RFP 真核表达载体转染至 CNE2 细胞，通过 CCK-8 比色绘制生长曲线、Transwell 小室侵袭实验、划痕修复实验、Caspase-3 活性检测、DNA 片段电泳检测等实验，探讨 SARI 过表达对 CNE2 鼻咽癌细胞生长增殖、凋亡等生物学特性的影响。Western blot 检测内源性线粒体凋亡途径相关蛋白的表达变化，探讨 SARI 过表达对 CNE2 细胞增殖、凋亡影响的分子机制。

结果 DNA 测序结果表明，SARI 全长 cDNA 序列已正确连接至 pDsRed2-C-RFP 载体。双酶切鉴定结果显示，pDsRed2-SARI-RFP 真核表达载体的构建成功。重组质粒转染至 CNE2 细胞后

可表达 SARI-RFP 融合蛋白。CCK-8 比色、Transwell 小室侵袭、划痕修复实验结果显示 SARI 过表达组细胞生长增殖、侵袭迁移能力显著低于空载体对照组和空白对照组（P＜0.05）；Caspase-3 活性及 DNA 梯状电泳结果显示，SARI 过表达诱导 CNE2 细胞产生凋亡，明显高于空载体对照组和空白对照组（P＜0.05）。Western blot 检测显示 SARI 过表达组 CNE2 细胞较空载体对照组和空白对照组 Bcl-2 表达下调，Bax、Cytochrome C 表达上调，同时伴有凋亡途径相关蛋白 Caspase-3 和 Caspase-9 剪接激活以及 PARP 的表达上调。

结论 成功构建 pDsRed2-SARI-RFP 真核表达载体； SARI 过表达可明显抑制鼻咽癌 CNE2 细胞增殖和侵袭迁移能力，诱导细胞凋亡； SARI 可能通过激活线粒体内源性凋亡途径诱导 CNE2 鼻咽癌细胞凋亡，发挥抑癌作用。

515. 肿瘤睾丸相关抗原 LDH-C4 在鼻咽癌中的表达及其功能研究

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目的 研究乳酸脱氢酶 C4（LDH-C4）蛋白在鼻咽癌癌组织中的表达情况以及在临床诊疗过程中的价值。明确 LDHC 基因过表达在 CNE2 鼻咽癌细胞的生物学作用，并初步探讨相关分子机制。

方法 通过免疫组化染色方法检测高通量鼻咽癌组织芯片中 LDH-C4 蛋白的表达量，根据染色的结果进行评分，分析鼻咽癌患者的临床和病理分期、转移、复发及预后等临床病理特征和 LDH-C4 蛋白表达的高低的相关性。通过慢病毒载体将外源性 LDHC 基因导入 CNE2 鼻咽癌细胞，并采用稀释法结合绿荧光表达情况筛选出单克隆化且 LDH-C4 表达阳性的细胞系。通过 CCK-8 比色、平板克隆形成、划痕修复实验、Transwell 小室等实验，研究 LDH-C4 表达上调后，CNE2 鼻咽癌细胞在体外增殖能力、迁移和侵袭能力的改变；通过 Western blot 检测 AKT/mTOR 信号转导通路相关蛋白的表达改变。

结果 129 例高通量鼻咽癌组织标本结果显示：LDH-C4 主要表达于鼻咽癌细胞的细胞质中，阳性率为 88.4%（114/129）；Spearman 相关性分析结果表明，鼻咽癌的临床分期、颈部淋巴结转移均与 LDH-C4 的表达水平呈正相关（P＜0.05）；Kaplan-Meier 生存分析表明，LDH-C4 低水平患者预后明显优于高水平患者（P＜0.05）。CCK-8 比色实验、克隆形成、划痕实验、基质胶 Transwell 小室等一系列实验，证明 LDH-C4 过表达可增强 CNE2 鼻咽癌细胞的生长增殖、克隆形成以及侵袭和迁移能力；Western blot 结果证实，LDH-C4 在 CNE2 细胞中过表达可上调 AKT、mTOR 等蛋白的表达。

结论 LDH-C4 蛋白在鼻咽癌癌组织中的表达量明显增高，并与患者的临床分期、颈部淋巴结转移呈现正相关关系；LDH-C4 可作为鼻咽癌预后监测的一项重要指标，其高表达提示患者临床预后不良。上调 LDH-C4 可明显增强 CNE2 细胞体外增殖、侵袭及迁移能力，可能通过激活 AKT/mTOR 信号通路起作用。

516. ARA55 基因在 CNE2 鼻咽癌细胞中的功能研究

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目的 研究 ARA55 过表达对 CNE2 鼻咽癌细胞生物学特性的影响，明确 ARA55 在 TGFβ1 介导的 CNE2 细胞上皮间质转化及侵袭、迁移中的作用。

方法 构建 pCMV-ARA55-EGFP 真核表达载体，经 ZLip2000 转染至 CNE2 鼻咽癌细胞，荧光显微镜和免疫印迹检测 ARA55-EGFP 融合蛋白的表达；通过 CCK-8 比色、划痕修复实验、Transwell 小室、Annexin V-PE/7-AAD 双荧光染色、DNA 梯状电泳等实验，探讨 ARA55 过表达对 CNE2 鼻咽癌细胞生物学特性的影响。一定浓度的 TGFβ1 诱导 CNE2 细胞株中 ARA55 的表达，免疫印迹检测 ARA55 蛋白及 EMT 相关标志物 N-cadherin、Claudin-1 等的表达变化；采用 ARA55 的 siRNA 质粒，经 X-treme GENE siRNA 转染至 CNE2 细胞株；通过 CCK-8 比色、划痕修复、Transwell 侵袭迁移等实验，研究 TGFβ1 介导的 ARA55 表达上调及沉默以 ARA55 表达对 CNE2 鼻咽癌细胞 EMT 及侵袭迁移的影响。

结果 DNA 测序及双酶切分析显示 pCMV-ARA55-EGFP 重组载体构建成功。pCMV-ARA55-EGFP 组细胞生长增殖、侵袭迁移能力明显低于 pCMV-C-EGFP 空载体组和/或空白对照组（P＜0.05 或 0.01）；Annexin V-PE/7-AAD 双荧光染色及 DNA 梯状电泳结果可见，pCMV-ARA55-EGFP 组细胞产生凋亡，且凋亡率明显高于 pCMV-C-EGFP 空载体组（P＜0.05）；免疫印迹显示 pCMV-ARA55-EGFP 组细胞 Bcl-2 表达下调，Cytochrome C 表达上调，同时伴有 Caspase-9 和 Caspase-3 的激活。TGFβ1 诱导后，免疫印迹显示 ARA55 在 CNE2 细胞中的表达上调；ARA55 诱导组细胞发生间质样改变，N-cadherin 的表达上升，Claudin-1 表达下降，同时细胞的生长增殖及侵袭迁移能力明显高于对照组（P＜0.05 或 0.01）；诱导表达的 ARA55 通过 siRNA 下调后，siRNA-ARA55 组细胞生长增殖及侵袭迁移能力下降（P＜0.05 或 0.01）。

结论 成功构建 pCMV-ARA55-EGFP 重组载体； ARA55 过表达可抑制 CNE2 鼻咽癌细胞生长增殖，诱导凋亡；3. ARA55 参与了 TGFβ1 介导的 CNE2 细胞 EMT 及侵袭迁移过程。

517. 乳酸脱氢酶 C4 在骨肉瘤中的表达与生物学功能研究

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目的 通过分析乳酸脱氢酶 C4（LDH-C4）在骨肉瘤（OS）组织中的表达情况，探讨其表达水平与骨肉瘤患者临床病理资料之间的相关性，明确 LDH-C4 表达上调后对骨肉瘤细胞 MG63 生物学行为能力的影响及相关分子机制。

方法 采用免疫组织化学染色方法对高通量骨肉瘤组织芯片进行检测，分析骨肉瘤组织中 LDH-C4 蛋白的表达水平与骨肉瘤患者临床病理特征的相关性。构建 LDHC 慢病毒过表达载体并感染骨肉瘤细胞 MG63，采用不同感染复数（MOI）和嘌呤霉素浓度筛选稳定感染的 MG63 细胞系。采用 RT-PCR 方法检测各组骨肉瘤细胞蛋白和 LDHC mRNA 表达情况。通过 CCK-8 实验、平板克隆形成实验、划痕修复实验以及 Transwell 细胞迁移、侵袭实验，检测上调 LDH-C4 后对骨肉瘤细胞 MG63 增殖和迁移侵袭等能力的影响。通过比色法检测乳酸和丙酮酸表达水平,葡萄糖氧化酶法检测葡萄糖消耗量。通过 Western blot，分析 LDH-C4 过表达对 AKT/mTOR 信号转导通路相关蛋白表达的影响。

结果 LDH-C4 蛋白主要表达于骨肉瘤细胞的细胞质中，软骨肉瘤表达在细胞核中，低表达/阴性表达占 54.29%（38/70），相关性分析结果显示，在骨肉瘤患者中临床分期和肿块直径与 LDH-C4 的表达水平呈负相关关系（$P<0.05$）。过表达 LDH-C4 在 CCK-8 实验、平板克隆实验、细胞划痕实验和 Transwell 小室迁移侵袭实验显示感染组 MG63 细胞的增殖能力、克隆能力、迁移能力和侵袭能力可被明显抑制。3.能量代谢实验结果显示感染组骨肉瘤细胞 MG63 葡萄糖摄取率降低，乳酸生成减少，丙酮酸生成增多。Western blot 实验发现过表达 LDH-C4 后，下调了感染组 PI3K、AKT、mTOR 蛋白表达，HIF-1a 蛋白无明显变化。

结论 在骨肉瘤组织中 LDH-C4 为中低表达状态，并与骨肉瘤患者临床分期及瘤体直径相关。上调 LDH-C4 可明显降低 MG63 骨肉瘤细胞体外的生长增殖、克隆形成以及侵袭和迁移能力。LDHC 过表达抑制细胞正常氧化耗能，通过抑制糖酵解和负向调控 PI3K/AKT/mTOR 信号通路发挥其生物学功能。

518. CDKN2-AS 与 RUNX1 在 MDS 高危患者中共表达分析

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目的 骨髓增生异常综合征(Myelodysplastic Syndromes, MDS) 是造血干细胞克隆性疾病，以骨髓一至多系无效造血为基本特征，具有发展为急性髓系白血病的倾向。长链非编码 RNA(long non-coding RNA)是一类长度大于 200 个核苷酸，来源于蛋白质编码基因的损坏、重构、合并，或者邻近 snRNA 的整合，因缺少有意义的开放阅读框而不具有编码蛋白质功能的一类非编码 RNA 分子。大量研究显示，lncRNA 的异常表达对血液肿瘤的形成和演进有重要的作用。因此，在 MDS 中进行 lncRNA 表达谱分析，探讨其作用靶点，将为 MDS 的治疗提供新的思

路。我们拟筛选出差异表达的 lncRNA 目标分子，并发现其作用靶标，以及在 MDS 中的表达情况。

方法 将 3 例 WPSS 分层为高危的 MDS 患者和 3 例健康供者骨髓样本用于 lncRNA 芯片检测，筛选出显著差异的 lncRNA 分子，结合课题组现有研究，选择显著差异的 hsa_lncRNA_0060063 即 CDKN2-AS(ANRIL)作为分子靶点；联合 NCBI 及 MEM 数据库行生物信息学分析，预测其潜在的相互作用分子 RUNX1，同时收集 20 例 MDS 高危患者和 20 例健康供者的外周血，Sybr-green qRT-PCR 法行 ANRIL 及 RUNX1 表达验证和共表达分析。

结果 通过基因芯片筛查出高危 MDS 中差异表达的 lncRNA 有 150 条，其中高表达 119 条，低表达 31 条，其中 CDKN2-AS(ANRIL)呈高表达，是健康供者表达的 3.27 倍（log Fold of Change，logFC）。生物信息学分析表明，RUNX1 分子可能是其潜在的作用靶点；ANRIL 在 20 例高危 MDS 患者中呈高表达，相对表达量为均值为 49.74±109.55，在健康供者中呈低表达，相对表达量为 0.56±2.35，两组表达差异显著，$p<0.01$;而 RUNX1 在高危 MDS 患者中呈低表达，相对表达量为 0.57±0.86，在健康供者中呈低表达，相对表达量为 2.56±3.93，RUNX1 在两组中表达差异显著，$p<0.05$。

结论 ANRIL 表达可能与 MDS 进展或预后相关，与 RUNX1 存在调控作用；ANRIL 可能是 MDS 发生发展及预后的潜在分子标志。但其在 MDS 中的确切调控机制仍需要进一步研究证实。

519. The emerging roles and mechanisms of SGK1 in human cancer

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Objective Serum and glucocorticoid-induced protein kinase 1 (SGK1) is a member of the ‘AGC’ subfamily of protein kinases, which shares structural and functional similarities with the AKT family of kinases and displays serine/threonine kinase activity.

Methods Aberrant expression of SGK1 makes profound cellular consequence, which is closely correlated with human cancer. SGK1is considered as a canonical factor affecting multiple gene expression and signal transduction, involving in the genesis and development of many human cancers.

Results Abnormal expression of tissue SGK1 was found, and may hopefully become an usefulindicatorfor cancer progression. In addition, SGK1 acts as a prognostic factor for cancer patient survival. This review systematically summarizes and discusses the role of SGK1as a diagnostic and prognostic biomarker of diverse types of cancers, focuses on its essential roles and fuctions in

tumorigenesis, cancer cell proliferation, apoptosis, invasion, metastasis, autophagy, therapeuticresistance, and finally summarizes the current understanding of the regulatory mechanisms ofSGK1 at the molecular level.

Conclusions Taken together, this evidence highlights the crucial role of SGK1 in the application of cancer diagnosis, prognosis, and treatment.

520. Exosomal miR-222-3p contributes to AIPC transformation and confers resistance to AR inhibition via activating mTOR signalling

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Objective Prostate cancer (PCa) remains the most common urologic malignancy and the second leading cause of male cancer-related deaths in developed countries. MicroRNAs (miRNAs) or exosomes have recently been shown to play vital regulatory or communication roles in cancer biology. However, the roles and mechanisms of exosomal (Exos) miRNAs inandrogen-independent prostate cancer (AIPC) remain unclear. In the present study, we aimed to investigate the detailed roles and mechanisms of tumor-generated exosomal miRNAs in the progression of AIPC.

Methods High-throughput sequencing was used to characterize the whole transcriptome profiles in both the androgen-independent PCa cell line. Exosomes were isolated using ultracentrifugation and characterized using transmission electron microscope(TEM).The effects of Exos-miR-222-3p on PCa cell viability, apoptosis, EMT, motility were evaluated by CCK8, flow cytometry, transwell and wound healing assays, immunofluorescence.The regulatory mechanisms of miR-222-3p were investigated by qRT-PCR, WB, dual-luciferase assays and immunofluorescence.

Results In our previously established stable ADT treatment-resistant LNCaP cell lines, cell growth wasstabilized and can grow well in androgen-depleted environment.Our CCK-8 and transwell migration/invasion results showed that LNCaP-AIcells exhibit stronger proliferation, metastasis and invasiveness activity than LNCaP cells. High-throughput RNA sequencing results found that miRNA-222-3p was mostly elevated in LNCaP-AI compared to LNCaP. In addition, exosomes secreted by AIPC cell line LNCaP-AI were successfully ingested by LNCaP, which dramatically promotedthe growth activity and enhanced the migration and invasion ability of LNCaP cells in androgen-free complete medium.Interestingly, we further found that miRNA-222-3p expression was significantly enhanced in LNCaP-AI exosomes than that of LNCaP exosomes. Moreover, overexpression of miRNA-222-3p can significantly promote the proliferation ability of LNCaP.These results strongly suggested thatExos-miR-222-3p plays a paramount role in facilitating AIPC transformation. What's more, the underlying mechanisms by whichExos-miR-222-3pcontributes to AIPC transformation were

investigated. Our results suggested that Exos-miR-222-3p mediated AIPC transformation was, at least in part, by activating mTOR signalling pathway via targeting MIDN. Exos-miR-222-3p confers resistance to androgen receptor (AR) inhibition.We found that eitherMDV3100 or AR shRNA mediated AR inhibition significantly decreased the proliferation activity of LNCaP, however, this anti-tumor effect was dramaticlly impaired aftertreatment of LNCaP-AI exosomes. Moreover, dual inhibitionof miR-222-3p and ARled to synergistic cytocidal effects both inLNCaP andLNCaP-AI. Exos-miR-222-3p may be a potential biomarker for castration-resistant prostate cancer (CRPC) diagnosis.Circulating exosomes from androgen dependent PCa (ADPC) and CRPC patients were isolated usingultracentrifugation, qPCR resultsindicated that miR-222-3p was more abundant in ADPC-exosomes compared to CRPC-exosomes, suggesting it could be a promising non-invasive biomarker for identifying ADPC and CRPC.

Conclusions In summary, our findingsshow that Exos-miR-222-3p plays a paramount role in promoting AIPC transformation and confers resistance to AR inhibition, which is mediated, at least in part, by activating mTOR signalling pathway via targeting MIDN,suggesting it could be a promising non-invasive biomarker for facilitating CRPC treatments.

521. NCAPH is negatively associated with Mcl-1 in non-small cell lung cancer

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Objective Lung cancer has been recognized as one of the main causes of cancer mortality. Non-SMC Condensin I Complex Subunit H (NCAPH), which has been identified as one of the regulatory subunits of condensin I complex essential for correct packaging and segregation of chromosomes in eukaryotes, is abnormally overexpressed in various cancer types. Mcl-1, one pro-survival member of Bcl2family, which is also frequently overexpressed in multiple cancers and correlates with worse clinical outcome. Except for the pervious findings, the correlation of the NCAPH and Mcl-1 proteins and the clinical and pathological features in non-small cell lung cancer (NSCLC) is still unknown.

Methods Immunohistochemistry (IHC) was performed to detect the expression and cellular location of NCAPH and Mcl-1, SPSS version 20.0 was used for statistical analysis.

Results In current research, we found that the positive percentage of NCAPH in the non-cancerous lung tissues was higher than that in NSCLC. On the contrary, the positive percentage of Mcl-1 in the non-cancerous lung tissues was obviously lower than that in NSCLC. Moreover, NCAPH high expression patients owned higher overall survival rate than low expression patients, whereas Mcl-1 high expression group correlated with lower survival rate. The pairwise association in 260 cases of NSCLC revealed that overexpression of NCAPH protein was negatively correlated with Mcl-1

expression and vice versa. The results of multivariate Cox proportional hazard regression analysis also indicated that the expression of NCAPH and Mcl-1 showed potential to exerts as distinct prognostic factors in NSCLC.

Conclusions Taken together, expression of NCAPH may correlate with Mcl-1 and acts as distinct molecular marks for poor prognosis prediction of NSCLC patients.

522. HDAC6-HSP90 途径通过调控蛋白折叠和降解参与肿瘤增殖与转移

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目的 为靶向 HSP90 -HDAC6 途径治疗肿瘤提供新的方向与思路。

方法 在这篇文章中，我们从 HDAC6 与 HSP90 间的交互调控入手，进一步解释肿瘤细胞如何调动活跃的蛋白折叠与降解机制促进其增殖和转移，并探讨 HDAC6 抑制剂与 HSP90 抑制剂在研究中应用时发现的利与弊。

结果 肿瘤细胞中蛋白质的折叠与降解是维持其生存的关键机制，而其中涉及的蛋白作用往往与目前普遍存在的肿瘤耐药相关。随着科学研究的深入，越来越多参与蛋白质折叠与降解的辅助蛋白进入人们的视野其中作为焦点的伴侣热休克蛋白 90（HSP90）既能够同其他伴侣蛋白（HSP40、HSP70、P23、CHOP 等）促进蛋白折叠发挥稳定蛋白构象的作用，还能辅助蛋白酶体降解客户蛋白。而目前研究认为，HSP90 的功能在一定程度上受乙酰化等翻译后修饰的调控。

结论 更有趣的是，组蛋白去乙酰化酶 6（HDAC6）一方面能够通过抑制 HSP90 的过度乙酰化，维持 HSP90 的伴侣功能从而保证伴侣 HSP90 的客户蛋白能够稳定折叠、成熟释放；另一方面还可以作为 HSP90 的客户蛋白及自噬受体，通过其募集泛素化蛋白并去乙酰化修饰自噬相关蛋白，从而在蛋白降解以及细胞自噬过程中发挥重要作用。因此，HDAC6 抑制剂与 HSP90 的抑制剂也被广泛应用于肿瘤治疗方面的相关研究中，并且研究表明 HDAC6 抑制剂与 HSP90 抑制剂的联合应用在抑制肿瘤增殖转移方面效果显著。

523. Autophagy Regulates the Stemness of Pancreatic Cancer Cells by Affecting the Nuclear Translocation of EHF

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Objective: Cancer stem cells are associated with recurrence and metastasis, but the mechanism underlying the stemness of pancreatic ductal adenocarcinoma (PDAC) cells remains unclear. Our previous study found the tumor suppressor role of EHF, and the upregulated level of autophagy also relates to malignant characteristics of PDAC. The relationships between autophagy/EHF and the stemness of PDAC cells need further exploration.

Methods: Eight pairs of fresh PDAC tissues and noncancerous tissues, and 96 formalin-fixed, paraffin-embedded (FFPE) sections of PDAC specimens were collected from patients who underwent a radical surgery without preoperative radiation or chemotherapy during 2013-2015 at the Tianjin Medical University Cancer Institute and Hospital. Normal FFPE pancreatic tissues were obtained from patients who underwent distal pancreatectomy for benign diseases. Another cohort of 185 pancreatic adenocarcinoma patients with mRNA expression profiling were included from The Cancer Genome Atlas (TCGA) database. Four human PDAC cell lines (PANC-1, MIA-PaCa-2, BXPC-3 and SW1990) were selected for in vitro studies. Luciferase assays, chromatin immunoprecipitation assays, IHC, Immunofluorescence, co-IP and GST-pull down were performed to explore the relationship between P62 (an indicator of autophagy) and EHF. And the effects of the Autophagy-P62-EHF axis on PDAC cells were determined by subsequent functional experiments. Xenograft mouse models were then constructed with Pan02 cells and PDX cells.

Results: In this study, we found that the expression of EHF and P62 were dramatically decreased in PDAC tissues in both our cohort and TCGA cohort. The downregulation of EHF/P62 were correlated with a decrease in survival in PDAC patients. As a transcription factor, EHF could up-regulate P62 and could inhibit the stemness of PDAC cells by restraining the activity of Wnt/β-catenin pathway. In return, P62 could promote the nuclear translocation of EHF by binding directly to EHF protein. The upregulated level of autophagy also affected the nuclear translocation of EHF by reducing the protein level of P62, followed by the downregulation of EHF and the inhibition of the stemness of PDAC cells. Moreover, autophagy inhibition with ULK-101 drastically increased EHF protein levels in nucleus and decreased the volume of tumor growth in a PDAC xenograft mouse model.

Conclusion: These in vitro and in vivo results showed that the Autophagy-P62-EHF axis was involved in the regulation of stemness of PDAC cells, which may clue to the treatment by targeting autophagy in cancer

524. 基于 CRISPR/Cas9 系统靶向敲减 miR-21 对鼻咽癌放疗抵抗的影响

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目的 本研究拟通过 CRISPR/Cas9 系统靶向敲减 CNE2 细胞中的 miR-21，评估对 CNE2 细胞生物学特性的影响并探讨分子机制。

方法 通过 CRISPR/Cas9 系统对放疗抗拒的 CNE2-R 和正常 CNE2 鼻咽癌细胞株进行内源性 miR-21 基因敲除，通过 T7EN1 酶切和 Real-time PCR 验证敲除效果。通过设置体外相关实验，探讨 miR-21 基因敲除对 CNE2-R 和正常 CNE2 细胞增殖状态、克隆形成、凋亡状态等生物学特性的影响，进行放疗敏感性及侵袭能力的比较。通过生物信息学分析预测 miR-21 在鼻咽癌中参与调控的信号通路，免疫印迹进一步验证。

结果 CRISPR/Cas9 载体系统可有效敲减对 CNE2-R 和 CNE2 细胞系中内源性 miR-21 基因，编辑效率接近 50%。miR-21 靶向敲减可明显抑制 CNE2-R 和 CNE2 细胞的生长增殖，克隆形成及侵袭转移等能力，并诱导细胞凋亡。生物信息学分析共找到 28 个 KEGG，并筛选出共同交集的通路。免疫印迹显示，miR-21 敲减组 PI3K/AKT/mTOR 通路相关蛋白及其磷酸化水平发生明显改变。Meta 分析结果显示，miR-21 联合其他 miRNA 分子表达谱在诊断鼻咽癌中的灵敏度、特异度、及曲线下面积（AUC）分别为 0.78、0.79 和 0.85。本项目研究结果证实，内源性 miR-21 与 CNE2-R 细胞的放疗抗拒有关，靶向敲减 miR-21 可通过阻断 PI3K/AKT/mTOR 信号通路来抑制 CNE2-R 和 CNE2 细胞的生长增殖，诱导细胞凋亡，从而增加放疗的敏感性。

结论 靶向敲减 miR-21 可通过抑制 PI3K/AKT/mTOR 信号通路抑制 CNE2-R 和 CNE2 细胞的生长增殖，诱导细胞凋亡，增加放疗的敏感性。

525. TP53 磷酸化修饰一个新的蛋白激酶 SASH1 促进乳腺癌增殖侵袭转移的分子机制研究

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目的 本研究探讨 SASH1 作为一个新的抑癌基因，在调节乳腺癌增殖、侵袭、转移中所涉及的作用机制。

方法 免疫组织化学法检测人乳腺癌组织中 SASH1、含 IQ 模序的 GTP 酶活化蛋白 1（IQGAP1）、E-钙黏蛋白（E-cadherin）以及 ERK1/2 总的蛋白和磷酸化蛋白表达，并分析其与乳腺癌发生发展的关系。通过分子克隆技术构建中 SASH1 质粒以及不同突变位点的质粒，

通过质谱技术寻找 SASH1 可能存在的相互作用的蛋白。免疫沉淀 IP-WB 检测与 SASH1 发生相互作用的蛋白。通过对乳腺癌细胞中能与 SASH1 发生蛋白质相互作用的 MAP4K4 单独（或同时）进行 RNA 干扰，检测 SASH1 对 MAP4K4-ERK1/2 信号通路的调节。

结果 人乳腺癌中 SASH1 与 IQGAP1 的表达与乳腺癌的肿瘤直径和肿瘤分级相关。在稳定转染野生型和突变型 SASH1 质粒的 A375 细胞中，在 250KD 处存在 SASH1 NEDD8 条带，0.8μM MLN4924 能抑制 SASH1 的 Neddylation 修饰。质谱显示 SASH1 存在 5 个磷酸化位点，SASH1 可能与 CUL4A、Cul1 E3 连接酶以及 ERK1/2 上游激酶 MAP4K4 和 MAP2K2 发生相互作用，Western blot 证实 SASH1 与 14-3-3s 和 TP53 之间存在自动负反馈调节， SASH1 可抑制 TP53 的表达。免疫沉淀证实 SASH1 与 IQGAP1 和 MAP4K4 之间存在蛋白相互作用。在 3 株不同的乳腺癌细胞中对 SASH1 和/或 MAP4K4 进行 RNAi 干扰，发现 SASH1 的表达下调后， ERK1/2 的磷酸化水平上调，而单独干扰 MAP4K4 则 ERK1/2 的磷酸化水平下调。

结论 SASH1 作为一个新的抑癌基因， SASH1 蛋白 表达与 IQGAP1 蛋白表达呈正相关，并且与肿瘤大小和肿瘤分级显著相关。P53 能够上调内源性 SASH1 的表达，TP53 与 SASH1 之间存在一个自动调节反馈回路。SASH1 的表达下调可通过 MAP4K4-ERK 信号通路来促进乳腺癌的增殖；可通过 SASH1-IQGAP1-E-cadherin 信号轴调控乳腺癌细胞粘附、侵袭和转移。

526. MicroRNA-26b-3p suppresses esophageal squamous cell carcinoma progression by targeting STAT3 and downregulated by promoter methylation

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Objective MicroRNAs have been identified to play vital role in the onset and progression of esophageal squamous carcinoma (ESCC). To explore the role and possible regulatory mechanism of miR-26b-3p in ESCC.

Methods The expression levels of miR-26b-3p and STAT3 in gastric cancer tissues and cell lines were detected by quantitative real-time PCR (qRT-PCR). Western blot and luciferase reporter assay were used to detect the effect of miR-26b-3p on STAT3 expression. Then, the proliferation, metastasis and invasion of ESCC cell lines transfected with miR-26b-3p mimics, inhibitor, and (or) pcDNA3.1-STAT3 were analyzed, respectively, by cell proliferation assay, wound healing assay and cell invasion assay. Meanwhile, the methylation status of the promoter CpG islands of miR-26b-3p in ESCC cell lines and tumor tissues was detected by methylation-specific PCR (MSP) and bisulfite sequencing PCR (BSP).

Results MiR-26b-3p expression was aberrantly downregulated in ESCC cell lines and tumor tissues.

In TE1 and KYSE150 cells, miR-26b-3p upregulation had tumor-suppressive effect on ESCC proliferation, migration and invasion. STAT3 is confirmed to be the downstream target of miR-26b-3p in ESCC. Overexpression of STAT3 inversely regulated the inhibition of miR-26b-3p on ESCC proliferation, migration and invasion. After treated with different concentration 5-Aza-2' deoxycytidine, the expression of miR-2b-3p was upregulated, while STAT3 protien was downregulated.

Conclusions MiR-26b-3p paly a tumor suppressive role in ESCC and is downregulated partly due to promoter hypermethylation. Furthermore, STAT3 is one of the putative target genes of miR-26b-3p.

527. IL-33 对人肝癌 Hep3B 与 Huh-7 细胞增殖、迁移与侵袭的影响

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目的 探讨白介素 33（IL-33）对人肝癌 Hep3B 和 Huh-7 细胞的增殖、迁移与侵袭能力的影响。

方法 设 IL-33 实验组及对照组，实验组选择 20、40 和 60 ng/L 不同浓度的 IL-33 分别处理人肝癌 Hep3B 和 Huh-7 细胞，对照组则加入等体积的生理盐水，采用 MTT 实验测定细胞的增殖能力；采用细胞划痕实验及 Transwell 实验测定 IL-33 对人肝癌 Hep3B、Huh-7 细胞体外迁移及侵袭的影响.

结果 实验组人肝癌 Hep3B 和 Huh-7 细胞的 OD 值明显高于对照组，且均具有显著的统计学差异（$P<0.001$），各组不同浓度 IL-33 之间的 OD 值中，20、40 ng/L 浓度组无统计学差异（$P>0.05$），其余组均随浓度增大而升高（$P<0.05$）；实验组人肝癌 Hep3B 和 Huh-7 细胞划痕愈合速度慢于对照组，且均具有显著的统计学差异（$P<0.01$）；侵袭接种 24 h 后实验组人肝癌 Hep3B 和 Huh-7 细胞穿透到底面的细胞少于对照组，且均具有显著的统计学差异（$P<0.001$）。

结论 IL-33 可能具有促进人肝癌 Hep3B 和 Huh-7 细胞增殖，抑制其迁移、侵袭的作用。

528. A multi-omics study: prognostic model construction with TCGA HNSCC data

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Objective Growing evidence suggests that any single omics analysis cannot fully clarify the complexity of tumors. Compared with single omics analysis, multiple omics analysis supplies an insight from a multiple perspective, a more comprehensive explanation of the molecular mechanism of tumor occurrence and development. The purpose of this study is to screen HNSCC prognostic factors based on multi-omics data in The Cancer Genome Atlas (TCGA).

Methods This study collected gene expression, methylation, CNV and mutation data from TCGA. By principal component analysis and cluster analysis, the cell processes that affect the prognosis of head and neck squamous cell carcinoma were screened. Through resampling cross-validation analysis, hub gene modules in the most important cell process were identified, and the biological markers of this cell process were screened and verified. Function annotation of the cell process through the Reactome analysis.

Results The pathway analysis based on multi-omics data figured out that five pathways, affected by gene expression and methylation, were significantly correlated with prognosis in HNSCC. The main functions of these pathways are relevant to the immune system. Combined with the results of gene module analysis correlated with prognosis, we found that gene module 1 in the IL-2 family signaling pathway correlated with the immune system. Through PCA, we found that gene expression of IL2RG and methylation of LCK are biomarkers of the gene module. High gene expression of IL2RG and low methylation of LCK are protective factors for the prognosis of HNSCC patients.

Conclusions As far as we know, this is the first study based on multi-omics data in HNSCC patients. Our results indicated that gene expression of IL2RG and methylation of LCK level, jointly participating in IL-2 family signaling affect the prognosis of HNSCC. This study pointed out that the prognosis of HNSCC patients was related to the immune components in the tumor microenvironment.

529. MiR-17 Cluster Promoted M2-polarized Tumor Associated Macrophages Related Cell Aggressiveness via Inducing the Imbalance of TGF-β1 /BMP7 Pathways in Hepatocellular Carcinoma

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Objective TGF-β1 and BMP7 are important members of TGF-β superfamily, which have similar downstream transduction pathways and interfere mutually. The antagonistic effects between both pathways has been widely studied in kidney disease and bone formation, and less studied in HCC. This study is intended to elucidate the crosstalk between TGF-β1/ BMP-7 pathways in the progression and invasion of HCC.

Methods The immunohistochemistry staining method was used to exam the expressions of TGFBR2, TGFBR1, BMP7, BMPR2 and ACVR1 proteins in 64 HCC samples. Genetically modified HCC cell lines HepG2 and Hep3B were applied to investigate the related molecule mechanisms of antagonistic effects of TGF-β1 and BMP7 pathway in HCC.

Results In 64 HCC samples, the expression of TGFBR2 was significantly negatively correlated with ACVR1 expression. TGFBR2-ACVR1+ HCC patients showed higher portal vein invasion and shorter survival time than non-TGFBR2-ACVR1+ HCC patients, which implied that down-regulated TGFBR2 and up-regulated ACVR1 dramatically promoted HCC invasion and metastasis in vivo. We separately knocked down TGFBR2 and overexpressed ACVR1 in HCC cell lines HepG2 and Hep3B cells, and found that down-regulated TGFBR2 and up-regulated ACVR1 dramatically promoted HCC invasion via enhancing EMT and stemness in vitro. The global miRNA profiling analysis indicated that miR17 cluster (including miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a) are the key triggers to cause the imbalance of TGF-β1/BMP7 pathways. The overexpression of MIR17HG inhibited the TGF-β pathway, but activated the BMP7 pathway simultaneously, which promoted HCC invasion and progression in vitro and vivo. The multicolor immunofluorescence staining assay indicated that the recruitment of M2-polarized tumor associated macrophages (M2-TAMs) in HCC tissues positively correlated with the imbalance of the TGF-β1/ BMP-7 pathways and poor clinical outcome. And co-culture of HCC cells with TAMs dramatically enhanced the levels of miR17 cluster and promoted HCC EMT.

Conclusions In summary, the miR-17 cluster promoted M2-TAMs related cell aggressiveness via inducing the imbalance of TGF-β1/BMP7 pathways in HCC.

530. Relationship between increased levels of BRD4, CDK7 associated with HIF-1α and the prognosis of hepatocellular carcinoma

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Objective The hypoxic microenvironment, widely existed in malignant solid tumors, was a major stimulus in the pathogenesis of hepatocellular carcinoma（HCC）. HIF-1α was regarded as a marker for hypoxia conditions in HCC. Hypoxia induced a range of cancer-related events, including cell proliferation, apoptosis, metabolism, genomic instability, immune responses and overexpression of oncogenes, etc. The super-enhancer(SE) region also contributes to overexpression of oncogenes by transcriptional activation. In this study, we attempt to explore whether the two modes of regulation, hypoxia and SE, work together in HCC.

Methods Therefore, we analyzed the expression levels of SE-related complexes and HIF-1α in tissue arrays from 110 paraffin-embedded HCC samples, and their effects on the prognosis of HCC. 110 pairs of HCC samples in tissue arrays were examined by immunohistochemistry for the molecule of BRD4, CDK7 and HIF-1α. The relationship and clinicopathological significance of the 3 markers with HCC were assessed by Paired t-test, Chi-square test, One-way anova test, Kaplan-Meier analysis with log-rank test.

Results In HCC cells, HIF-1α staining was located both in the cytoplasm and nucleus, while BRD4 and CDK7 staining was only located in the nucleus. The expression levels of BRD4 and CDK7 in HCC tissues was higher than that in adjacent tissues. The expression levels of BRD4 and CDK7 was associated with the pathologic grade and the lymph node metastasis in HCC. In addition, CDK7 was also associated with overall survival in HCC. HIF-1α was up-regulated in HCC tissues than in corresponding adjacent tissues. HIF-1α was associated with the prognosis, HCC grade and lymph node metastasis in HCC patients. High expression of HIF-1α was accompanied with high expression of BRD4

Conclusions Subsequent joint analysis showed upregulated HIF-1α was associated with elevated levels of BRD4 not CDK7 in HCC. BRD4 and CDK7 are considered as candidate for diagnostic and prognostic markers in HCC patients. BRD4 was positively correlated with CDK7 expression, which revealed a new strategy for the combination of small-molecule inhibitors in the treatment of HCC.

531. Screening and verification of autophagy-related genes and lncRNAs as biomarkers in prognostic effects of colorectal cancer

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Objective Cellular autophagy plays an important role in the occurrence and development of colorectal cancer (CRC). Whether autophagy-related genes can be used as ideal markers in CRC is still controversial. The purpose of this study is to identify novel treatment and prognosis markers of CRC.

Methods We downloaded the colorectal cancer gene transcription data from the GEO database, screened for differentially expressed autophagy genes (DEAGs), constructed a prognostic model, and analyzed its relationship with overall survival and clinical factors by cox analysis and nomogram model. Then, we calculated the immune cells infiltration score using CIRBERSORT and immune score of tumor microenvironment on all samples, and also compared them in two risk model groups respectively. TCGA data validated the effect of the model. Oncomine database and immunohistochemistry from Human Protein Atls verified the expression of differential genes. In addition, we obtained differentially autophagy-related lncRNAs through WGCNA co-expression analysis and a risk prognosis model was constructed to verify whether the trend for predicting prognosis was consistent.

Results We obtained a total of 151 DEAGs in the GEO training set and TCGA verification set collaboratively. Gene enrichment analysis confirmed that these genes were closely related to autophagy. For the training set, we divided the CRC samples into two clusters based on unsupervised clusters. In cluster1 low-grade malignant clinical factors such as low T stage, wild-type tp53 gene status and braf gene status were more significant, and in cluster2 they were opposite results. Then we constructed a risk prognostic model through lasso regression to obtain 15 prognostic DEAGs (DAPK1, CAPN2, RAF1, MYC, BIRC5, PRKAB1, BCL2, HDAC1, CASP3, CASP1, BAG3, ULK3, MTMR14, DAPK2 and BID) from the training set. The low-risk group survived longer than the high-risk group. In the TCGA verification set, the survival comparison results of model were consistent. Age, gender, pathological stage, and TNM stage were related to the prognostic risk of colon cancer in two sets, and braf status, RFS event and tumor location were significant risk factors of CRC in the training set. The immune score of the low-risk group was higher than that of the high-risk group. The content of CD8 + T cells, active NK cells, macrophages M0, macrophages M1, and active dendritic cells was more in the high-risk group. The content of plasma cells, resting memory CD4 + T cells, resting NK cells, resting mast cells and neutrophil cells was higher in the low-risk group. Oncomine database and immunohistochemistry verified that the expression levels of key autophagy-related genes were

consistent with the results that we found. In addition, we obtained 6 lncRNAs (AC022893.2, AC111149.2, AL359313.1, LINC00616, NAALADL2-AS2 and TBX5-AS1) co-expressed with differentially expressed autophagy genes from the training set, and found that the survival time of patients in the low-risk group was longer in the risk prognosis model. The model was verified in the verification set and the same to the above results.

Conclusions These results indicate that autophagy-related genes and lncRNAs can be used as therapeutic and prognostic markers for colorectal cancer.

532. Chemical compound cinobufotalin potently induces FOXO1-stimulated cisplatin sensitivity by antagonizing its binding partner MYH9

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Objective In this study, we present novel molecular mechanisms by which FOXO1 functions as a tumor suppressor to prevent the pathogenesis of nasopharyngeal carcinoma (NPC).

Methods The FOXO1 expression was examined by real-time PCR and in clinical sample. MTT, Sphere formation, flow cytometry analysis， Transwell assays, and MTT cytotoxicity were respectively performed for cell stemness, metastasis, and chemoresistance; Western blotting was performed to analyze the pathways by FOXO1 and MYH9. The miRNA microarray and luciferase reporter assays were respectively used for the FOXO1-mediated miRNAs and target genes of FOXO1. The ChIP, EMSA assays, and coimmunoprecipitation combined with mass spectrometry were respectively designed to analyze the DNA–protein complex and FOXO1/MYH9/GSK3β complex.

Results Firstly, we observed that FOXO1 not only controlled tumor stemness and metastasis but also sensitized NPC cells to Cisplatin (DDP), in vitro and in vivo. Mechanistic studies demonstrated that FOXO1 induced miR-200b through GSK3β/β-catenin/TCF4-stimulated ZEB1 reducing tumor stemness and the epithelial-mesenchymal transition (EMT) signal. Furthermore, we observed that FOXO1 interacted with MYH9 and suppressed MYH9 expression by modulating the PI3K/AKT/c-Myc/P53/miR-133a-3p signal. Decreased MYH9 not only reduced interactions with GSK3β, but attenuated TRAF6 expression, which thus decreased the ubiquitination degradation of GSK3β protein.

Increased GSK3β expression stimulated β-catenin/TCF4/ZEB1/miR-200b and its downstream tumor stemness and EMT signals. Subsequently, we observed that chemically synthesized cinobufotalin(CB) powerfully increased FOXO1-induced DDP chemosensitivity by reducing MYH9 to modulate GSK3β/β-catenin and its downstream tumor stemness and EMT signal in NPC. In clinical samples, the combination of low FOXO1 expression and high MYH9 expression indicated the worst overall survival rates.

Conclusions Our studies demonstrated that CB potently induced FOXO1-stimulating DDP sensitivity by antagonizing its-interactive protein MYH9-stimulated tumor stemness in NPC.

533. CpG-ODN 或可作为胃癌治疗潜在药物

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目的 小分子寡聚核苷酸 CpG-ODN，可靶向 Toll 样受体-9(TLR-9)，可抑制肿瘤细胞生长，诱导肿瘤细胞凋亡。CpG-ODN 也能够诱导 CD4 阳性 T 细胞表面的 OX40 的表达，有效地刺激了 T 细胞的活性，增强抗肿瘤作用。CpG-ODN 可作为免疫佐剂单独刺激或与其他疗法结合，促进抗原提呈反应以及 T 细胞与 B 细胞的抗肿瘤免疫效应。本研究探讨 CpG-ODN 单独作用对胃癌细胞的直接抑制作用为后续单独或联合疗法提供研究依据。

方法 培养胃癌 SGC-7901 细胞，进行 CCK8 实验检测。观察 CpG-ODN 与阳性对照药 CpG-1826 及阴性对照药对胃癌 SGC-7901 细胞的体外增殖抑制效果并进行分析比较其体外直接抑制作用。

结果 CpG-ODN 可呈浓度依赖性和时间依赖性，显著抑制胃癌 SGC-7901 细胞的生长，并且体外细胞抑制效果比阳性对照药 CpG-1826 更显著。

结论 寡核苷酸片段 CpG-ODN，具有显著抑制肿瘤细胞生长的特性，其单独作用或作为免疫佐剂，或能发挥抗肿瘤免疫效应以抑制肿瘤的生长，亦有潜力与免疫检查点抑制剂联合使用，对抗肿瘤免疫逃逸，诱导肿瘤细胞凋亡，发挥治疗胃癌、肺癌等癌症的作用，CpG-ODN 可作为肿瘤免疫治疗的潜在治疗药物。

534. VEGF-VEGFR 通路在胆管细胞癌发生发展及治疗中的研究进展

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目的 胆管细胞癌（cholangiocarcinoma，CCA）是一种胆道上皮来源恶性肿瘤，其恶性程度高、侵袭性强，严重危害人类生命健康。尽管目前 CCA 的治疗方式多样，但是缺乏有效的治疗药物，多数患者预后不良，因此需要进一步阐明 CCA 的发生发展机制，探索新型药物改善 CCA 患者的预后。研究表明，血管内皮生长因子（vascular endothelial growth factor，VEGF）及其受体 VEGFR 调控的血管生成过程对 CCA 的发生发展至关重要。本文通过文献综述，总结 VEGF-VEGFR 信号通路在 CCA 中的作用以及抗血管生成药物在 CCA 中的应用，深化临床医生对 CCA 抗血管生成治疗的认识，指导临床用药。

方法 查阅近 10 年文献，收集并整理基础及临床数据，针对 VEGF-VEGFR 信号通路在 CCA 的临床病理特征及预后中的作用以及 CCA 抗血管生成治疗和耐药相关研究进展进行综述。

结果 以 VEGF-VEGFR 为代表的多种促血管生成因子，均可调节 CCA 的血管生成，促进 CCA 增殖、侵袭和迁移，参与 CCA 的发病与进展并影响 CCA 患者的预后。因此，以 VEGF-VEGFR 等信号通路为靶点的抗血管生成药物，包括贝伐珠单抗等单克隆抗体，以及索拉非尼、阿帕替尼等小分子抑制剂等，陆续进入临床，也逐渐成为 CCA 治疗的研究热点。结果显示，VEGF-VEGFR 信号通路对 CCA 临床分期、转移等临床病理特征高度相关，并且对患者预后产生影响。一些临床前研究初步探索了抗血管生成药物对 CCA 细胞增殖和凋亡的影响，阐述了其治疗作用或耐药机制，并取得了一定成果，但是具体的分子机制尚未深入研究。一些临床研究也初步证实了抗血管生成药物对 CCA 的有效性和安全性，多数单药治疗效果不佳，联合免疫检查点抑制剂将成为具有前景的联合治疗策略。

结论 VEGF-VEGFR 信号通路在 CCA 的发病与进展中占重要地位，而抗血管生成药物治疗 CCA 的临床数据不尽如人意，与免疫检查点药物联合可提高有效率，但需更多临床研究数据进一步证实。

535. Notch 信号通路介导新 m/z 6449 Da 生物肽在抗胃腺癌中的活性及其分子机制研究

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目的 胃腺癌在我国高发，缺乏生物活性强、毒副作用弱且靶点专一的多肽类抗肿瘤药物。组织中高频低表达的 6449Da 活性肽是胃腺癌血清特异性非炎症性生物标志物。本研究拟探索胃腺癌新 m/z 6449 Da 生物活性肽对胃腺癌细胞的生物学行为影响及其作用机制，为新型抗胃腺癌活性肽药物的临床转化及问世提供理论基础。

方法 使用生物信息学方法对 6449 Da 活性肽进行性能预测及分析，固相合成法合成该活性肽，同时从 C-端逐个敲除氨基酸以寻找其最短功能片段，通过体外细胞实验及荷瘤鼠体内实验方法检测该活性肽的最短功能片段及其对胃腺癌细胞增殖、凋亡、迁移、跨膜侵袭、细胞周期、细胞定位和瘤体组织生长的作用及其分子机制。

结果 6449 Da 活性肽 C 端前 20 个氨基酸为信号肽，活性位点主要集中在信号肽以外的 40 个氨基酸组成的 WSGC 肽；WSGC 肽对胃腺癌细胞的毒性作用要比对正常胃粘膜上皮细胞作用强，对胃腺癌细胞细胞毒性作用有相对特异性；IC50 和 IC80 浓度的 WSGC 肽能抑制胃腺癌细胞增殖，诱导细胞分裂 S 期的阻滞，提高肿瘤细胞凋亡比例，降低或抑制细胞迁移及跨膜侵袭；WSGC-FITC 主要分布于胃腺癌细胞膜表面，很少进入胞质或胞核；经过 IC50 及 IC80 剂量的 WSGC 肽干预胃腺癌细胞 48h 后，IC50 及 IC80 组胃腺癌细胞中 Bax 和 Caspase-3 的 mRNA 及蛋白表达水平均高于对照组，而 IC50、IC80 组胃腺癌细胞中 Bcl-2，Ki67, PCNA，NOTCH1，Jagged 1，MAML3，CSL 及 HES1 的 mRNA 及蛋白表达水平均明显低于对照组。通过梯度 WSGC 肽浓度干预胃腺癌荷瘤免疫缺陷小鼠模型，发现经过 40 nmol/g、80 nmol/g 剂量 WSGC 治疗后，胃腺癌瘤体重量及体积均低于对照组；随着 WSGC 肽用药剂量的增加，胃腺癌荷瘤小鼠模型瘤体组织中细胞凋亡率均呈递增趋势；与对照组相比，胃腺癌荷瘤小鼠模型瘤体组织中 Bax 和 Caspase-3 蛋白的表达随着 WSGC 肽剂量的增加而增高，而 Bcl-2，Ki67 及 PCNA 蛋白的表达随着 WSGC 肽剂量的增加而递减。

结论 Notch 信号通路及其下游调控网络介导定位于细胞膜表面的 6449 肽功能片段 WSGC 肽对胃腺癌细胞有相对特异性的促凋亡、抑制增殖作用，诱导细胞 S 期的阻滞，降低或抑制细胞迁移及跨膜侵袭，抑制瘤体组织生长，对催生一种新型抗胃腺癌多肽药物的问世及促进胃腺癌的防治工作提供理论基础。

536. Dimethylitaconate suppresses ulcerative colitis and colitis associated colorectal cancer by reducing the recruitment of macrophages

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Objective Chronic inflammation plays a key role in tumor initiation in colitis-associated colorectal cancer (CRC). Macrophages contribute to ulcerative colitis and colitis associated colorectal cancer development.

Methods Here, we found that immune response gene 1 (Irg1) was highly expressed in macrophages sorted from peritoneal lavage and lamina propria of colitis-associated CRC mice. Itaconate is a metabolite synthesized by the enzyme encoded by Irg1. We described the use of a membrane permeable itaconate derivative, dimethyl itaconate (DI), for the treatment of ulcerative colitis and colitis associated cancer in mouse models.

Results We found that DI decreased the high inflammatory state of ulcerative colitis and reduced the tumorigenesis of colitis-associated CRC in mouse models. Mechanistically, DI reduced the secretion of cytokines IL-1β and CCL2 from intestinal epithelial cells, and therefore reduced the recruitment of macrophages in chronic inflammation and tumor microenvironment.

Conclusions Our findings potentiate the clinical applications of DI for the treatment of ulcerative colitis and colitis-associated CRC.

537. 秋水仙碱体外添加实验对 CA72-4 检测结果影响分析

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目的 秋水仙碱，也称秋水仙素，在药理方面的作用主要表现为抗炎、减轻肝纤维化以及对细胞的抑制作用，是经典的抗炎、镇痛药物。目前痛风患者在检测肿瘤标志物过程中发现有 CA72-4 一过性升高的案例屡见报道，经过药物史排查及实验研究，发现口服秋水仙碱对 CA72-4 的检测结果具有明显影响。为便于在免疫实验室顺利开展试剂盒药物干扰的评估，本文主要对秋水仙碱的体外添加实验进行验证，确认是否能重复出其对 CA72-4 检测结果的影响，并用于试剂盒的药物干扰评估验证。

方法 收集不同浓度梯度的 CA72-4 临床样本 86 例及随机样本 52 例，每例样本分为 4 份，分别设对照组，实验 1 组，实验 2 组，实验 3 组；实验组秋水仙碱添加浓度分别为 1ug/mL、5ug/mL、10ug/mL（实验组秋水仙碱添加浓度根据药物服用浓度设置梯度，最高浓度为口服浓度上限的 3 倍）。实验组进行药物添加后样本在室温放置 24h 后进行检测，本次检测使用磁微

粒化学发光法在安图 AutoLumo A2000 Plus 全自动化学发光测定仪上进行，比较实验组与对照组检测结果是否具有显著差异。

结果 使用三种添加浓度的实验组检测结果均与对照组基本一致，分别比较与对照组的临床相关性 R^2 与斜率偏差，结果均无统计学差异。表明秋水仙碱体外添加实验不能重复出体内服用时所呈现出的药物干扰现象，体外添加的方法不能用于实验室评估秋水仙碱对 CA72-4 检测结果的药物干扰。

结论 体外药物添加实验缺少体内代谢过程，因此不能评估出药物代谢物可能对肿瘤标志物 CA72-4 的影响，综合此次体外添加实验结果分析，口服秋水仙碱患者相关 CA72-4 检测结果一过性升高可能主要是由于秋水仙碱的代谢物影响了 CA72-4 的代谢过程或者产生 CA72-4 的结构类似物，因此对试剂盒的检测结果形成了干扰，而体外添加实验不能重复出药物代谢过程及标志物的代谢变化，因此不能使用体外添加实验评估秋水仙碱对 CA72-4 检测结果的药物干扰。

538. Identification of Aurora kinase A as a biomarker for prognosis in obesity patients with early breast cancer

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Objective Obesity is associated both with a higher risk of developing breast cancer, particularly in postmenopausal women, and with worse disease outcome for women of all ages. The molecular mechanisms that link obesity-breast cancer are complex, the effects of obesity to increase local and circulating pro-inflammatory /proangiogenic cytokines and stimulate the most malignant cancer stem cell population to drive cancer growth, invasion, and metastasis. Previous investigation suggested Aurora A kinase was able to partially restore the functionalities of obese adipose-derived mesenchymal stem cells by stabilizing their primary cilia and reestablishing a balance of multiple stemness-associated genes. The association between Aurora A and obesity breast cancer is still unclear. We hypothesized that overexpression of Aurora A was associated with poor survival in obesity breast cancer and related axis mechanism were involved.

Methods Fifty hundred and eighteen primary breast cancer specimens were collected from First Affiliated Hospital of China Medical University between January 2011 and November 2016. Our independent variable was BMI at baseline, categorized as overweight (BMI ≥ 25 kg/m2, as Obesity cohort), and normal (18.5 ≤ BMI < 25 kg/m2, as Non-obesity cohort). The Immunohistochemical (IHC) staining was performed with Aurora A, Survivin, MMP11, Cyclin B1 and Cathepsin L. Kaplan-Meier curve was used to analyze overall survival in our cohorts and TCGA-BRCA data (GSE3494).

Log-rank test was used to calculate P value. PPI network analysis and MCODE model was used to analysis Aurora- altered signal pathway from GSE78958.

Results We validated Aurora A over expression using an independent cohort with a total of 517 breast carcinoma tissues (319 Non-Obesity patients and 198 Obesity Patients). The expression level of Aurora A-positive was significant higher in obesity breast carcinoma compared with non-obesity cancer carcinoma (c2=9.79, P=0.002). In the immunohistochemistry assay, the results confirmed that the expression level of Aurora A-positive was significantly associated with hormone receptor status (68.4% vs 77.9%, P=0.015) and HER2 status (28.7% vs 17.9%, P=0.003). Aurora A-positive tumors had larger tumor size, though not statistically significant (78.1% vs. 71.1%, P=0.070). High Aurora A expression was remarkably and significantly associated with OS (8-year OS ratio: 69.5% vs 81.1%, OR=1.76, 95% CI:1.03~3.02, P=0.041) in Obesity Cohort. Interesting, higher expression of Aurora A was not associated with a shorter overall survival time among the Non-obesity breast cancer (8-year OS ratio:81.4% vs 85.8%, OR=1.40, 95% CI:0.79~2.45, P=0.229). As for RFS, the expression levels of Aurora A expression genes have no significance with RFS statistically in Non-Obesity patients. The in Aurora A low expression group was in high Aurora A expression in Non-Obesity Cohort (5-year RFS ratio:82.2% vs 83.2%, OR=1.29, 95% CI: 0.77~2.16, P=0.307). While 5-year RFS ratio in high Aurora A expression group of Aurora A were 71.3% was a little shorter than the 5-year RFS ratio in low Aurora A expression group (OR=1.58, 95% CI:0.96~2.57, P=0.072). Aurora A and Lymph node metastases were significantly poor prognostic factors for OS, and borderline significance was noted for high BMI. Kaplan–Meier survival analysis from TCGA database confirmed that the high Aurora A expression group had worse prognosis (HR=1.47, 95%CI:1.14-1.90, P=0.003). The KEGG pathway enrichment results were consistent with GO biological process term analysis, in which CCNB1 was enriched for upregulated Aurora A. In IHC correlation analyasis, Aurora A level on tumor cytoplasm had broad connections with Cyclin B1 (correlation coefficient = 0.227, P=0.001).

Conclusions Our finding demonstrate here for the first time that high expression of Aurora A was notably correlated with early recurrence and poor overall survival in obesity patients with early breast cancer. The Aurora A-Cyclin B1 axis could be a potential promising therapeutic target for cancer intervention and therapy.

539. Metformin as A Primary Preventative Treatment for Cholangiocarcinoma：Long-Term Use of Metformin and Reduced Cancer Risk.

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Objective Consistent use of metformin is associated with reduced incidence of neoplastic disease in diabetic patient populations. Metformin as a preventative intervention may be more effective from a risk-benefit perspective. In this study, we explored the efficacy of metformin treatment for the prevention of cholangiocarcinoma (CCA) carcinogenesis.

Methods The iTRAQ assay was used to screen for proteins involved in the development of cholangiocarcinoma. CCA cells were treated with metformin, and were performed for cDNA microarray analysis. Metformin was evaluated in a thioacetamide-induced rat model of CCA to evaluate the effect of metformin on the CCA induction process. Livers were harvested and examined histologically by light microscopy and deep-learning convolutional neural network. RNA-seq was used to analyze the genetic changes after metformin treatment in TAA-induced CCA animal models.

Results A total of 62 proteins were dysregulated during CCA carcinogenesis, most of which are targeted by metformin. In the rat model of CCA, the incidence and the average number of tumors in the liver were higher in the TAA control group (100% and 12.0) than in the metformin-treated group (70% and 3.3). Interestingly, progression from normal cholangioles to invasive CCAs was accompanied by the up-regulation of multiple proteins essential for metabolic processes and the tumor microenviroment, and these changes were significantly inhibited by metformin treatment.

Conclusions These findings strongly suggest that long-term use of metformin is an effective primary chemoprevention strategy for CCAs.

540. IL-33/ST2 axis affects tumor growth in the microenvironment by regulating mitophagy of macrophages to reshape their polarization

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Objective Macrophages are major components of the tumor microenvironment. M1 secrete proinflammatory factors to inhibit the occurrence and development of tumors, and tumor-associated macrophages (TAMs) are mainly the M2 type. Our previous studies have shown that the interleukin (IL)-33/ST2 axis is essential for activation of M1[1]. This study was to investigate the role of this

signaling axis in TAMs, whether it participates in the mutual conversion between M1 and M2, and the effect on tumor growth.

Methods Bone marrow-derived macrophages from wildtype, Il33-overexpressing, or receptor knockout (ST2-/-) mice were extracted and differentiated with IL-4. The number and location of mitochondrial and lysosomes, and the expression of related proteins were detected to analyze mitophagy. Oxygen consumption rates, glucose and lactate levels, etc. were indicated metabolic changes.

Results We found IL-33/ST2 axis played an important role in the metabolic conversion of macrophages from OXPHOS to glycolysis by altering mitophagy levels. This metabolic shift was not due to mitochondrial damage, because the mitochondrial membrane potential was not altered significantly by IL-4 stimulation or ST2 knockout, but may be related to the activity of mTOR.

Conclusions These results clarified the interaction between IL-33/ST2 and macrophages, and ultimately promote the development of new cancer immunotherapies targeting the IL-33/ST2 axis.

541. Hypoxia-Induced GBE1 Expression Promotes Tumor Progression through Metabolism Reprogramming in Lung Adenocarcinoma

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Objective Hypoxia induces a switch from oxidative phosphorylation to glycolysis and increases glycogen synthesis. We previously showed that glycogen branching enzyme (GBE1) is downstream of the hypoxia-inducible factor-1 (HIF1) pathway in hypoxia-conditioned lung adenocarcinoma (LUAD); however, the molecular mechanism underlying HIF1 regulation of GBE1 expression remains unknown.

Methods Herein, the effect of GBE1 on tumor progression via changes in metabolic signaling under hypoxia in vitro and in vivo was evaluated, and GBE1-related genes from human specimens and datasets were analyzed.

Results Hypoxia induced GBE1 upregulation in LUAD cells. GBE1-knockdown A549 cells showed impaired cell proliferation, clone formation, cell migration and invasion, angiogenesis, tumor growth, and metastasis. GBE1 mediated metabolism reprogramming in LUAD cells. Expression of

gluconeogenesis pathway molecules, especially Fructose-1, 6-bisphosphatase (FBP1), was markedly higher in shGBE1 A549 cells than control. FBP1 inhibited tumor progression of LUAD. GBE1-mediated FBP1 suppression via promoter methylation further enhanced HIF1α levels through NF-κB signaling. GBE1 may be a negative prognostic biomarker for LUAD patients.

Conclusions Altogether, hypoxia-induced HIF1α mediated GBE1 upregulation, further suppressing FBP1 expression by promoter methylation via NF-κB signaling in LUAD. FBP1 blockade upregulated HIF1α, switched to anaerobic glycolysis, and enhanced glucose uptake. Therefore, targeting the HIF1α/GBE1/NF-kB/FBP1 axis may be a potential therapeutic strategy for LUAD.

542. High-Dimensional Single-Cell Analysis Delineates Radiofrequency Ablation Induced Immune Microenvironmental Remodeling in Pancreatic Cancer

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Objective Radiofrequency ablation (RFA) is a local therapy that accepted to the treatment of cancer patients with liver metastases. RFA treatment of liver metastases in pancreatic cancer could reduce tumor volume and induce anti-tumor immune responses on distant non-RFA tumors. However, these immune responses transformed into exhausting in a few days after RFA treatment. So far, the alterations of tumor immune microenvironment in distant non-RFA tumor after RFA treatment are still unclear.

Methods In this study, by using syngeneic tumor models and single-cell RNA and TCR sequencing, we investigated the alterations of tumor-infiltrating immune cells in distant non-RFA tumor on day 3 after RFA treatment.

Results Single-cell RNA sequencing identified six distinct lymphoid clusters, five distinct monocyte/macrophage clusters, three dendritic cells clusters, and one cluster of neutrophils. We found that RFA treatment could reduce the proportions of immunosuppressive cells including regulatory T cells, tumor-associated macrophages and tumor-associated neutrophils, whereas increase the percentages of functional T cells in distant non-RFA tumor. Moreover, RFA treatment also altered gene expression on a per cell in each cell cluster. And by using pseudo-time analysis, we described the biological processes of tumor-infiltrating $CD8^+$ T cells and monocytes/macrophages based on transcriptional profiles. In addition, the immune checkpoints including PD-1, TIM3, LAG3 and CTLA4 were upregulated in T cells in distant non-RFA tumor after RFA treatment.

Conclusions In conclusion, our data indicated that RFA treatment induced tumor immune microenvironmental remodeling in non-RFA tumors in pancreatic cancer mouse model and provided an evidence for combination of RFA and immune checkpoint inhibitors.

543. 结直肠癌免疫细胞浸润模式及与临床特征的相关性分析

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目的 研究结直肠癌的免疫细胞浸润模式，探索免疫细胞浸润与临床特征的相关性，并进一步分析免疫细胞浸润与预后的关系。

方法 从 TCGA 数据库下载结直肠癌数据共 615 例，包括肿瘤样本 571 例，正常样本 44 例。下载的结直肠癌临床数据共 552 例，包括生存时间、生存状态、年龄、性别、分期、肿瘤部位等信息。使用 CIBERSORT 反卷积算法，基于标准化的基因表达数据计算出 22 种免疫细胞的含量。使用 R 语言分析免疫细胞浸润与临床特征及生存的相关性。从 GEO 数据库下载结直肠癌数据共 60 例，包括肿瘤样本 30 例，正常样本 30 例，使用类似方法分析作为验证。

结果 下载到的 615 例样本数据使用 CIBERSORT 方法运行后，以 $p<0.05$ 的标准过滤筛选出肿瘤样本 282 例，正常样本 16 例。使用这 298 例样本分析结直肠癌中免疫细胞的组成，发现所有样本中 M0、M1、M2、CD8、未活化的 CD4 记忆性 T 细胞表达较高。在肿瘤样本中，M0、M1、活化的 CD4 记忆性 T 细胞、未活化的 NK 细胞表达较高，而正常样本中，M2、活化的 NK 细胞表达较高。与临床分期的分析显示，活化的 CD4 记忆性 T 细胞、活化的 NK 细胞、M1、CD8 细胞随着分期的升高表达量降低，浆细胞、调节性 T 细胞随着分期的升高表达量升高。生存分析显示初始 B 细胞表达高预后好，M2 型巨噬细胞、活化的肥大细胞、嗜中性粒细胞表达高预后差。使用 GEO 数据库下载的 60 例样本数据，分析结果与以上 TCGA 数据结果基本一致，验证了所得结果的准确性。

结论 结直肠癌中存在不同种类的免疫细胞的浸润，浸润的免疫细胞与肿瘤的发生发展密切相关，可以作为影响结直肠癌患者预后的重要因素。

544. SOSOCS3 deficiency blocked autophagy-dependent myeloid differentiation of early-stage myeloid-derived suppressor cells via the miR-155/C/EBPβ/Wnt axis

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Objective Early-stage myeloid-derived suppressor cells (eMDSCs) are a newly defined subset of myeloid-derived suppressor cells (MDSCs) that accumulate in tumors and potently suppress antitumor immune responses. We previously identified a subset of eMDSCs in human breast cancer. The development of these eMDSCs correlated with SOCS3 deficiency-dependent hyperactivation of the

JAK/STAT signaling pathway, although the distinct molecular regulation has not been fully elucidated.

Methods We genetically constructed conditional SOCS3 knockout mice with SOCS3 deficiency specifically in the myeloid linage (SOCS3MyeKO). And a miRNA microarray and whole-genome RNA sequencing were performed to screen the potential regulatory ceRNA network in eMDSCs from SOCS3MyeKO mice (eMDSCsSOCS3KO).

Results We delineated that the number of eMDSCs with the murine GMP phenotype increased significantly in SOCS3MyeKO mice, and these cells suffered from a differentiation block in the myeloid lineage. The differentiation block in eMDSCsSOCS3KO was caused by limited autophagy activation in an AMPK-independent manner. and demonstrated that miR-155 overexpression and Wnt/β-catenin pathway activation were involved in the SOCS3 knockout-mediated myeloid differentiation block and autophagy repression. Further experiments revealed that miR-155 was induced by activation of the STAT3/NK-κB pathway upon SOCS3 deficiency, which consequently activated the Wnt/β-catenin pathway via targeting C/EBPβ. Furthermore, applying a specific miR-155 antagonist or the autophagy agonist rapamycin efficiently suppressed tumor growth and eMDSC infiltration in vivo.

Conclusions SOCS3 deficiency blocked autophagy-dependent myeloid differentiation of e-MDSCs via the miR-155/C/EBPβ/Wnt axis, and thus targeted therapy against this pathway could be a potential therapeutic target in breast cancer.

545. Predicting gastric cancer outcome from resected lymph node histopathology images using deep learning

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Objective N staging is a determining factor for prognostic assessment and decision-making for stage-based therapeutic strategies. Visual inspection of whole-slides of all lymph nodes is the only method used by pathologists to assess the status of each lymph node and calculate the number of metastatic lymph nodes.

Methods Totally，7505 whole-slide images of lymph nodes (with an average slide height × width of 60,466×53,205 pixels/whole-slide image) were generated from these cohorts: 7095 with metastatic lesions and 8920 without metastases. We trained a deep minding framework (U-Net and ResNet-50) on whole-slide images of lymph nodes of gastric cancer to accurately and automatically outline each intact lymph node and identify the metastatic regions in them.

Results The performance of our method is comparable to that of an experienced pathologist, with the area under the curve (AUC) score of 0.982. Our model was validated on independent datasets of lymph nodes of gastric cancer, and of a varity of tumors, including esophageal squamous carcinoma,

colorectal, pancreatic, cholangiocarcinoma, and breast cancer. Furthermore, our model precisely calculated the proportion of metastatic lesions on the lymph node and visualized the spatial distribution of metastatic lymph node. We found that metastatic lymph node area could classify patients with gastric cancer at each N stage into two groups: better prognosis and poor prognosis, with P value from <0.001 at N1, 0.005 at N2, to 0.020 at N3.

Conclusions These findings prove that deep-learning models not only can assist pathologists in detecting metastatic lymph nodes, but also can assist oncologists in predicting patients' outcome and determining appropriate therapeutic strategies.

546. 可用于循环肿瘤细胞培养的集成储液腔超疏水悬滴式芯片

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目的 体外扩增的患者血源循环肿瘤细胞（CTCs）集群可用于抗癌药物测试和筛选，并有助于临床诊断和治疗决策。悬滴法常用于培养形成三维（3D）细胞团簇，具有无支架、促聚集和易实现等优势，但是，传统的悬滴培养系统存在液滴容纳培养基量较少、培养基更新困难且换液易引起细胞扰动和损失等局限性，仅适用于短期细胞团簇培养。而 CTCs 具有数量稀少、生长缓慢的特点，为了获得实现有效的 CTCs 扩增及团簇，长期培养建立细胞系通常耗时较长（＞6 months）且效率低下（＜20%）。可以改进克服传统悬滴法的局限，使之适用于相对长期（1-2 weeks）的细胞稳定培养。为此，我们开发了一种集成储液腔的超疏水悬滴式芯片，应用于 CTCs 培养。

方法 首先通过倒模工艺制作包含微腔阵列的 PDMS 片，用于形成储液腔阵列；再利用激光刻蚀制备具有超疏水表面图案的 PDMS 薄膜，用以形成悬滴位点阵列；然后通过等离子体处理实现两层结构的键合组装，且通过制作通孔阵列结构实现每个储液腔连接一个悬滴位点。藉由储液腔储存的培养基，该芯片能在不换液、不扰动的前提下持续为悬滴内的细胞提供营养，维持较长时间的培养。另外，芯片表面图形化的超疏水结构，利于悬滴形态维持和球形细胞团簇的形成。首先通过在芯片中培养肝癌细胞株 MHCC97H，并与无储液腔结构的悬滴芯片进行对比，以验证其功能。随后将该芯片用于 CTCs 培养。CTCs 来源于恶性转移患者血样，常规破红处理后以 CD45 标记分选尽量去除白细胞，剩余有核细胞群推定包含潜在 CTCs。稀释细胞量以悬滴为单位培养（约 100-200 个细胞/滴），因其数量稀有可概率推测每滴中仅含有 0 或 1-2 个 CTCs。低氧（1% O2）培养后，考察各悬滴中的细胞生长、成团簇等，并鉴定 CTCs。

结果 芯片中培养的 MHCC97H 能形成球体结构且持续生长至 30 天，而无储液池结构芯片由于营养缺失和代谢物积累，其中细胞团逐渐出现解体（day 6）。同时，图案化的超疏水处理表

面可维持培养液滴近似球形以利于其中细胞形成紧凑团簇。此外，使用该芯片培养血源CTCs，也成功获得CTCs细胞团簇（CK+/EpCAM+，day 14）。

结论 集成储液腔的超疏水悬滴芯片能够实现不换液且无扰动的长期悬滴细胞培养，且更易形成紧密的细胞团簇，有望为 CTCs 的体外培养和后续更深入的研究提供了一种简便有效的平台。

547. Clinical analysis of bloodstream infection of Escherichia coli in patients with pancreatic cancer

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Objective Pancreatic cancer patients are particularly predisposed to develop Escherichia coli (E. coli) bloodstream infection (BSI), however, little information is currently available. We set out to find the risk factors of E. coli BSI in pancreatic cancer to provide valuable experience.

Methods Retrospectively analyze the clinical data of pancreatic cancer patients (31 cases with E. coli BSI and 93 cases without BSI) for 8 years by a case-control study at a Comprehensive Cancer Prevention Center. SPSS 17.0 was adopted to do univariate and multivariate analysis. Bacterial resistance analysis was performed by Whonet 5.6. Graphpad Prism 7.0 was used to analyze quantitative data differences.

Results Multivariate logistic regression analysis showed that hospitalization days≥7, chemotherapy and neutrophil>5.5×109/L were independent risk factors for pancreatic cancer patients with E. coli BSI ($P < 0.05$). Quantitative analysis of serum indicators in infection and non-infection patients showed significant differences between albumin, prealbumin and neutrophils ($P < 0.05$). The ratio of E. coli producing extended-spectrum ß-lactamase was 49.3 and 48.1 in pancreatic cancer and non-pancreatic patients. E. coli resistant to carbapenems was rare, they were highly sensitive to Cephamycin and Piperacillin/tazobactam.

Conclusions The independent risk factors of pancreatic cancer patients with E. coli BSI include hospitalization days≥7 days, chemotherapy and neutrophils larger than 5.5×109/L. Quantitative indicators of neutrophil counts, albumin and prealbumin contribute to the early diagnosis of bloodstream infections. Early use of medication and timely adjustment based on clinical drug sensitivity results will help reduce patient morbidity and mortality.

548. FGF13 对乳腺癌增殖和侵袭能力的影响及其作用机制

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目的 探究 FGF13 对乳腺癌迁移增殖影响的的作用方式和调控分子机制。

方法 利用 RT-qPCR 方法分析河北医科大学第四医院乳腺癌手术切除标本 21 例（其中导管浸润癌 13 例，导管原位癌 8 例），比较 FGF13 表达差异。在乳腺癌细胞系（MCF-7 细胞，MDA-MB-231 细胞）中过表达 FGF13，利用 MTS、克隆形成实验检测不同类型乳腺增殖能力，划痕实验、transwell 实验检测乳腺癌迁移能力。接下来我们利用 RT-qPCR 法，Western blot 法检测 FGF13 过表达后，EMT（epithelial-to-mesenchymal transition，上皮-间质转化）相关标记物 mRNA 及蛋白质水平的表达情况。

结果 生物信息数据库筛选结合临床标本验证，相对于正常乳腺组织，乳腺癌中 FGF13 表达明显升高，而导管原位癌中 FGF13 的表达高于导管浸润癌（$p<0.05$）。MTS、克隆形成实验显示 FGF13 过表达组吸光度、集落形成数均低于对照组（$p<0.05$），划痕实验表明过表达组愈合能力减慢，transwell 实验检测发现相对于对照组，过表达组迁移细胞数明显减少（$p<0.05$）。筛查 EMT 相关标记物显示 FGF13 过表达组 CDH1 mRNA 升高。

结论 FGF13 抑制乳腺癌细胞的增殖迁移，对乳腺癌迁移能力的影响可能与 EMT 过程有关。所获得的研究成果帮助我们更好判断乳腺癌预后，作为迁移增殖特征性的分子标志物，提示风险，并为相关靶点应用于临床提供一定的理论基础。

549. 如何评价肿瘤标志物在肺癌免疫治疗中的作用

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目的 肺癌是全世界发病率、死亡率最高的恶性肿瘤，一直以来对人类生命造成巨大威胁。近年来免疫治疗发展迅猛，各种免疫检查点抑制剂在国内外迅速获批，其疗效给广大患者带来巨大希望。然而，并不是所有患者均能够从中获益，有些患者接受免疫治疗时出现了各种不良反应、耐药，甚至超进展等情况。本文对肿瘤标志物作为预测因子，在肺癌免疫治疗中的作用做一浅析。

方法 对肿瘤标志物预测免疫检查点抑制剂治疗肺癌的疗效、不良反应、超进展相关的试验、研究、文献进行检索和综述。

结果 肺癌免疫检查点抑制剂治疗过程中，各种肿瘤标志物作用不同。有的预测疗效，有的预测不良反应或超进展等；有的单项起作用，有的联合起作用，有的作用重叠；有的已经进入指南，有的还需进一步研究论证。

结论 目前中国人群的大宗样本试验数据仍较少，随着中国肺癌 ICIs 临床试验不断开展，治疗病例数目不断增加，相信肿瘤标志物在预测免疫检查点抑制剂疗效、不良反应、超进展等方面会显现出越来越重要的作用。

550. MAGE-A genes as predictors for the outcome of laryngeal squamous cell carcinoma

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Objective The laryngeal squamous cell carcinoma (LSCC) is one of the most common malignant tumor in head and neck area. melanoma-associated antigens A (MAGE-A) antigens are strictly tumor specific and express in many kinds of tumors. So far there is still no research report that MAGE-A genes can be potential markers for circulating tumor cells (CTCs) in patients with LSCC. This study aimed to evaluate the expression and the possible prognostic significance of MAGE-As in peripheral blood of patients with LSCC.

Methods In this study, the expression of MAGE-A genes in peripheral blood of LSCC patients was performed by multiplex semi-nested PCR and restriction endonuclease treatment. The relationship between MAGE-A gene expression and clinicopathological parameters and prognosis was evaluated.

Results The expression of MAGE-A was related to the predictors indicating poor prognosis. The expressions of MAGE-A and each individual MAGE-A genes were also associated with low overall survival of LSCC patients.

Conclusions MAGE-A genes may be as the prognostic markers for LSCC patients.

551. 细针穿刺活检 BRAFV600E 突变分析在甲状腺结节诊断中的应用价值

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目的

背景：术前通过对甲状腺结节进行超声引导下细针穿刺细胞学检查(US-FNAC)是目前公认的鉴别其良恶性的较好诊断方法。分子遗传学研究进展，证实 BRAF V600E 点突变是甲状腺乳头状癌(PTC)最常见的突变类型。对于 US-FNAC 不能确定性质的甲状腺结节，$BRAF^{V600E}$ 突变分析能否作为一个有效的检测手段为临床诊断提供依据，正是本文旨在回答的问题。**目的：**探讨超声引导下细针穿刺活检(FNAB)$BRAF^{V600E}$ 突变分析对鉴别甲状腺结节良恶性的临床应用价值。

方法 收集 2018 年 1 月至 2019 年 6 月南京鼓楼医院收治的疑似病变的 2719 例甲状腺结节患

者，其中男 685 例，女 2034 例；年龄 23 -80 岁，平均（44.1±15.9）岁；结节直径 0.5～2.3cm，平均（1.1±0.3）cm。患者经 FNAB 取样，分别送检进行 BRAF ^{V600E} 突变分析和细胞学检查。BRAF ^{V600E} 突变采用基于实时荧光定量 PCR 技术的扩增阻滞突变系统(ARMS)法检测，细胞病理诊断分类采用 BSRTC 系统 6 分类标准，即细胞病理诊断分为以下 6 类（①未诊断，②良性病变，③滤泡性病变，④滤泡性肿瘤，⑤可疑恶性，⑥恶性病变）。比较 BRAF ^{V600E} 突变结果与细胞学诊断结果，以术后组织病理作为诊断标准，判断 BRAF ^{V600E} 突变分析对甲状腺恶性病变的诊断价值。

结果 2719 例甲状腺结节患者中，有 593 例行甲状腺结节切除术。593 例患者术前 FNAB 结果示：BSRTC I-III 144 例，其中 BRAF^{V600E} 突变 115 例（79.9%），其中 111 例经组织病理证实为 PTC；BSRTC V-VI 449 例，其中 BRAF^{V600E} 突变 404 例（90.78%），经组织病理证实均为 PTC。对于 BSRTC I 即 FNAC 不能诊断的 75 例患者，术后组织病理结果表明 BRAF ^{V600E} 突变分析的诊断符合率为 82.7%。以术后组织病理为金标准，FNAC 单独诊断甲状腺癌的灵敏度为 77.8%，诊断符合率 78.1%；联合 BRAF ^{V600E} 突变分析后，灵敏度为 90.4%，诊断符合率为 90.1%。，FNAC 联合 BRAF ^{V600E} 突变分析使甲状腺结节诊断灵敏感性可提高到 97.2%。

结论 细针穿刺活检 BRAF ^{V600E} 突变分析能提高甲状腺结节诊断准确性，与穿刺细胞学结合有助于术前有效筛选高危甲状腺结节人群，具有重要的临床应用价值。

552. Evaluation of plasma exosome-derived miRNAs as biomarkers for colorectal cancer liver metastasis: comparison with plasma total miRNAs and cancerous tissues

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Objective Over 50% of colorectal cancer (CRC) develops into the liver metastatic disease (CRLM). Biomarkers for CRLM are essential for a better understanding of the patient's tumor status and to provide personalized treatment. Here we aim to use exosomes which have the potential for early detection of many diseases to optimize CRLM diagnostics and use plasma exosomes as a source of miRNA biomarkers.

Methods Exosomes were isolated by ultracentrifugation from 12 CRC patients (6 primary CRC and 6 CRLM). Analysis of exosome-associated miRNAs was performed using Agilent Microarray Technology to identify 112 exosome-enriched miRNAs with differential expression seen between primary CRC and CRLM. This was combined with the Cancer Genome Atlas dataset and miR-146a-5p, miR-200a-5p and miR-625-3p were selected for further RT-qPCR validation in 50 independent

participants (plasma: 20 primary CRC, 20 CRLM and 10 controls; tissues: 20 primary CRC and 17 CRLM).

Results The AUC of 3 individual miRNAs ranged from 0.720 to 0.873. A logistic model that combines 3 miRNAs achieved an AUC of 892. Addition of the total plasma miRNA, CEA and B cells % (CD3-CD19+) into this model further increased the AUC to 0.963. Although side-by-side comparisons show that exosomal miRNA profiles were superior to cell-free plasma miRNAs in the diagnosis of CRLM, by combining other clinical indicators (CEA and B cells), the diagnostic efficiency was further improved.

Conclusions Exosomes derived miRNAs may be promising biomarkers to detect CRLM, but the combination of these miRNAs with other biomarkers could potentially improve the sensitivity and specificity for CRLM diagnosis.

553. 血清 KL-6 水平在预警食管癌患者发生放射性肺炎中的意义

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目的 探讨放疗前后血清 KL-6、LDH 水平变化在预警放射性肺炎（RP）发生的意义，为开展放射性肺炎实验室检查方法提供理论依据，为放射性肺炎患者提供用于早期辅助诊断的有效监测手段。

方法 留取在福建省肿瘤医院进行放疗的 39 例食管癌患者放疗前后 6 个月实验室检查剩余血清，并将这 39 例患者分为 RP 组（9 例）和非 RP 组（30 例）。然后检测患者血清 KL-6 水平，并进行统计分析。

结果 两组治疗方案中是否同时化疗、放射总剂量、性别没有显著性差异（P＞0.5），但是两组年龄有显著性差异（P＜0.5）。在放疗之前，RP 组和非 RP 组的血清 KL-6 水平差异没有统计学意义。而放疗开始后 RP 组和非 RP 组的血清 KL-6 水平，从放疗开始后 1 个月到 4 个月，RP 组的血清 KL-6 水平显著高于非 RP 组。而 RP 组和非 RP 组血清 LDH 水平变化的差异没有统计学意义（P＞0.5），并且和血清 KL-6 水平变化无相关性（P=0.843）。 对放疗前后 KL-6 水平增高比值进行 ROC 分析，结果显示诊断界限最佳为 1.4，灵敏度为 66.7%，特异度为 96.7%,阳性似然比为 20，阴性似然比为 0.34，youden 指数为 0.634。

结论 RP 的发生风险在不同年龄的患者上有差别，老年患者在放疗剂量的制定上应更加谨慎。血清 KL-6 水平在监测食管癌患者发生 RP 方面有重要意义，当食管癌病人接受放疗后血清 KL-6 水平升高且与放疗前水平之比大于 1.4 时，提示该患者罹患 RP 的可能性大。

554. Zinc-finger protein ZNF382 induces G0/G1 cell cycle arrest via CDC25A signaling pathway and inhibit cell migration by decreasing the expression of ZEB1 in breast cancer

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Objective With advancements research, the role of zinc-finger protein has been widely recognized. Recent studies suggest that ZNF382 (zinc-finger protein 382) plays an anti-oncogene role in esophageal, nasopharyngeal and gastric cancers. However, the biological role of ZNF382 in breast cancer remains unclear.

Methods Semi-quantitative real-time PCR and real-time quantitative PCR were performed to detect the expression of ZNF382 in breast cancer cells and tissues. The biological effects of ZNF382 were detected by cell viability assay, colony formation assay, Transwell assay, and flow cytometry assay in vitro. The effects of ZNF382 in vivo were detected via xenografts and immunohistochemistry. The mechanism of ZNF382 was studied by immunofluorescence, luciferase reporter assay,ChIP assay and western blot.

Results We showed that overexpression of ZNF382 inhibited cell proliferation, the ability of colony formation and migration in MDA-MB231 and MCF7 cells. The growth of xenograft tumors in nude mice was also suppressed. Furthermore, ZNF382 knockdown promoted BT549 cell growth and invasive ability. Overexpression of ZNF382 induced G0/G1 cell cycle arrest and apoptosis via inhibiting the CDC25A signaling pathway and inhibited cell migration and invasion via regulating the epithelial- mesenchymal transition (EMT) by inhibiting the ZEB1and cell stemness.

Conclusions The ZNF382 acts as tumor suppressor by inhibiting CDC25A gene expression and suppressing breast tumor cell migration /invasion through reversing EMT and cell stemness in vitro and in vivo.

555. 现实世界不同瘤种 PD-L1 表达状态

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目的 目前将 PD-L1 作为一种免疫治疗疗效预测标志物，抗 PD-1/PD-L1 免疫治疗主要的适应症包括：无驱动基因突变的肺癌、肝细胞癌、晚期肾细胞癌、恶性黑色素瘤、胃和食管-胃结合部癌等。不同瘤种 PD-L1 表达状态有相关报道，为了对比现实世界不同瘤种 PD-L1 表达状态与报道中存在的差异，收集陕西省肿瘤医院不同瘤种检测 PD-L1 的表达水平。

方法 收集 2018.05-2019.05 就诊于陕西省肿瘤医院行 PD-L1 检测的患者共 80 例。分析对比现实世界不同瘤种 PD-L1 表达状态。

结果 收集检测 PD-L1 患者 80 例，其中黑色素瘤 5 例，非小细胞肺癌 47 例，鼻咽癌 1 例，结肠癌 5 例，肝细胞癌 4 例，尿路细胞癌 1 例，卵巢癌 2 例，胃癌 7 例，食管癌 3 例，胰腺癌 1 例，肾细胞癌 1 例，乳腺癌 3 例。对比相关报道与现实世界中不同瘤种 PD-L1 表达状态。 不同瘤种现实世界 PD-L1 表达与报道的对比如下：黑色素瘤（16% VS 70%），非小细胞肺癌（24% VS 65%），鼻咽癌（70% VS 80%），结肠癌（6% VS 53%），肝细胞癌（阴性 VS 64%），尿路上皮癌（40% VS 64%），卵巢癌（30% VS 47%），胃癌（11% VS 42%），食管癌（3% VS 42%），胰腺癌（1% VS 39%），肾细胞癌（阴性 VS 19%），乳腺癌（31% VS 33%）。

结论 现实世界不同瘤种 PD-L1 表达状态与报道数据之间存在一定差异。 通过比较现实世界与报道的不同瘤种 PD-L1 表达的数据可以看出，鼻咽癌、尿路上皮癌、胰腺癌及肾细胞癌等发病率较肺癌、胃癌等常见癌种低，收集病例数各仅为 1 例，考虑收集病例数有限，因此可能会产生一定的偏倚。除了乳腺癌 PD-L1 表达状态与报道中一致外，其余均与报道中存在较大差异。提示我们 PD-L1 的表达状态可能与检测克隆号、检测组织类型（手术标本或活检组织）等诸多因素相关。因此，在治疗时应根据患者实际 PD-L1 表达状况来将其作为免疫治疗疗效预测标志物去筛选免疫治疗获益人群。

556. BTB/POZ zinc-finger protein ZBTB16 inhibits breast cancer proliferation and metastasis through upregulating ZBTB28 and antagonizing BCL6/ZBTB27

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Objective Breast cancer remains in urgent need of reliable diagnostic and prognostic markers. Zinc-finger and BTB/POZ domain-containing family proteins (ZBTBs) are important transcription factors functioning as oncogenes or tumor suppressors. The role and regulation of ZBTB16 in breast cancer remain to be established.

Methods Reverse-transcription PCR and methylation-specific PCR were applied to detect expression and methylation of ZBTB16 in breast cancer cell lines and tissues. The effects of ZBTB16 in breast cancer cells were examined via cell viability, CCK8, Transwell, colony formation and flow cytometric assays. Xenografts and immunohistochemistry analyses were conducted to determine the effects of ZBTB16 on tumorigenesis in vivo. The specific mechanisms of ZBTB16 were further investigated using Western blot, qRT-PCR, luciferase assay and co-IP.

Results ZBTB16 was frequently downregulated in breast cancer cell lines in correlation with its promoter CpG methylation status. Restoration of ZBTB16 expression led to induction of G2/M phase arrest and apoptosis, inhibition of migration and invasion, reversal of EMT and suppression of cell proliferation, both in vitro and in vivo. Furthermore, ectopically expressed ZBTB16 directly formed heterodimers with ZBTB28 or BCL6/ZBTB27 and exerted tumor suppressor effects through upregulation of ZBTB28 and antagonistic activity on BCL6.

Conclusions Low expression of ZBTB16 is associated with its promoter hypermethylation, and restoration of ZBTB16 inhibits tumorigenesis and improves prognosis. ZBTB16 functions as a tumor suppressor through upregulating ZBTB28 and antagonizing BCL6. Our findings also support the possibility of ZBTB16 as an prognostic biomarker for breast cancer.

557. 前列腺特异性抗原在前列腺疾病中的诊断意义

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目的 前列腺癌（prostrate adenocarcinoma，PCA）是一种中老年男性泌尿生殖系统中最为常见的一种恶性肿瘤，是人类特有的疾病[1]。近年来随着我国诊断技术的发展、社会老龄化以及生活方式的变化，前列腺癌在我国的发病率呈明显上升的趋势[2]。因此本文旨在探讨前列腺特异性抗原(tPSA)、游离前列腺特异抗原(fPSA)与总前列腺特异抗原比值（f/t PSA）、年龄参数对前列腺癌的诊断价值。考察不同 tPSA、f/t PSA 检测水平下的前列腺癌患者检测符合率，为临床筛查前列腺癌提供参考。

方法 依据病理检查结果分别选取 70 例前列腺癌(前列腺癌组)及 162 例良性病变患者、21 例健康对照组进行回顾性分析，比较三组患者的年龄水平、tPSA、fPSA、f/t PSA 等相关参数的区别。以前列腺穿刺活检作为前列腺癌确诊依据，建立 tPSA、fPSA、f/t PSA 受试者工作曲线，计算曲线下面积，分析 tPSA、fPSA、f/t PSA 诊断前列腺癌的价值以及不同年龄区段患者人数与 tPSA、fPSA、f/t PSA 水平的相关性水平。

结果 前列腺癌组中位血清 tPSA、fPSA 分别为 44.86（3.2-1000）、8.22（0.41-150）ng/mL，显著高于良性疾病组以及其他疾病组。前列腺癌组与其他两组差别显著（均为 P<0.0001）。三组的中位血清 f/t PSA 的差异无统计学意义（P>0.05），但中位血清 f/t PSA 均高于 0.16。前列腺癌组 tPSA 及 f/t PSA 水平均显著高于良性疾病组及健康对照组。血清 tPSA（tPSA>4 ng/ml）、f/t PSA（f/t PSA>0.16 ng/ml）诊断前列腺癌的曲线下面积（前列腺癌患者组 vs 健康对照组）依次为 0.726、0.341，敏感度为 42%、33%，特异性为 88%、59%。当将参数设定为 tPSA>4 ng/ml、f/t PSA>0.16 ng/ml 时，敏感度和特异性可提升为 43%、88%。由此可见，血清 tPSA 与 f/tPSA 综合参考对于前列腺癌诊断具有重要的意义。

558. Prognostic values of tumor immune icroenvironment related genes in Ovarian Cancer:A gene expression-based study

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Objective Ovarian cancer is the most common malignant diseases in women and the leading cause of cancer-related death. The high mortality rate of ovarian cancer stems from a variety of factors, such as difficulty in screening, delayed diagnosis and limited treatment options. In The Cancer Genome Atlas (TCGA) ovarian cancer cohort, based on the tumor microenvironment cell infiltration level and

immune-related genes, we tried to systematically determine predictive molecular networks and key genes as prognostic markers.

Methods The normality of the variables was tested by the Shapiro-Wilk normality test [12]. For comp-arisons of more than two groups, Kruskal–Wallis tests or Mann-Whitney U were used to assess statistical significant [13]. Correlation coefficients were computed by partial Spearman and distance correlation analyses. Two-sided Fisher exact tests were used to analyze contingency tables.

Results We identified 13 nodes(hub-genes) in ovarian cancer, functional annotations indicated that the 13 hub-genes were mostly involved in Cell adhesion molecules (CAMs) , Natural killer cell mediated cytotoxicity，Leukocyte trans endothelial migration , TNF signaling pathway ,Phagosome ,etc.

Kaplan-Meier method indicated that expression of C3AR1, CD86, CXCL10 and FN1 significantly correlated with favorable outcome for OS ($p<0.001$). Moreover, we found that these genes also correlation with level of immune infiltrates (Macrophages, NK cells, Neutrophils). C3AR1, CD86, CXCL10 were significantly positive correlation with several immune checkpoint genes(PDCD1, PDCD1LG2, CTLA4, CD80)（average correlation coefficient was 0.71）.

Conclusions In summary, we identified genes C3AR1, CD86, CXCL10 and FN1 that are potentially associated with prognosis, while also being correlated with immune checkpoint expression. So, whether it can be used as an evaluation indicator for immunotherapy needs further study.

559. SBP-1 蛋白作为肺腺癌潜在诊断标志物的验证

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目的 肺癌作为最常见的恶性肿瘤之一，具有很高的发病率和死亡率，之所以如此是因为患者确诊时已经处于晚期或肿瘤发生了转移。胸部 X 光片、组织活检或穿刺活检和细胞学检查等传统诊断技术由于具有侵入性、对人体有伤害、价格昂贵、漏诊误诊等不足难以满足临床的需求，而生物标志物的发现和应用将提前发现肺癌并进行干预以降低肺癌死亡率。SBP-1 作为一种肿瘤抑制因子，在多种肿瘤中都有表达。在先前的蛋白质组学研究中发现硒结合蛋白 1（SBP-1）在肺腺癌中表达上调。为了验证该结果，进行了肺癌和良性疾病的对照研究。

方法 对 36 例非小细胞肺癌患者和 21 例肺结核患者的样本进行分析。通过免疫组织化学技术和超高分辨率激光扫描共聚焦显微镜进行 SBP-1 表达和细胞定位分析。并通过受试者操作特征曲线（ROC）确定 SBP-1 鉴别非小细胞肺癌的敏感性和特异性。

结果 与匹配的癌旁组织或肺结核组织相比，肺腺癌中 SBP-1 表达上调（$P<0.05$）。在非小细

胞肺癌和癌旁的对照研究中，ROC 曲线显示 SBP-1 鉴别非小细胞肺癌的特异性为 95.7%。另外，还发现 SBP-1 在非小细胞肺癌和肺结核组织的细胞质和细胞核中表达，而且在癌旁组织中更集中于细胞核。

结论 SBP-1 蛋白表达水平与肺腺癌的发展和预后有关，有希望成为有价值的预后标志物。

560. MiRNA-625-3p promotes the proliferation, migration and invasion of lung adenocarcinoma cell by directly targeting KLF9 and RASSF8

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Objective MicroRNAs (miRNAs) are endogenous small non-coding RNAs and have been reported to play important roles in tumor progression of various cancers. Lung adenocarcinoma (LUAD) is the most common histological subtype of lung cancer (approximately 40%). MiR-625-3p has been demonstrated to be dysregulated in different types of cancer. However, the regulatory roles of miR-625-3p are yet to be elucidated in LUAD. In the present study, we aimed to investigate the mechanism of miR-625-3p in LUAD.

Methods Serum samples from 7 LUAD patients and 7 healthy individuals were detected by miRNA microarray including 2549 miRNAs probes to obtain differentially expressed miRNA. Quantitative real-time PCR (qRT-PCR) was carried out to detect the candidate miRNA expression in LUAD and normal serums. In addition, the expression level of target miRNA in LUAD and normal tissues was detected based on the TCGA database. Next, LUAD cell lines were transfected with miR-625-3p mimic or inhibitor. CCK-8, transwell metastasis and invasion assays were used to detect the effects of miR-625 on LUAD cells proliferation, migration and invasion, respectively. We predicted the target genes of the miRNA by using TargetScan, miRWalk and miRDB. Moreover, the specific target genes of miR-625-3p in LUAD were verified by the luciferase reporter assay. The target genes mRNA and protein expression levels were examined in LUAD cell lines by RT-qPCR and western blot analysis, respectively.

Results Through microarray analysis, we identified significantly higher levels of miR-625-3p in serum from patients with LUAD. And the relative expression of miR-625-3p in LUAD serums significantly increased compared with normal serums, which is verified in another 46 normal tissues and 521 LUAD tissues from TCGA database. Moreover, overexpression of miR-625-3p promoted the

proliferation, migration and invasion of the LUAD cells, and the inhibition of the miR-625-3p had the opposite effect. Furthermore, we verified KLF9 and RASSF8 were specific targets of miR-625-3p in LUAD cells and these two genes could attenuate the growth, migration and invasion ability of LUAD cells regulated by miR-625-3p.

Conclusions In conclusion, we indicated that miR-625-3p serves an important role as a tumor promoter in LUAD development by directly targeting KLF9 and RASSF8, suggesting that miR-625-3p could serve as a therapeutic target for LUAD.

561. Diagnostic model based on LDCT and CEA for benign and malignant pulmonary nodules

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Objective Serum CEA, as a cancer biomarker, is used in clinic widely to assist in cancer diagnosis, containing lung cancer (LC). Low dose CT (LDCT) screening is an effective method to discover pulmonary nodules, however, the high false positive rate limited its application. In this study, we aim to combine CEA with LDCT characteristics to establish an appropriate model for distinguishing benign from malignant pulmonary nodules (MPNs) effectively.

Methods Levels of plasma CEA were measured on MPNs (n=277) and BPNs (n=92) by using ELISA. The samples were divided into training set and validation set, randomly. 14 characteristic variables of LDCT were described by two experienced radiologist. The models were established based the CEA level and the characteristics of LDCT using three methods, namely binary logistic regression, classification trees, neural network. The diagnostic efficiency of CEA, the characteristic variables and models were described by ROC curves, and evaluated by AUC, sensitivity, specificity.

Results Though screening, we sorted out CEA and 9 characteristic variables (nodule diameter, margin, shape, numbers, swollen mediastinal lymph nodes, lobulation sign, vascular incisure, spicule sign, spines) of LDCT which had good diagnostic efficiency for distinguish BPNs from MPNs. Among them, lobulation sign own the highest AUC, which is 0.776 (95% CI: 0.724-0.828) and the sensitivity and specificity were 67%, 88%, respectively. Combining CEA and 9 characteristic variables of LDCT, we established three models based on binary logistic regression, classification trees, neural network, respectively. Among them, the model established by binary logistic regression based on CEA and 7 characteristic variables (nodule diameter, margin, swollen mediastinal lymph nodes, lobulation sign, vascular incisure, spicule sign, spines) of LDCT have the best diagnostic efficiency. In the training set

and validation set, the AUC, sensitivity, specificity were 0.931 (95% CI: 0.900-0.963), 79%, 98% and 0.790 (95% CI: 0.706-0.873), 72%, 76%, respectively.

Conclusions In this study, we established a model based on LDCT and CEA which may have the favourable diagnostic efficiency for BPNs and MPNs in clinic.

562. SIK2 enhances synthesis of fatty acid and cholesterol in ovarian cancer cells and tumor growth through PI3K/Akt signaling pathway

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Objective Salt-inducible kinase 2 (SIK2) has been established as a regulator of diverse biological processes including cell metabolism. A recent study has reported that SIK2 is required for adipocyte-induced ovarian cancer (OC) survival through facilitating fatty acid oxidation. However, whether SIK2 also plays a role in the lipid synthesis in OC cells remains elusive.

Methods We showed that SIK2 significantly promoted the lipid synthesis in OC cells.Moreover, in vitro and in vivo assays indicated that the SIK2-regulated fatty acid and cholesterol synthesis played a critical role in the growth of OC cells.

Results On the one hand, SIK2 enhanced fatty acid synthesis through upregulating the expression of sterol regulatory element binding protein 1c (SREBP1c) and thus the transcription of major lipogenic enzyme FASN. On the other hand, SIK2 promoted cholesterol synthesis through upregulating the expression of sterol regulatory element binding protein 2 (SREBP2) and thus the transcription of major cholesterol synthesis enzymes HMGCR. Moreover, PI3K/Akt signaling pathway was found to be involved in the upregulation of SREBP1c and SREBP2 in OC cells.

Conclusions Our findings demonstrate that SIK2 is a critical regulator of lipid synthesis in OC cells and thus promotes OC growth, which provides a strong line of evidence for this molecule to be used as a therapeutic target in the treatment of this malignancy.

563. Combination of ultrasound examination and serum tumor abnormal protein test improves the diagnostic efficiency of thyroid carcinoma

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Objective The purpose of this study was to investigate the clinical significance of ultrasound examination combined with tumor abnormal protein (TAP) in the diagnosis of thyroid cancer.

Methods The clinical data of 338 patients with thyroid nodule who received thyroidectomy and 632 health population in Chongqing University Cancer Hospital from January 2018 to August 2019 were analyzed

Results At a cut-off TI-RADS (Thyroid Imaging, Reporting and Data System) value of 4b, the sensitivity and specificity of TI-RADS in the distinguish of thyroid nodule were 71.7% and 89.5%, respectively. TAP level in patients with thyroid nodules was significantly higher compared to healthy population. At a cut-off TAP level of 225 μm^2, the sensitivity and specificity of TAP level in the diagnosis of thyroid nodule were 85.2% and 100%, respectively. In the distinguish of benign and malignant thyroid nodules, however, there was no significant difference in TAP level between thyroid cancer group and thyroid adenoma group. The sensitivity and specificity of TAP test in the distinguish of thyroid nodule were 88.3% and 19.5% respectively, which suggesting that TAP test has high sensitivity and low specificity in the diagnosis of benign and malignant thyroid nodules. More importantly, the combination of ultrasound examination and serum TAP effectively improves the diagnostic efficiency of benign and malignant thyroid nodules, the sensitivity and specificity were 86.2% and 84.0%, respectively.

Conclusions TAP can be used as a good biomarker to assist TI-RADS in the diagnosis of thyroid nodules. Furthermore, the level of TAP was significantly decreased after surgery ($P<0.001$), indicating that TAP test can also be used to judge the efficacy of treatment. Taken together, our results indicated that TAP would be used to screen out the high-risk population of thyroid cancer, and then TI-RADS is applied to distinguish benign and malignant nodules, which is more conducive to the diagnosis of thyroid cancer.

564. TC-1 激活 Wnt/β-catenin 信号通路介导 TBC1D3 诱导人乳腺癌细胞转移机制研究

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目的 探讨 TBC1D3 以 TC-1 依赖的方式激活 Wnt/β-catenin 信号通路促进人乳腺癌细胞的迁移，使 TBC1D3 成为 Wnt/β-catenin 信号通路的一个新的调节子。

方法 构建 Flag-TBC1D3 和 Flag-TC-1 质粒，转染质粒于 MCF-7 细胞和 BT-549 细胞中，培养过程中用或不用相应的抑制剂如 POM、CAPE、BGJ-398 或 XAV-939 等， 使用 shRNA 慢病毒沉默 TC-1，1.5μg/ml 嘌呤霉素筛选符合要求的稳定转染细胞株。RT-PCR 和 Western blotting 检测和鉴定各种细胞相应蛋白的转录和表达情况，划痕实验和 Transwell 实验检测人乳腺癌细胞的迁移。

结果 TBC1D3 分别刺激了非三阴性乳腺癌 MCF-7 细胞和三阴性乳腺癌 BT549 细胞中 TC-1 mRNA 的上调和蛋白水平的提高，但 POM 或 CAPE 的加入，而不是 BGJ-398 的加入，大大降低了 TBC1D3 的这一影响。TBC1D3 和 TC-1 均能促进 MCF-7 细胞和 BT549 细胞的迁移。敲低 TC-1 抑制 TBC1D3 诱导的人乳腺癌细胞迁移。Flag-TBC1D3 过表达显著增加了 MCF-7 细胞 MT1-MMP、c-Myc 和 Cyclin D1 的转录和蛋白表达。然而，TC-1 基因敲除完全抑制了 TBC1D3 对这些细胞中 Wnt/β-catenin 信号通路中这些靶基因表达的刺激作用。临床样本进行免疫组织化学染色，结果显示 TBC1D3、TC-1 或 β-catenin 的表达使三阴性乳腺癌比非三阴性乳腺癌更容易转移。TBC1D3、TC-1 和 β-catenin 阳性的乳腺癌患者比 TBC1D3、TC-1 和 β-catenin 阴性的乳腺癌患者更有可能复发。

结论 TBC1D3 是 Wnt/β-catenin 信号通路的一个新的上游调节因子。TBC1D3 激活这一信号通路，以 TC-1 依赖的方式促进人乳腺癌细胞迁移。TBC1D3、TC-1 和 β-catenin 在人乳腺癌组织中的表达不仅呈中度正相关，而且与人浸润性乳腺癌的转移和复发呈正相关。

565. 高效液相色谱-质谱法检测血清氨基酸在乳腺癌患者中表达水平情况及其意义

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目的 研究血清氨基酸在乳腺癌与正常人中表达水平的差异，探讨其在乳腺癌诊疗中的价值。

方法 招募 2019 年 4 月至 6 月经重庆大学附属肿瘤医院病理科确诊的乳腺癌女性患者 59 例为乳腺癌组，正常女性体检者 53 例为正常组。采用高效液相色谱-质谱法(high performance liquid chromatography-mass spectrometry, HPLC-MS)对招募者血清中 20 种氨基酸表达水平进行检测，探索性地分析乳腺癌组与正常组血清中氨基酸表达水平的差异，并对差异血清氨基酸在乳腺癌诊断中的效能进行系统性地评估。

结果 乳腺癌组血清氨基酸 Ala、Asn、Cit、Glu、His、Ile、Leu、Lys、Orn、Phe、Pro、Thr、Tyr、Val 表达水平均高于正常组（t=-3.884、-2.080、-2.068、-2.907、-2.468、-3.235、-2.877、-2.207、-2.430、-3.215、-3.406、-2.339、-2.069、-3.120, P 均＜0.050）；乳腺癌组血清氨基酸 Arg 表达水平低于正常组（t=3.050, P=0.003）；血清氨基酸 Ala、Pro 单独诊断乳腺癌的效能较高，受试者工作特征曲线 (receiver operating characteristic curve, ROC)下面积 (Area Under Curve, AUC)均为 0.75；Ile 单独诊断乳腺癌时有最高的灵敏度，达 0.82；Lys 单独诊断乳腺癌时有最高特异度，达 0.94；当 14 种差异表达氨基酸联合检测时能够提高乳腺癌患者的诊断效能，AUC 为 0.88，灵敏度为 0.69，特异度为 0.94；20 种血清氨基酸在乳腺癌各分子亚型中表达无差异（P 均＞0.050）；早期乳腺癌患者血清氨基酸 Val 表达水平高于晚期患者（t=2.086, P=0.044），而其他血清氨基酸表达水平在早、晚期乳腺患者中表达水平无差异（P 均＞0.050）。

结论 血清氨基酸在乳腺癌与正常人中表达水平存在差异，可用于乳腺癌的诊断，其联合检测有利于提高乳腺癌诊断效能，是非常有潜力的生物标志物。

566. 循环肿瘤细胞快速检测新策略-表面增强拉曼光谱

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目的 循环肿瘤细胞（CTC）是从肿瘤组织脱落到血管中的癌细胞，在血液中循环并侵入其他器官，从而导致致命的转移。外周血中的循环肿瘤细胞是大多数癌症患者死亡的主要原因。循环肿瘤细胞的快速检测非常重要，在癌症的早期诊断，评价个体化治疗效果，体内耐药性测试，肿瘤复发检测和生存时间判断等具有重大的科学意义和临床应用价值。

方法 表面增强拉曼光谱（SERS）的检测技术具有以下特点：超高检测灵敏度，无损检测，无标记检测，快速光谱响应和分子指纹图谱，使其在检测领域具有巨大潜力。在过去的十年中，由于其独特的检测优势，用作生物探针的 SERS 技术已越来越多地应用于生物成分的检测和分析。

结果 本文中，我们介绍以贵金属为基础构建的高灵敏度 SERS 生物传感检测探针，以及用于循环肿瘤细胞快速检测的的最新方法，并就高性能 SERS 生物探针的设计方法和在 CTC 检测的应用提供了独特的见解，检测灵敏度可以达到单细胞水平，检测特异性可以达到 1/10000 细胞。

结论 我们着重介绍了不同形貌和种类贵金属 SERS 生物探针的检测 CTC 功能，其对目标分子的超高灵敏度检测将成为独特的优势。高性能 SERS 生物探针的制备，能够在有效应用于外周血样的不同癌种循环肿瘤细胞检测，也为 SERS 技术在液体活检中的新应用铺平了道路。

567. Identification and development of immune genes-based prognostic signature and TFs-immune genes network in breast cancer

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Objective Aim: To identify the significant immune genes in the prognosis prediction of breast cancer (BRCA) patients.

Methods Methods: We used bioinformatic analysis methods to screen differentially expressed genes (DEGs) in BRCA using high-throughput RNA-seq data of BRCA patients from The Cancer Genome Atlas (TCGA). The univariate Cox regression analysis was used to screen immune-related DEGs, which correlated with the overall survival (OS) of BRCA patients. The genes list of immune-related genes and transcription regulators (TF) were downloaded from the ImmPort database and the

Cistrome Cancer database, respectively. Immune-related DEGs (IRDEGs) and tumor-related transcription factors in DEGs (TFDEGs) were gene overlap between the above gene list and DEGs. We established the regulation network between the TFDEGs and PIRDEGs using protein interaction network analysis. A risk score model was built using the formula: Risk Score. N is the number of the IRDEGs; Expi is the expression value of each IRDEG, and Coei is the estimated regression coefficient of each IRDEG derived from the multivariable Cox regression analysis. Risk scores of BRCA patients calculated using this model were applied to analyze the prognosis prediction value.

Results Results: We discovered 4,575 DEGs, 366 IRDEGs, and 80 TFDEGs using high-throughput RNA-seq data of BRCA patients from TCGA. The univariate Cox regression analysis showed that 55 IRDEGs correlated with the overall survival (OS) of BRCA patients. We established the regulation network between the TFDEGs and PIRDEGs. A prognostic risk model containing eleven-PIRDEGs signatures (PSME2, ULBP2, MMP9, IGHE, FGF7, SCG2, TSLP, NPR3, SDC1, SSTR1, and TRDV1) was funded using the multivariate Cox analysis. Risk scores of BRCA patients calculated using this model showed a high accuracy on prognosis prediction (area under the receiver operating characteristics curve /AUC of ROC value: 0.746) and can be an independent prognosis factor of BRCA patients ($p<0.001$). The risk scores also correlated with the abundance of four types of immune cells in BRCA patients (B-cells: $p=0.037$; CD4+T cells: $p=0.026$; CD8+8 T cells: $p=0.007$; Neutrophil: $p=0.020$).

Conclusions Conclusion: Our study revealed that the eleven-IRDEGs signature could be a candidate prognostic biomarker for predicting the OS of patients with BRCA.

568.肝癌差异表达长链非编码 RNA 的筛选及临床诊断价值初探

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目的 基于癌症基因组图谱（TCGA）的肝细胞癌（LIHC）队列分析，筛选肝癌特异性 lncRNA，并在 HCC 癌组织及血清样本中验证所筛选出的 lncRNA 的临床诊断价值，为临床工作提供有力的支持。

方法 获得数据库 369 例 HCC-lncRNA 表达谱，构建风险评分模型，ROC 曲线评估模型的准确性，Kaplan-Meier 法绘制差异表达 lncRNA 的生存曲线，卡方检验分析 lncRNA 表达与年龄、性别、AJCC 肿瘤病理分期、肿瘤分期等的相关性。选取 30 例 HCC 癌和癌旁组织，35 例 HCC 患者血清及 30 例正常人血清，利用 qRT-PCR 验证上步筛选的差异 lncRNA 在肝癌中的表达水

平，ROC 曲线分析其诊断价值，统计分析 lncRNA 的表达与肝癌的临床、组织学和病理学特征的关系。

结果 筛选得到 3 个差异性表达的 lncRNAs（SREBF2-AS1、AL031985.3、TMCC1-AS1）；构建了 3-lncRNAs 的风险评估模型，该模型有助于预测个体死亡风险并确定高死亡率风险的患者；SREBF2-AS1、AL031985.3 在肝癌组织中表达明显上调，差异显著（$p<0.05$）；ROC 曲线显示，二者的诊断效能较高。SREBF2-AS1、AL031985.3 在肝癌血清与健康对照组血清无差异，不具备血清学生物学标志物的潜能。

结论 SREBF2-AS1、AL031985.3 在肝癌组织中高表达，提示参与了肝癌的发生和发展，其表达模式可作为肝脏部分切除的 HCC 患者的诊断分子标志物。

569. 游离前列腺特异性抗原第 2 次国际标准品协作标定

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目的 参与游离前列腺特异性抗原（free Prostate Specific Antigen，free PSA）第 2 次国际候选标准品（批号 17/102）协作标定，为 WHO 评估其作为国际标准品的适用性提供数据支持。

方法 按照 WHO 研究方案，采用多种化学发光法、酶联免疫荧光法、流式荧光发光法和时间分辨免疫荧光法标定 free PSA 第 2 次国际候选标准品（批号 17/102）。

果 本实验室上报数据：free PSA 第 2 次国际候选标准品（批号 17/102）免疫效价的几何均值为 0.547 μg•安瓿$^{-1}$（95 %置信区间 0.480 μg•安瓿$^{-1}$ ~ 0.624 μg•安瓿$^{-1}$，n=10，GCV 20.1 %），与 WHO 报告数据相对偏差为 0.4 %。全球 8 个国家 10 个实验室提交了数据。经标定，free PSA 第 2 次国际候选标准品（批号 17/102）的免疫效价几何均值为 0.545 μg•安瓿$^{-1}$（95 %置信区间 0.508 μg•安瓿$^{-1}$~ 0.586 μg•安瓿$^{-1}$，n=21，GCV 17.0 %），稳健均值为 0.533 μg•安瓿$^{-1}$；且稳定性和均匀性满足要求。

结论 经 WHO 生物标准专家委员会审核通过，最终确定 free PSA 候选国际标准品（批号 17/102）可作为第 2 次 free PSA 国际标准品使用，每安瓿效价定为 0.53 μg。

570. Spatial Distribution of TILs in Tumor Micronenvironment and Prognosis of Patients with Gastric Cancer

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Objective Tumor-infiltrating lymphocytes (TILs), the adaptive immune response of the host to cancer cell and valuable prognostic factors in gastric c ancer (GC), are difficult to characterize due to their

heterogeneity in routine clinical workflow. Multiple approaches, including assessing the density and location of TILs mannually, drawing TILs map structure by deep-learning, have been used to elucidate this issue and achieved promising findings. However, due the limitation of most of these methods, the frequency of spatial distribution of TILs remains far more to be explored.

Methods Here we systemically demonstrate the relationship between TILs heterogeneity and tumor context by immunohistochemistry on consecutive slides of 102 humanGC cases and multipleximmunohistochemistry of 10 selected GC cases. Using distinct statastic algorithms, we report the frequency of TILs distribtuion and the density of TILs, further established the ImmunoScore and APClusters of TILs mapping structure of GC.

Results These models refect the heterogeneity and polarization of TILs in whole slide image of GC. High density of CD8+ TILs within the tumor or invasive margin is associated with improved patients' survival. High ImmunoScore and Intensive TILs cluster, derived from the density and spatial distribution of TILs, are associated with improved clinical outcome of GC patients. The density and spatial distribution of intramacular TILs are correlated with GC patient's prognosis.

Conclusions Our resutls showed that Tils, especially the CD8+ in gastric cancer could be a effictive tools to predict the patients' overall survival.

571. 肺原发上皮样血管肉瘤临床病理分析并文献复习

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目的 探讨肺上皮样血管肉瘤（Epithelioid Angiosarcoma, EA）的临床病理特征。

方法 报道 1 例肺原发上皮样血管肉瘤，分析其临床病理特征、免疫表型及鉴别诊断，并进行文献复习。

结果 患者为 54 岁男性，主因咳嗽半年，痰中带血 1 周入院治疗。CT 显示患者右肺门增大，可见不规则软组织密度影，长径约 7.6cm，边缘清楚，增强扫描不均匀强化，病变阻塞右肺上叶支气管，肿物边缘可见多发结节样影。术中见肿瘤位于右肺门，呈冰冻状态，与周围胸膜中度粘连，分离粘连后，见肿物侵及右上纵隔，约 5cm×4cm×3cm，质硬，活动度差，向上侵及上腔静脉，下界与奇静脉弓上缘关系密切，其后与支气管关系密切，分离困难，予以切除部分肿物送检。大体所见肿物切面灰黄灰红质软，部分区域可见出血。病理组织学形态显示瘤细胞具有上皮样细胞的形态学特征，核大，空泡状，核仁突出，异型性明显。部分区域可见分支状血管性腔隙，有大片的坏死出血区。免疫组化显示肿瘤细胞 Vimentin、CD31 和 CD34 弥漫阳性，AE1/AE3、ERG、Fli-1、FVIII-R-Ag 部分阳性，Ki67 增殖指数为 70%。最终诊断为肺上皮样血管肉瘤。

结论 肺上皮样血管肉瘤是一种形态特殊且罕见的血管源性恶性肿瘤，具有软组织上皮样血管肉瘤的特点，是血管肉瘤的一种特殊类型，需通过组织学形态结合免疫组化做出诊断。鉴别诊断主要包括未分化癌、无色素性恶性黑色素瘤、上皮样肉瘤和肉瘤样癌等。

572. 儿童胃肠间质瘤 1 例报告

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目的 胃肠间质瘤（gastrointestinal stromal tumor，GIST）是最常见的原发性间叶源性肿瘤，具有侵袭性特点，最常见的转移部位是肝脏和腹膜表面，在儿童中比较罕见。探讨儿童 GIST 的诊断及治疗方法。

方法 对 1 例 11 岁女童胃肠间质瘤进行探讨，该患者无明显诱因出现上腹部持续疼痛间断加重，随后对其临床表现、诊断性检查方法、病理标本及最后结果进行了回顾。

结果 计算机断层扫描（computed tomography，CT）扫描显示在胃体远端胃后壁黏膜下可见大小约 7.6cm×4.5cm×7.7cm 的椭圆形软组织肿块影。病理诊断确诊为胃肠间质瘤，形态学上可见梭形细胞、上皮样细胞及混合细胞 3 中细胞类型，免疫组化结果显示 CD117 和 DOG-1 阳性，并行基因检测，提示呈野生型突变，即既不含有 C-kit 也不存在 PDGFRA 基因活化突变。2018 年于我院进行手术切除，之后给予了伊马替尼治疗，随访 18 个月，目前无复发转移。

结论 儿童 GIST 比较罕见，但近年来有所增加，目前主要以手术治疗为主，但因相关研究及报道较为少见，所以对儿童 GIST 术后靶向治疗及预后尚需进一步研究。

573. 黑色素瘤进行 PD-L1 染色时最佳脱色素法的探索

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目的 探索黑色素瘤进行 PD-L1 染色时所需的最佳脱色素法。

方法 选取河北医科大学第四医院诊断为恶性黑色素瘤的手术标本 6 例，使用 Ventana 染色平台和 Dako 染色平台分别进行 PD-L1（SP263）和 PD-L1（22C3）的染色。在染色前后分别用 0.5％高锰酸钾处理 3 min、5 min、10 min，然后用 1％的草酸漂白处理 1～3 min。

结果 在免疫组化染色后使用高锰酸钾脱色素的切片，不同程度的出现了 DAB 染色减弱的情况，无法进行判读。而在染色前脱色素的切片中：高锰酸钾处理 3 min 时，标本小，黑色素少的组织基本祛除，而标本大，黑色素多的组织无法完全除净；高锰酸钾处理超过 10 min 时，一些切片由于抗原丢失，很难进行判读；而高锰酸钾处理 5min，草酸 3min 时，效果较好，组织抗原在一定的耐受空间内不会过多的丢失，对病理诊断很有帮助。

结论 在含有黑色素的肿瘤中，大量浓密的色素颗粒遮 盖了肿瘤的组织结构，在免疫组化染色中，棕色部位是抗原表达还是黑色素沉积很难区别，对诊断造成障碍。因此，如何更好地脱去黑色素颗粒，一直是病理工作者共同探索的问题。高锰酸钾和草酸是最常使用的方法，但是其浓度和时间一直是大家争论的焦点。选择时要依据组织切片和抗体的不同情况，选择最佳的方案。

574. An optimized integrin α6 targeted peptide for positron emission tomography/magnetic resonance imaging of pancreatic cancer and its precancerous lesion

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Objective Pancreatic ductal adenocarcinoma (PDAC) is one of the solid tumors with the poorest prognosis because most of cases are at advanced stages by the time of diagnosis. There is a need for the development of better early diagnostic methods to improve PDAC patient survival.

Methods Previously, we have identified an integrin α6-targeted and tumor specific homing peptide CRWYDENAC (RWY) that has been employed for tumor targeted imaging and nanotherapeutics. Here, we demonstrated that integrin α6 could be used as biomarker for PDAC as it was overexpressed in PDAC and was associated with poor prognosis of the patients. We then optimized an integrin α6-targeted CRWYDANAC (S5) peptide based on RWY peptide by using the alanine scan mutation strategy, and translated S5 peptide into a tracer ^{18}F-S5 for positron emission tomography/magnetic resonance (PET/MR) imaging of PDAC lesions in three kinds of PDAC mouse models and in the precancerous lesion pancreatic intraepithelial neoplasia (PanIN) mouse model as well.

Results ^{18}F-S5 produced high PET signals in subcutaneous PDAC tumor tissues that were reduced by the blocking study by using the nonradiolabeled S5 peptide. Moreover, ^{18}F-S5 produced high PET signals in both orthotopic PDAC tumor tissues and genetically engineered PDAC tumor tissues with tumor-to-background ratios of 3.48 ± 0.62 and 4.32 ± 0.65, respectively. Additionally, ^{18}F-S5 could detected metastatic PDAC tumors as well. Importantly, ^{18}F-S5 PET/MR imaging enabled to visualize PanIN tissues with PanIN-to-background ratios of 3.35 ± 0.43.

Conclusions These findings highlight the potentiation of this integrin α6-targeted PET tracer ^{18}F-S5 for the early detection of PDAC.

575. 周围型小肺癌的 MRI 诊断价值研究

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目的 本研究旨在探讨周围型小肺癌（small peripheral lung cancer, SPLC）的 MRI 特点及诊断价值。

方法 收集 20 例经病理证实的 SPLC 患者的临床及 MRI 资料，所有患者均行 MRI 平扫、多期增强扫描及 DWI 检查，并对病灶的部位、大小、形态、信号特点及强化特征等进行统计分析。

结果 20 例 SPLC 中，男 13 例，女 7 例，年龄 28~72 岁，平均（57.65±11.43）岁。主要 MRI 表现为：①部位：病灶均表现为孤立性肺结节，位于尖后段 12 例，位于背段 4 例，位于前段、外侧基底段、内侧基底段、后基底段各 1 例。②大小：直径 0.9~2.8 cm，平均（1.96±0.55）cm。③伴随征象：出现毛刺征、分叶征、血管集束征及胸膜凹陷征分别为 8 例(40%)、7 例(35%)、13 例(65%)及 11 例(55%)，2 例(10%)见空洞，洞壁不光整。④平扫信号特点：15 例(75%)T1WI 呈稍低信号、5 例(25%)呈等信号，T1WI 信号值为（205.52±35.45）；12 例(60%)T2WI 呈高信号、7 例(35%)呈等信号、1 例(5%)呈外高内低信号，T2WI 信号值为（303.98±52.41）；15 例(75%)DWI 呈高信号、5 例(25%)呈等信号，ADC 值为（1.141±0.150）$\times 10^{-3}$mm/s^2。⑤强化特点：呈不均匀强化、均匀强化及环形强化分别为 13 例、5 例及 2 例，呈中重度强化，强化峰值及强化增值分别为（428.11±72.95）、（224.63±47.66）。

结论 MRI 形态学改变、信号值及强化特点有助于 SPLC 的诊断。

576. 原发鼻腔鼻窦少见恶性肿瘤的 18F-FDG PET/CT 表现（附 17 例报告）

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目的 探讨原发鼻腔鼻窦少见恶性肿瘤的 ^{18}F-FDG PET/CT 表现，以提高诊断准确率和认识。

方法 回顾性分析 17 例经病理证实的原发鼻腔鼻窦少见恶性肿瘤患者的临床及 ^{18}F-FDG PET/CT 资料，观察病灶部位、范围、密度特点、周围骨质破坏、邻近组织结构侵犯、远处转移及 SUVmax 等特征。

结果 17 例中，男性 10 例，女性 7 例，年龄范围 6～79 岁，平均年龄（52.76±21.41）岁。包括 NK/T 细胞淋巴瘤 9 例，Burkitt 淋巴瘤、浆细胞瘤及黑色素瘤各 2 例，软骨肉瘤及低度恶性肌纤维母细胞肉瘤各 1 例。CT 平扫显示形态欠规整，边界清楚或不清楚，位于鼻腔 6 例，主要

累及中下鼻甲，沿鼻甲形状蔓延生长，位于鼻窦 2 例，以上颌窦最明显，沿壁生长而中央残留气腔，同时累及鼻腔、鼻窦者 9 例，其中累及鼻前庭（及/或皮肤）5 例，累及鼻咽 3 例。呈软组织密度影，12 例密度均匀，5 例密度不均匀，其中 1 例见大量钙化、骨化影。11 例发生于单侧，6 例发生于双侧。3 例见溶骨性骨质破坏，1 例见膨胀性骨质破坏，3 例骨质吸收、变形。1 例淋巴结转移，2 例远处脏器受侵。PET/CT 检查示 SUVmax3.5～23.9，平均 SUVmax（11.89±4.19）；5 例不均匀放射性摄取，12 例均匀放射性摄取；1 例轻度摄取（SUVmax0～5），2 例中度摄取（SUVmax5～10），14 例明显摄取（SUVmax＞10）。

结论 原发鼻腔鼻窦少见恶性肿瘤的 PET/CT 表现呈高摄取，PET/CT 能够显示病灶部位、邻近重要结构的侵犯、周围骨质破坏及远处转移等情况，但明确诊断需依靠病理活检。

577. Heterochronous double primary tumors of dermatofibrosarcoma protuberans and gastric cancer: a case report and literature review

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Objective This paper reports a case of double primary tumors: dermatofibrosarcoma protuberans and gastric cancer, and reviews the related literature.

Methods The patient was a 72 years'old man. On January 27, 2016, he found a tumor on his left upper arm,the postoperative examination showed: solitary fibrous tumor. Liao Songlin, Professor of Beijing Medical University, considered the diagnosis of malignant peripheral neurilemmoma of left upper arm muscle. The immunohistochemical phenotypes were SMA +, vimentin +, desmin (-), S-100 (focal+), p53 (-), bcl-2 (+), CD68 (focal+), HMB-45 (-), PCK (-), CD99 (+ -), Ki-67 positive rate was 3%. Stage pt2bn0m0, stage IIB, postoperative radiotherapy and chemotherapy were not performed, and no tumor recurrence and metastasis were found in regular reexamination.In 2018, the patient palpated a package of blocks again at the original operation site, about 2cm * 2cm in size, accompanied by pain and discomfort. Ultrasound showed that the left upper arm muscle layer was hypoechoic, considering solid space occupying; MRI of the left upper arm showed that the abnormal signal of the mass outside the middle and lower segment of the left triceps brachii was abnormal; on March 19, 2018, under general anesthesia, the "enlarged resection and biopsy of the left upper arm tumor" was performed, and the postoperative examination was as follows: (mass of the left upper arm) fusiform Considering nodular fasciitis, immunohistochemistry was used to detect CD34 +, desmin (0), SMA (0), CK (0), S-100 (0), EMA (0), CD68 (+, bcl-2 (0), CD99 (+, vimentin (+), Ki-67 (+, about 2%), which supported the above pathological diagnosis. After the operation, the tissue was sent to the West China pathology department for consultation, which showed that: sarcoma (pleomorphic

sarcoma), combined with the history, it was considered as dermatofibrosarcoma protuberans with fibrosarcoma transformation; immunohistochemistry: CD34 (+), CD99 (-), STAT-6 (-), DES (-), SMA (-), MIB-1 (+, 10%), S100 (-), MSA (-), myo D1 (-), CD57 (-), Cr (-), EMA (-), CD10 (-) 。radiotherapy was carried out, using electronic wire irradiation, with an area of 9 * 13cm, a depth of 3.0cm, an energy of 9MeV, and a DT of 5000cgy / 25F / 200cgy / F. No tumor recurrence was found after radiotherapy.In May 2019, the patient suffered from loss of appetite, poor spirit, anorexia of oil, accompanied by middle and upper abdominal distention and pain. NRS score was 1-2 points. CT showed that the liver had multiple metastatic tumors. Color Doppler ultrasound: lymph nodes were found in both sides of the neck, and the structure was unclear; limb MRI: a few chordal shadows in the soft tissue of the middle part of the upper arm of the left upper limb and the adjacent skin, considering the changes after the operation. Tumor markers: NSE: 29.89ng/ml, AFP: more than 1210.00ng/ml, CEA: 38.49ng/ml.PET / CT findings (Figure 1, figure 2): no tumor recurrence was found in the operation area of the left upper arm; uneven thickening of the gastric wall in the antrum area with increased FDG uptake suggested malignant lesions (antrum cancer), please combine with pathology; diffuse lesions of the liver, multiple lymph node metastasis in the omentum around the antrum area, the root of the mesentery, and the space between the portal cavity; no definite metastasis was found in the rest of the body; upper and lower lobes of the right lung The FDG uptake was not increased in the scattered dense nodules (2 nodules), suggesting that the lesions were mostly chronic infectious lesions (induration). Gastroscope showed that a huge ulcerative new organism could be seen in the great bend of the anterior wall. The body of the new organism could still pass through. The surface of the new organism was covered with turbid moss, and it was eroded and bleeding. The surrounding mucosa was rough. Gastroscope biopsy showed that: (gastric antrum) a few heteromorphic glands were found and adenocarcinoma was inclined. Liver biopsy showed adenocarcinoma, immunohistochemistry: CK (+), CEA (+), EMA (-), PSA (-), AFP (-), CK7 (-), VIM (-), CD68 (-), CD34 (-), S100 (-), SMA (-), Ki-67 (+, about 20%). Diagnosis: gastric adenocarcinoma with liver metastasis (ctxnxm1, IVB stage),given liver protection treatment, family members and patients strongly demand chemotherapy, one cycle of Sox chemotherapy (oxaliplatin 200mg + tegio 60mg bid d1-d14), after chemotherapy, the patients' liver function further fails, jaundice appears, tumor markers are: NSE: 136.50ng/ml, CA199: 197.60u/ml, CA153: 22.40u/ml, CA125: 246.70u/ml, AFP: large At 1210.00ng/ml, CEA: 99.39ng/ml. Blood biochemistry: alkaline phosphatase: 763u / L, alanine aminotransferase: 108u / L, aspartate aminotransferase: 883u / L, direct bilirubin: 133.2 μ mol / L, glutamyltranspeptidase: 1644u / L, indirect bilirubin: 31.6 μ mol / L, total bile acid: 120.2 μ mol / L, total bilirubin: 164.8 μ mol / L, uric acid: 978 μ mol / L.

Results The second day after admission, the blood pressure of the patients decreased gradually, and the patients were discharged automatically.

Conclusions For rare metastatic diseases, multidisciplinary consultation is recommended to coordinate treatment. Clinical trials, imatinib mesylate, chemotherapy, radiotherapy or resections under specific clinical conditions should be considered. The combination or single drug chemotherapy commonly used for tumors can be considered for DFSP. These drugs include adriamycin (adriamycin / ifosfamide / mesna), adriamycin, ifosfamide, epirubicin, gemcitabine, dacarbazine, adriamycin liposomes, temozolomide, vinorelbine, or pazopani. Considering the high local recurrence rate of DFSP [8], the primary focus should be followed up every 6 to 12 months and any suspicious area should be re biopsied. Although history and physical examination are rare for metastatic diseases.

578. Different classification algorithms and serum Raman spectroscopy for histologic grades classification of Colorectal Cancer

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Objective With the growth of population and changes in living habits, the number of patients with colorectal cancer is increasing rapidly around the world. In clinical practice, preoperative endoscopic biopsy can evaluate the histological grade of colorectal cancer. Traditional endoscopy only depends on observing the gross morphological changes of the tissue, which leads to poor diagnostic sensitivity. However, it depends on the pathologist's experience, knowledge, skills and many other factors and is less reproducible. Since excisions biopsy is an invasive procedure, it is difficult to track and predict postoperative pathology. Moreover, the heterogeneity of the tumor may further increase the differences between the observers and lead to a lack of correspondence between the grades observed in the biopsy and those found in the resection specimens. Raman spectroscopy (RS) was widely used in screening for the diagnosis of colorectal cancer (CRC) as a non-invasive technique. The potential of this optical technique for different kinds of disease applications has been proved. The histopathological grades classification is vital for the treatment and prognosis of colorectal cancer. In this study, Raman spectroscopy (RS) combined with multivariate statistical analysis was used to research the spectral characteristics of blood serum for histopathological grades classification.

Methods According to World Health Organization histologic grading system, serum samples from 128 colorectal cancer patients were collected in different histologic grades. Linear discriminant analysis (LDA) and support vector machine (SVM) were used with principal component analysis (PCA) to classify the samples and the classifications were validated by leave-one-out-cross-validation

(LOOCV). Firstly, principal component analysis (PCA) was used to reduce the dimensionality of the original spectral data. Then, the classification methods support vector machine (SVM) and linear discriminant analysis (LDA) were used for the evaluation of classification ability.

Results Raman spectroscopy can obtain the structural characteristics and composition information of biological macromolecules in the blood. The serum Raman spectra from the CRC patients with distinct pathological conditions was similar, except that some spectral peaks had subtle differences. The difference in Raman spectra of serum samples may be due to the changes of biomolecules in serum, such as nucleic acid, protein, lipid and so on. It is difficult to distinguish the CRC patients with different pathological states directly by comparing the characteristics of Raman peaks. Multivariate statistical analysis is an ideal method to extract a large amount of significant information from Raman spectra. So that investigate the classification ability of human serum, the spectral data was analyzed by two kinds of multivariate statistical analysis. Accuracies of 82.8% and 68.0% were gained for PCA-LDA, PCA-SVM, respectively. The PCA-LDA classifier model outperformed the PCA-SVM classifier.

Conclusions In this study, the PCA-LDA diagnostic model had more stable and accurate prediction performance. The model studies suggested that protein, nucleic acid, and carotenoid variations are the main biomolecular difference markers for detecting colorectal cancer. Raman spectroscopy combined with multivariate statistical methods had a favorable potential to analyze the colorectal cancer patients in different histologic grades.

579. Study on Laboratory Diagnosis Methods and Application of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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Objective To review the current laboratory diagnostic methods of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and their advantages and disadvantages, and propose countermeasures.

Methods Sixty-six literatures on laboratory diagnostic methods of new coronaviruses published from December 2019 to April 2020 were collected for retrospective research, and the advantages and disadvantages of various methods were compared.

Methods Sixty-six literatures on laboratory diagnostic methods of new coronaviruses published from December 2019 to April 2020 were collected for retrospective research, and the advantages and disadvantages of various methods were compared.

Results The most commonly used laboratory diagnostic methods for SARS-CoV-2 currently include: (1) high-throughput sequencing (NGS) technology; (2) real-time fluorescent reverse transcription PCR (RT-PCR) detection; (3) serum Immunological tests. NGS can determine the sequence of unknown genomes, identify new strains and monitor strain mutations. However, its detection threshold and cost are high, and currently it cannot be widely used for routine clinical testing of SARS-CoV-2. Detection of viral nucleic acids by RT-PCR is the preferred method for laboratory diagnosis of SARS-CoV-2 infection. However, this method is affected by factors such as sample type, quality, experimental factors, kit performance, and patient infection cycle, and it is necessary to comprehensively analyze the accuracy of the results. Serum immunological tests, that is, IgM antibody and IgG antibody tests, can be used as a useful supplement to molecular tests. It helps to confirm the diagnosis of people who are negative for nucleic acid test but clinically suspected to be infected; and it has low detection threshold, fast speed and low cost, which is suitable for large sample screening in ordinary laboratories and primary hospitals.

Conclusion Various laboratory diagnostic technologies have played an important role in the early diagnosis, monitoring of viral mutations, monitoring of disease progression, and predicting the effect of patients with neo-coronary pneumonia. But each technology has its own advantages and disadvantages. In practical work, we need to apply various technologies flexibly, cooperate with each other, and learn from each other's strengths. Clinical laboratory personnel should also strengthen communication with clinicians and fully understand the occurrence, development, and clinical manifestations of diseases in order to provide accurate testing reports and individualized interpretation services for the clinic.

580. EB 病毒感染与 XRCC1- Arg399Gln 基因多态性在鼻咽癌发生中的交互作用研究

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目的 探讨 VCA-IgA、EA-IgA、Rta-IgG 三种抗体在鼻咽癌中的临床应用价值，评估 XRCCl-Arg399 Gln 单核苷酸多态性在鼻咽癌发病中的风险；研究 XRCCl-Arg399 Gln 单核苷酸多态性与 EB 病毒感染的交互作用。

方法 采用 ELISA 检测 2155 例未经治疗的鼻咽癌患者及 6957 例健康体检者血清中 VCA-IgA、EA-IgA、Rta-IgG 水平；采用病例对照研究，并按照性别和年龄 1∶1 配对，抽取全血基因组 DNA 进行 PCR 扩增，对扩增产物再进行酶连接检测反应扩增，最后测序分析得出 XRCC1 Arg399Gln 的基因型。

结果 VCA-IgA、EA-IgA、Rta-IgG 在鼻咽癌组中阳性率分别达 89.88%、46.59%和 63.25%；ROC 曲线分析显示，曲线下的面积 VCA-IgA>Rta-IgG >EA-IgA；危险度分析显示，VCA-IgA、EA-IgA 和 Rta-IgG 三项检测均阳性者危险度最高，其次为 VCA-IgA 和 Rta-IgG 两项阳性，三项抗体均阴性者危险度最低；VCA-IgA 抗体检测在鼻咽癌中以 41~60 岁阳性率最高（P<0.01），而 Rta-IgG 阳性率随着年龄增加而增高，另外 VCA-IgA 以非角化未分化性鳞癌阳性率最高（P<0.01）；EA-IgA 阳性率与 T 分期具呈线性相关（P<0.01），三种抗体检测阳性率分别与 N 分期、临床分期均呈线性关系（P<0.01）；EB 病毒感染能增加鼻咽癌发病风险：VCA-IgA、EA-IgA 和 Rta-IgG 抗体三项阳性时可以增加鼻咽癌风险因素，但单项 VCA-IgA 阳性是鼻咽癌发病的最强危险因素，单因素分析显示与携带 XRCC-1 Arg399Gln 的 AA 基因型相比，携带 XRCC-1 Arg399Gln 的 GG 基因型可以增鼻咽癌发病风险；XRCC-1 Arg399Gln 的 GA 基因型与 VCA-IgA 存在交互作用（OR=20.755）。

结论 三种抗体诊断价值以 VCA-IgA 最优，其次是 Rta-IgG，EA-IgA 相对较弱。鼻咽癌筛查中，以 VCA-IgA、EA-IgA 和 Rta-IgG 三项阳性危险度最高，VCA-IgA 和 Rta-IgG 两项阳性危险度次之，而三项抗体均阴性者危险度最低；XRCC-1 基因的 Arg399Gln 基因多态性能够增加患鼻咽癌的风险，且 Arg399Gln 的 GA 基因型与 EB 病毒感染具有一定的交互作用。

581. 血清降钙素原和内毒素检测在恶性肿瘤患者 PICC 置管后感染中的价值

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目的 通过检测并比较导管相关性血流感染的恶性肿瘤患者血清降钙素原（PCT）、和内毒素水平，比较两者在恶性肿瘤患者 PICC 置管后感染中的早期临床诊断价值。

方法 收集 2018 年 1 月至 2020 年 1 月于赣州市肿瘤医院就诊的 53 例疑似导管相关性血流感染的恶性肿瘤病人，其中感染组 25 例，非感染组 28 例。通过免疫荧光分析法和酶标分析法分别检测两组患者中血清降钙素原和内毒素的含量，通过受试者工作特征曲线（ROC）比较血清降钙素原和内毒素对恶性肿瘤患者 PICC 置管后感染的评估价值。应用 SPSS25.0 统计软件进行数据分析，计量资料采用均数±标准差(`x±s)表示,资料间均数比较采用独立样本 t 检验；各组间计数资料比较采用 χ^2 检验,采用受试者工作特征曲线(ROC)评价分析血清 PCT 和 ET 水平在恶性肿瘤患者 PICC 置管后感染中的价值。P＜0.05 表示差异有统计学意义。

结果 血清 PCT、ET 用于诊断恶性肿瘤患者 PICC 置管后导管相关性血流感染时，AUC 面积分别为 0.716（95% CI：0.574-0.857）和 0.703（95% CI：0.558-0.848），具有一定诊断价值。用

Logistic 回归模型预测血清 PCT 和 ET 联合检测用于诊断恶性肿瘤患者 PICC 置管后导管相关性血流感染中，AUC 面积为 0.844（95% CI：0.731-0.956），具有早期诊断价值。

结论 血清降钙素原和内毒素在 PICC 置管后发生导管相关性血流感染的恶性肿瘤患者中具有诊断价值，两者联合检测早期诊断价值更高。

582. Risk prediction of recurrence and survival after radical resection in patients with AFP-negative HCC

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Objective Currently, there is still a lack of effective biomarkers for the recurrence monitoring and survival prognosis assessment of hepatocellular carcinoma (HCC) patients with alpha-fetoprotein (AFP) negative (≤ 20 ng/ml) after radical resection.

Methods The clinicopathological data of 606 patients (303 in the AFP-negative group and 303 in the AFP-positive group) who underwent radical resection of HCC were analyzed retrospectively.

Results The GLR of patients in the AFP-negative group was lower than that in the AFP-positive group (58.36 ±51.18 vs. 95.07 ±87.11, p < 0.001). The GLR level of the early-recurrence group was higher than that of the no early-recurrence group (107.03 ±76.50 vs. 84.50 ±66.65, p = 0.003). The optimal cutoff value of GLR for postoperative prognostic monitoring in AFP-negative HCC patients was 45.0, the sensitivity and specificity were 67.9% (95% CI, 0.537-0.801) and 60.8% (95% CI, 0.544-0.669), respectively. Univariate analysis showed that tumor size < 5 cm, no microvascular, single tumor, no metastasis, BCLC stage 0 – A, no recurrence and GLR £45.0 had longer disease-free survival (DFS) and overall survival (OS) in AFP-negative HCC patients. In addition, multivariate Cox proportional hazards regression analysis showed that tumor size < 5 cm (p = 0.003), no recurrence (p < 0.001) and GLR < 45.0 (p < 0.001) were independent predictors of longer OS.

Conclusions GLR may be a potential indicator for early recurrence monitoring and prognosis evaluation in HCC patients with AFP negative after radical resection.

583. 血清及外泌体 LDH-C4 在肝癌中的表达及临床意义

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目的 目前 HCC 仍缺乏有效的标志物用于早期诊断和预后监测。LDHC 基因编码的 LDH-C4 是一类仅在睾丸的生发上皮和一些肿瘤组织中表达的 CTA 分子。然而，LDH-C4 在 HCC 中的表达及临床意义尚不明确。

方法 本研究提取肝细胞癌患者血清及血清外泌体中的总 RNA，通过透射电镜（TEM）和免疫印迹检测鉴定纯化的外泌体；qRT-PCR 检测 LDHC mRNA 在 HCC 患者血清及血清 exosome 中的表达，同时基于高通量组织芯片结合 IHC 检测 HCC 组织中 LDH-C4 蛋白的表达，分析其表达与患者临床病理特征和预后的相关性。

结果 TEM 显示，获得血清来源的 exosome 大小在 80-120 nm 之间，为具有膜结构的小囊泡，符合 exosome 的形态学特征。免疫印迹检测到 exosome 标志性蛋白 CD9 和 CD63 的表达。LDHC mRNA 在 HCC 患者血清和血清 exosome 中表达阳性率分别为 96.5%和 90.7%，明显高于对照组。Serum and exosomal LDHC 诊断 HCC 患者和健康对照者的 AUC 分别为 0.9128 和 0.8916；血清及 exosomal LDHC 表达与 HCC 患者的临床分期相关，与 AFP 的表达呈正相关。治疗组 HCC 患者血清及血清 exosome 中 LDHC 水平高于初诊组，而低于复发。IHC 结果显示，LDH-C4 蛋白主要表达于 HCC 组织细胞的胞质中，其在肝细胞癌组织中表达明显上调，高表达（++/+++）的比例占 55.84%（43/77），明显高于 LDH-C4 在癌旁组织中高表达的比率 26.32%（20/76，P<0.0001）。生存分析显示，LDH-C4 的表达与 HCC 的预后呈正相关，高表达者较低表达者更能在 OS 中获益；COX 回归显示 LDH-C4 水平是影响肝细胞癌患者预后的独立危险因素。

结论 血清及 exosomal LDHC 可作为 HCC 诊断、疗效评估及复发检测的 biomarker；LDH-C4 可作为 HCC 预后监测的一项重要参考指标。

584. GALAD 和 BALAD-2 模型在原发性肝细胞癌诊断及短期疗效评价中的临床意义研究

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目的 探讨 GALAD 模型在原发性肝细胞癌患者诊断价值以及 BALAD-2 模型在肝细胞癌短期疗效评估中的价值。

方法 收集某院 2017 年 8 月—2018 年 2 月 87 例首诊肝癌（HCC）患者、53 例肝脏良性疾病（BLD）患者、49 例表观健康体检者(HC)血清，采用微流控免疫荧光电泳技术检测血清中 AFP、AFP-L3 和 DCP 水平，建立基于性别、年龄和血清中 AFP、AFP-L3 和 DCP 水平的 GALAD 模型，分析 GALAD 模型对于肝癌患者的诊断价值；采用溴甲酚紫法检测血清中白蛋白及重氮法检测血清中胆红素水平，建立基于 ALB、BIL、AFP、AFP-L3 和 DCP 的 BALAD-2 模型，对随访资料完整的 41 例原发性肝癌患者动态观察治疗前后 BALAD-2 模型变化，分析 BALAD-2 模型与肝癌患者短期疗效的关系。

结果 GALAD 模型评分与患者的性别和年龄显著相关，差异有统计学意义,多数肝癌患者伴有乙肝病毒感染，肝硬化是肝癌的高危因素；肝癌患者血清 AFP、AFP-L3、DCP 水平以及 GALAD 模型评分均显著高于肝脏良性疾病组(P<0.05)和表观健康对照组(P<0.05)，差异均有统计学意义；GALAD 的特异性（94.3%）和准确性（60.8%）均高于 AFP（分别为 85.1%和 55.7%）、AFP-L3(分别为 71.3%和 55.0%）、DCP（分别为 85.1%和 59.1%）,特异性(95.1%)低于 AFP-L3(97.1%)和 DCP(97.1%)，高于 AFP(90.2%),研究表明，GALAD 模型诊断肝癌优于单一指标；肿瘤控制组治疗后 AFP、AFP-L3、DCP 水平以及 BALAD-2 较治疗前均显著下降（P<0.05）差异有统计学意义；肿瘤进展组 AFP、AFP-L3、DCP 和 BALAD-2 均未显著下降（P>0.05）。

结论 GALAD 模型可提高原发性肝癌的早期诊断率，BALAD-2 模型有助于肝细胞癌患者短期疗效评估。

585. 自身抗体检测在肺癌早期诊断中的价值

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目的 探讨血清自身抗体检测联合低剂量螺旋 CT 在早期肺癌筛查中的临床效果及应用价值。

法 选取 2018 年 5 月至 2019 年 12 月间在该院门诊就诊的 400 例肺癌高危人群为实验组,选取在该院体检中心查体的 420 例肺癌高危人群为对照组。实验组采用低剂量螺旋 CT 联合 7 种血清

自身抗体检测；对照组采用胸部 X 线(CXR) 筛查, 比较两组肺癌高危人群的初筛阳性率、 早期肺癌筛查的确诊率。

结果 实验组肺癌高危人群初筛阳性率 (27.3%)显著高于对照组(10.7%),差异有统计学意义($\chi2$ =36.7,P<0.01)；实验组早期肺癌筛查的确诊率(6.8%)显著高于对照组(2.1%),差异有统计学意义($\chi2$ =10.36,P<0.05)。

结论 血清自身抗体检测联合低剂量螺旋 CT 在早期肺癌筛查中效果明显,可明显提高肺癌高危人群的初筛阳性率,提高早期肺癌的确诊率,使肺癌高危人群中的肺癌患者能够得到早期诊断,并予以早期治疗,该两种方法联合筛查明显提高了早期肺癌的检出率,值得在临床推广及应用。

586. S-1 monotherapy after SOX treatment improves disease-free survival of patients with stage III gastric cancer

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Objective To summarize the effectiveness and safety of adjuvant chemotherapy with S-1 (tegafur/gimeracil/oteracil) plus oxaliplatin followed by S-1 monotherapy after D2 radical gastrectomy for gastric cancer.

Methods Retrospective analysis was conducted of data from 183 patients with Stage III gastric cancer who received D2 radical gastrectomy in our department. They were divided into Group A (receiving the regimen: SOX→S) and Group B (receiving the SOX regimen). The clinical effectiveness and adverse reactions of the regimens as adjuvant chemotherapy in the two groups were analyzed.

Results The 1-, 3- and 5- year DFS rates of patients in Group A were all higher than those in Group B, and the intergroup differences regarding the 1- and 3- year DFS rates (83.3% & 49% in Group A vs. 60.9% & 34.5% in Group B) were statistically significant (P<0.05); the 1-, 3- and 5- year OS rates (85.4%, 56.3% and 29.2%) of patients in Group A were all slightly higher than those (79.3%, 52.9% and 26.4%) in Group B, but all their differences were not statistically significant (P>0.05). Kaplan-Meier survival curve was drawn for analysis. The DFS of patients in Group A was (38.2 ± 3.871) months, and the DFS of patients in Group B was (31.2 ± 3.436) months. Their difference was statistically significant (P<0.05). The OS of patients in Group A was (43.9 ± 2.38) months, and the OS of patients in Group B was (43.1 ± 2.8) months. Their difference was not statistically significant (P> 0.05). The most common adverse reactions in the two groups included decreased appetite, leukopenia, anemia, nausea and peripheral neurotoxicity. The intergroup difference regarding adverse reactions was not statistically significant (P> 0.05).

Conclusions Compared with the SOX regimen alone, the SOX regimen followed by S-1 as adjuvant chemotherapy for 1 year after D2 radical gastrectomy for Stage III gastric cancer was able to

significantly improve the 1- and 3- year DFS rates and prolong DFS without affecting OS. In addition, it did not increase adverse reactions related to chemotherapy and thus had good tolerability.

587. Retrospective analysis of first-line progression free survival compared endocrine therapy and chemotherapy in patients with HR+/HER2- metastatic breast cancer

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Objective Endocrine therapy is preferred recommendation by clinical guidelines in premenopausal as well as postmenopausal women with hormone receptor(HR)-positive, HER2-negative metastatic breast cancer (MBC). However, in real-world clinical practice, chemotherapy was treated in the first-line in HR+/HER2- MBC, in particular aggressive tumor behavior and younger age. The aim of this retrospective study is to assess the clinical anti-tumor activity of endocrine therapy versus chemotherapy as first-line in HR+/HER2- MBC patients.

Methods This is a retrospective study of the first-line endocrine therapy compared with chemotherapy for hormone receptor-positive and HER2-negative MBC. 544 female patients were enrolled from Jan 2000 to Dec 2018 in Liaoning Cancer Hospital & Institute. The patients were hierarchical categoried as three cohorts: Only Endocrine Cohort (n=329), Only Chemotherapy cohort (n=159) and Sequential therapy of chemotherapy followed by endocrine therapy (n=56). Primary endpoint was Progression-Free Survival (PFS).

Results Among 544 patients enrolled, Median ages were 56, 51 and 53 in Only Endocrine Cohort (n=329), Only Chemotherapy cohort (n=159) and Sequential therapy (n=56), respectively. The proportion of premenopause was found equally in three arms (30%). 35.0%, 64.2% and 42.9% of patients had visceral metastases in only Endocrine cohort, only Chemotherapy and Sequential therapy. Median estimated PFS was superior in only endocrine cohort and sequential therapy than in only chemotherapy arm [19.0 months (95% CI: 16.4~21.6), 20.0 months (95% CI: 13.2~26.8) vs. 11.3 months (95% CI: 7.0~14.0), p = 0.000028 by log-rank (Mantel-Cox)]. Approximately 70% of the patients were post-menopause in the advanced setting (77.2% for only Endocrine, 68.6% for only Chemotherapy vs. 67.9% for Sequential therapy). In post-menopause, median PFS was longer in only Endocrine [20.0 months (95% CI: 8.3~15.7)] and Sequential therapy [20.0 months (95% CI: 12.8~27.2)] than that in only Chemotherapy cohort [12.0 months (95% CI: 13.2~26.8)]. The superior in PFS was similar in pre-menopause cohort [15.0 months (95% CI: 6.0~24.0), 20.0 months (95% CI: 11.1~28.9) vs. 7.0 months (95% CI: 4.3~9.7). Grade III or more hematologic toxicities were more

common in only Chemotherapy and Sequential therapy than in only Endocrine therapy (67.2%, 64.3% vs. 25.8%).

Conclusions Endocrine therapy and Sequential therapy chemotherapy followed by endocrine therapy showed superior clinical benefit in terms of PFS compared with only chemotherapy as first-line in patients with HR+/HER2- MBC.

588. 白蛋白结合型紫杉醇治疗晚期乳腺癌疗效及血清氨基酸标志物预测分析

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目的 本研究探讨晚期乳腺癌患者接受含白蛋白结合型紫杉醇方案的疗效，以及血清色氨酸和肌氨酸等 10 种氨基酸的变化，预测其指导晚期乳腺癌白蛋白结合型紫杉醇敏感性的价值。

方法 选取 2016-03-01—2018-11-30 辽宁省肿瘤医院一线应用含白蛋白结合型紫杉醇的晚期乳腺癌患者 55 例。LC-MS/MS 检测 10 种血清氨基酸（色氨酸和丙氨酸等）的含量水平及临床疗效相关性。

结果 55 例晚期乳腺癌患者应用含白蛋白结合型紫杉醇方案客观缓解率为 20.0%（11/55），疾病控制率为 78.2%（43/55）。基于 LC-MS/MS 测定基线血清氨基酸预测疗效结果显示，与 PR 病例的色氨酸（平均值为 4.67±1.31）相比，PD 患者的基线色氨酸相对含量（平均值为 9.32±1.72）较高，P=0.091。PD 患者的基线 L-丝氨酸（平均值为 1.39±0.18）和 L-瓜氨酸相对含量（平均值为 0.52±0.11）分别高于 PR 患者（L-丝氨酸 0.55±0.18，P=0.003；L-瓜氨酸 0.22±0.05，P=0.099）；色氨酸与疗效相关系数为 0.393。L-丝氨酸（PR 组为 0.55±0.18，SD 组为 0.75±0.12，PD 组为，W=11.616，P=0.003）和 L-瓜氨酸（PR 组为 0.22±0.05，SD 组为 0.30±0.05，PD 组为 0.52±0.11，W=4.616，P=0.099）提示效应与色氨酸相似。色氨酸，L-丝氨酸和 L-瓜氨酸可以作为区分白蛋白结合型紫杉醇疗效（鉴别快速 PD）的主要标志物。基于 P<0.10 且相对含量高，色氨酸的预测疗效进一步行亚组分析，结果显示在年轻、绝经前、ER 阳性和 Ki-67 阳性基线色氨酸预测快速 PD 效能更好。

结论 白蛋白结合型紫杉醇在晚期乳腺癌患者的疗效肯定，基线血清色氨酸联合丝氨酸和瓜氨酸具有一定的预测白蛋白结合型紫杉醇疗效（鉴别快速 PD）价值，色氨酸预测疗效在年轻、绝经前、ER 阳性和 Ki-67 阳性患者效能更好。色氨酸、丝氨酸和瓜氨酸作为生物标志物有助于优化晚期乳腺癌的患者治疗策略。

589. Utidelone plus capecitabine versus capecitabine for heavily pretreated metastatic breast cancer and Peripheral Neuropathy: Analysis of a single centre cohort

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Objective In BG01-1323L trial, utidelone, a novel genetically engineered epothilone analogue, combined with capecitabine improved progression-free survival and overall survival in heavily pretreated metastatic breast cancer prior to anthracycline and taxane. Chemotherapy-induced peripheral neurotoxicity (CIPN) was the most common dose-limiting toxicity of utidelone plus capecitabine. This study aimed to assess the efficacy of utidelone plus capecitabine in our centre and predictive role of mutations for CIPN, further to identify whether Ganglioside monosialic acid (GM1) improved CIPN.

Methods Fifty-five eligible female patients with metastatic breast cancer refractory to anthracycline and taxane were enrolled in our single centre in Phase 3 BG01-1323L trial. We randomly assigned to 39 cases in utidelone plus capecitabine and 16 cases in capecitabine alone. Progression-free survival and overall survival were assessed. Drug exposure and CIPN ratio were analyzed and SNP of enzymes and susceptible genes were detected in germline panel by NGS.

Results In our single centre, median progression-free survival in the utidelone plus capecitabine group was 238 days compared with 189 days in the capecitabine alone group, P=0.263. Median overall survival improved in combined therapy (20.9 months vs. 12.9 months, HR=0.69; 95% CI, 0.37 to 1.30; P = 0.326). The median time to the serious reported CIPN were 29 day in Grade 1, 49 day in Grade 2, 103 day in Grade 3. The median improvement time were 77 day in Grade 1, 20 day in Grade 2, 13 day in Grade 3. In combined group, 19 patients with G2 or G3 CIPN were assigned to the GM1 group and 9 patients to the control group. After intervention, the GM1 group reported demonstrated a statistically lower incidence of grade 3 CIPN [GM1 group: 1 of 19 (5.3%); Control group: 4 of 9(44.4%), P=0.026]. No associated germline SNP was found between Grade 3 and Grade 1 CIPN.

Conclusions Utidelone plus capecitabine was more efficacious compared with capecitabine alone for progression-free survival with mild toxicity except for CIPN, less grade 3 CIPN was assessed in our single centre with GM1 intervention, further investigation need to validate manageable efficacy of GM1 in CIPN in patients with utidelone plus capecitabine.

590. 中性粒细胞分泌 IL-6 通过 G3BP1 蛋白促进骨肉瘤细胞化疗耐药

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目的 本研究通过中性粒细胞与骨肉瘤细胞共培养体系，探讨中性粒细胞对骨肉瘤细胞化疗耐药的作用及其机制。

方法 提取分离骨肉瘤患者血液中的中性粒细胞并与骨肉瘤细胞 MG63 共培养，CCK8 法检测共培养后骨肉瘤细胞对顺铂和异环磷酰胺的敏感性，细胞因子抗体芯片鉴定共培养体系中可能促进骨肉瘤细胞化疗耐药的细胞因子，rhIL-6 刺激骨肉瘤细胞后检测细胞对顺铂和异环磷酰胺敏感性，TMT 蛋白质组学筛选经 rhIL-6 刺激和顺铂处理后的差异表达蛋白，生信分析并进行 western 验证。

结果 与骨肉瘤患者体内中性粒细胞共培养 48 小时后，骨肉瘤细胞对顺铂和异环磷酰胺敏感性降低，IC50 分别为 43.42 μg/mL 和 795.70 μg/mL，与共培养前的 10.56 μg/mL 和 218.71 μg/mL 相比差异显著；细胞因子抗体芯片结果显示，与骨肉瘤细胞共培养后中性粒细胞能够分泌更多的 IL-6；应用 60 ng/mL rhIL-6 刺激骨肉瘤细胞 6 h 后，9 μg/mL 顺铂作用于骨肉瘤细胞 24 h，肿瘤细胞蛋白表达较未经 rhIL-6 刺激的骨肉瘤细胞发生显著改变；结合文献及生信分析结果，我们选取差异较为显著的 FUBP1、G3BP1 和 FXR1 进行 western 初步验证，验证结果显示，G3BP1 蛋白的表达与组学结果相一致；Uniprot 数据库检索后发现，G3BP1 可对周期蛋白家族成员 CCND2 进行正向转录调控。

结论 中性粒细胞可以通过分泌 IL-6 上调 G3BP1 的表达，进而调控细胞周期蛋白促进骨肉瘤细胞化疗耐药。

591. 蟾毒灵对食管癌细胞增殖的影响及机制研究

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目的 探讨蟾毒灵对食管癌细胞增殖的影响，并初步探讨其可能分子机制。

方法 采用四甲基偶氮唑蓝 (MTT)法和乳酸脱氢酶细胞毒性检测法 (LDH Assay Kit)检测蟾毒灵对食管癌细胞株 KYSE-70 活力的影响。通过细胞克隆形成法和 EdU (5-Ethynyl-2,-deoxyuridine)细胞增殖实验研究蟾毒灵对 KYSE-70 细胞增殖的抑制作用。利用 DAPI 染色、TUNEL、流式细胞术检测蟾毒灵对 KYSE-70 细胞凋亡的影响。采用实时荧光定量 PCR 技术 (quantitative real time-PCR, qPCR)、蛋白免疫印迹 (Western blotting)法检测细胞凋亡相关因子 Bcl-2、Bax、NF-

κBp65、NF-κB p65 mRNA 和蛋白表达水平的变化。通过 JC-1 荧光探针试剂盒和 ATP 检测试剂盒研究蟾毒灵作用后对 KYSE-70 线粒体功能的影响。最后，利用裸鼠体外成瘤实验研究蟾毒灵在体内对食管癌生长的影响。

结果 MTT、LDH 实验结果表明蟾毒灵对 KYSE-70 细胞活力具有明显的抑制作用。克隆形成实验和 EdU 结果表明蟾毒灵可显著抑制 KYSE-70 细胞增殖。DAPI 染色结果显示，蟾毒灵处理后 KYSE-70 细胞的核出现染色质不均匀、浓缩、聚集、碎裂等凋亡形态。TUNEL 染色和流式细胞检测结果显示，蟾毒灵作用后可促进 KYSE-70 细胞凋亡。qPCR 和 Western blot 结果显示，蟾毒灵处理后 KYSE-70 细胞内 Bcl-2 表达下调，Bax 表达上调，Bax/Bcl-2 表达比例升高。另外，蟾毒灵作用后，KYSE-70 细胞的线粒体膜电位呈现明显的下降趋势，ATP 的生成量也显著减少。裸鼠体外成瘤实验表明，蟾毒灵能够明显抑制体内肿瘤的生长。

结论 蟾毒灵能够抑制食管癌 KYSE-70 细胞的增殖，促进食管癌细胞凋亡，并能够显著影响食管癌细胞线粒体功能。

592. 帕博利珠单抗联合安罗替尼治疗 PD-L1 阴性咽旁间隙恶性多形性腺瘤 1 例及文献复习

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目的 报道咽旁间隙肿瘤术后快速进展及复发，应用免疫治疗联合安罗替尼治疗 PD-L1 阴性咽旁间隙多形性腺瘤 1 例。

方法 患者男，49 岁，教师，2019 年 6 月无明显诱因出现牙龈疼痛，后出现右侧面部肿胀，于 2019 年 9 月 6 日入院，CT 示：口咽右侧咽旁间隙囊实性占位伴钙化。鼻咽镜示：右后鼻孔、鼻咽部肿物。于 2019 年 9 月 10 日在全麻下行气管切开+右侧颅底肿瘤切除+右侧颈淋巴结清扫+右侧颌下腺切除+右侧上颌骨次全切开+下咽肿瘤切除+下颌骨切除，术后病检提示：（右咽旁、颅底）倾向恶性多形性腺瘤（大量软骨肉瘤和骨肉瘤形成，仅见少量腺上皮），送检右颈部 8 枚淋巴结为反应性增生，未见肿瘤转移，免疫组化：SATB2(+),PCK 灶性（+），P63 灶性（+），SMA 弱（+），Desmin（-），Calponin（-），MSA(-),S-100(-),MYB(-),SSTR2(-),CD117(-),M1B1(95%,+),IDH1/IDH2 未检出第 132 和第 172 号密码子突变，PLAG-1 基因 FISH 检测：检出 PLAG-1 基因不平衡易位，支持上述诊断。

结果 术后患者出现右侧面部及右侧眼睑肿胀，伴疼痛，疼痛影响睡眠。MRI 提示：右侧颈动脉鞘区及周围不规则软组织肿块占位，范围约 8.0*5.4*7.1cm，考虑恶性肿瘤所致，病灶包绕右侧颈内动、静脉，向下侵及口咽右侧壁及咽旁间隙，向上侵及翼腭窝，翼内外肌及右侧头长

肌受侵，右侧颌面部结构紊乱并明显软组织肿胀，右侧牙龈区、右侧咬肌明显受侵。右颈动脉鞘区数枚肿大淋巴结，大者大小约 2.5*2.3cm，考虑转移。斜坡部分骨质 T2WI 呈稍高信号，转移待排。患者重度癌痛，给予芬太尼透皮贴 4.2mg q72h 止痛治疗。于 2019 年 11 月 8 日开始使用安罗替尼 12mg qd d1-d14/q3w 靶向治疗，PD-L1 检测为阴性。于 2019 年 11 月 21 日、2019 年 12 月 14 日行帕博利珠单抗 100mg 治疗。治疗后患者面部及眼睑肿胀明显消退，右侧面部包块明显缩小，疼痛好转，不需使用芬太尼透皮贴。

结论 手术切除是治疗咽旁间隙肿瘤的首选方法。对于咽旁间隙良性肿瘤，不需要进行特殊的辅助治疗，对于恶性的肿瘤，可根据病理学类型给予术后辅助放化疗。本病例为 PD-L1 阴性患者，采用免疫联合靶向治疗，有初步获益。

593. Analysis of the Clinical Efficacy of DC-CIK Cell-based Adoptive Immunotherapy for Colorectal Cancer

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Objective To analyze the efficacy and safety of dendritic cell –cytokine –induced killer (DC-CIK)immunotherapy combined with chemotherapy for colorectal cancer.

Methods A retrospective analysis was conducted in 116 patients being treated from February 2012 to December 2017, who were divided into postoperative adjuvant chemotherapy group alone and conbined DC-CIK immunotherapy group, advanced cancer palliative care group, and palliative care + DC-CIK immunotherapy group, to evaluate cellular immune function, DFS and OS.

Results In the adjuvant therapy and palliative care group, the percentages of CD3+, CD8+ and NK cells after treatment were significantly lower than before, whereas in the other two groups given DC-CIK immunotherapy, the percentages of CD3+, CD8+, NK and NKT cells after treatment were all higher than before, with a significant increase compared with the chemotherapy group($P<0.05$). DFS (42.4±5.26m) in the group receiving postoperative adjuvant chemotherapy + DC-CIK immunotherapy was significantly longer than that (23.5 ± 2.79m) in the group only given postoperative adjuvant chemotherapy($P<0.05$). OS in the group receiving palliative care + DC-CIK immunotherapy was slightly longer than that in the group only given palliative care for advanced cancer (29m vs 26m) ($P>0.05$).

Conclusions In combination with DC-CIK immunotherapy was able to effectively improve cellular immune function. Postoperative adjuvant chemotherapy in combination with DC-CIK immunotherapy was able to significantly prolong DFS, but palliative care in combination with DC-CIK immunotherapy did not significantly prolong OS in patients with advanced cancer.

594. 肿瘤缓解深度在常见实体瘤中的应用情况

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目的 近年来肿瘤的发生率和死亡率逐步升高，肿瘤的治疗方式的不断被探索和创新，原有的实体肿瘤疗效评价标准(RECIST 1.1)在应用过程中逐渐暴露出一些局限性，新的疗效评估指标也在被探索和试用。肿瘤缓解深度（Depth of response,DpR）在实体瘤中的应用范围越来越广，但是关于 DpR 在各种实体瘤中的应用结果不一，目前尚缺乏具体的总结，为梳理和总结近年来 DpR 在常见实体瘤中的应用情况进行这项调查。

方法 在中国知网检索“缓解深度”、pubmed 检索关键词”depth of response”或者“deepness of response”，以及查阅在美国临床肿瘤学会（ASCO）和欧洲医学肿瘤学会（ESMO）年度会议上提交的会议摘要，一共检索到 33 篇符合条件的文献。

结果 目前共有 33 篇文章报道了 DpR 作为实体瘤临床预后指标的作用。研究关注了 DpR 在全球三个癌症死亡率排名前三的肿瘤中的应用，即肺癌、结直肠癌、胃癌，以及在恶性黑色素瘤和胰腺癌中的应用情况。DpR 首先在结直肠癌中提出和应用，在对结直肠癌多项临床试验数据进行分析及进行回顾性研究的 15 篇报道中，确认了 DpR 在接受单纯化疗或化疗联合靶向治疗的转移性结直肠癌患者预后的预测价值。DpR 在胃癌中的研究与应用相对结肠癌较少，在现有的 4 篇报道中，根据对几项临床试验数据分析显示 DpR 在接受单纯化疗或化疗联合曲妥珠单抗治疗的胃癌患者的预后有临床指导意义。DpR 在肺癌的三种治疗方式中的预测价值并不一致，在化疗和免疫治疗中，DpR 的预测价值在目前的报道中得到了确认，但是在靶向治疗中 DpR 作为一种疗效评估指标仍然存在争议。两项关于 ALK 抑制剂的随机对照试验（RCT）数据和 EGFR-TKI 的一项回顾性研究，结果表示较高的 DpR 与较长的 PFS 显著相关，但另外两项关于 EGFR-TKI 试验的报道表示 DpR 不能有效评估患者的预后。

结论 在结直肠癌、胃癌、肺癌等多种实体瘤的疗效评价标准中，DpR 被认为能够预测患者的 PFS 和 OS，成为除了传统的临床预后变量外，可以提供预后预测价值的指标。但目前在肺癌靶向治疗中的应用价值中存在争议，期望通过在更多人群和更多肿瘤类型的前瞻性试验中进一步验证，形成一个完善的应用规

范，更好地应用于临床工作。

595. Methyltransferase METTL18 is a critical regulator for breast cancer metastasis

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Objective Lysine methylation are key players in cancer. However, the methylation of nonhistone proteins remains to be unclear.

Methods Here, we identified methyltransferase like 18 (METTL18) as a critical regulator of breast cancer, where it is highly expressed. METTL18 upregulation was associated with reduced survival in breast cancer patients. RNA sequencing analysis revealed that METTL18 knockdown is accompanied by a suppression of cell metastasis and the YAP signaling pathway. In breast cancer cell lines, METTL18 depletion inhibited metastasis both in vitro and in vivo. Furthermore, mass spectrometry analysis identified a METTL18-binding protein, smad nuclear interacting protein 1 (SNIP1). Mechanistic investigations demonstrated that SNIP1 is associated with and methylated by METTL18 at a lysine residue (K301). Furthermore, we observed that METTL18-dependent methylation of SNIP1, recruiting its co-activator lysine acetyltransferase 2A (KAT2A) to promote c-MYC binding to the promoters of c-MYC target genes, resulted in YAP transcription activation and breast cancer cell metastasis. Overexpression of YAP restored the reduced metastasis in cells owing to METTL18 or SNIP1 knockdown. Conversely, overexpression of SNIP1, but not of METTL18 methyltransferase activity-deficient mutants or SNIP1 isoforms lacking METTL18 binding sites, induced c-MYC binding to the promoters of c-MYC target genes, thereby resulting in increased YAP transcription and breast cancer metastasis.

esults Our results define a critical role for METTL18 in breast cancer metastasis and establish METTL18 as a novel target in breast cancer.

Conclusions Collectively, our data identify METTL18 as an attractive target in TNBC treatment. Furthermore, our results reveal a SNIP1/KAT2A/c-MYC/YAP signaling cascade by which METTL18 promotes TNBC metastasis. These studies provide crucial insights in furthering our understanding of METTL18 roles in TNBC.

596. 乳腺癌合并甲状腺癌患者的临床病理特征分析

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目的 通过分析乳腺癌合并甲状腺癌的临床病理特征，探讨甲状腺癌、甲状腺激素功能及甲状腺相关抗原抗体在乳腺癌发生发展的作用。

方法 回顾性分析福建省肿瘤医院 2001 年 1 月-2017 年 12 月期间收治的乳腺癌合并甲状腺癌患者 76 例（合并癌组），并随机收集同期收治的单纯乳腺癌患者（对照组）116 例，同时收集患

者治疗前甲状腺激素（T3、T4、FT3、FT4、TSH）、甲状腺自身抗原和抗体 (TG 、TPOAb、TGAb)、临床病理（TNM 分期、临床分期、淋巴转移、原发结节大小）和乳腺癌免疫组化指标（ER、PR、HER-2、Ki-67）等；通过 SPSS 25.0 软件统计分析合并癌组和对照组各临床病理和免疫组化指标，进一步探讨甲状腺癌在乳腺癌发生发展中的作用。

结果 合并癌组的淋巴受累率高于对照组（60.9% VS 37.7%），具有统计学差异（p＜0.05）；甲状腺的功能状态：合并癌组与对照组 T3（1.74 VS 1.68）和 TSH（2.19 VS 10.27）具有统计学差异（p＜0.05）；甲状腺相关抗原抗体：合并癌组与对照组 TPOAb（3.693 VS 12.3)和 TG（10.71 VS 2.77）的表达水平具有统计学差异（p＜0.05）；其它病理特征：合并癌组与对照组在 ER、PR、HER-2、Ki-67 和 TNM 分期等免疫组化和病理特征上不具有统计学意义（p＞0.05）。

结论 乳腺癌合并甲状腺癌组的淋巴受累率明显高于对照组（60.9% VS 37.7%）；同时发现乳腺癌合并甲状腺癌组 T3 和 TG 表达水平高于对照组，TSH 和 TPOAb 表达水平低于对照组，提示甲状腺癌在乳腺癌的发生发展中起作用，其机制可能与 T3 和 TG 的升高和 TSH 和 TPOAb 降低有关。

597. 雄激素受体在三阴性乳腺癌中的表达及意义

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目的 明确雄激素受体（androgen receptor, AR）在三阴性乳腺癌（triple negative breast cancer, TNBC）中的表达情况，并明确其与预后的相关性。

方法 收集 2015 年 2 月至 2016 年 8 月期间在浙江省肿瘤医院进行治疗的 191 例非晚期初治 TNBC 患者的临床病理学资料，并进行随访，明确无瘤生存期（disease-free survival, DFS）及总生存期（overall surviva, OS）。按照 AR 表达情况不同将其分成 AR 阳性 50 例和 AR 阴性 131 例。分析 AR 表达情况及与预后相关性。

结果 随访截止时间 2019 年 12 月，平均随访时间为 49.6 个月，最长随访时间 59 个月，最短随访时间 40 个月。在人口学和临床病理特征资料统计分析中，其中 AR 阳性与 AR 阴性组在细胞分级II级及III级中表达具有统计学差异（P=0.022<0.05），而在年龄、月经状态、BMI 分级、分期和 KI67 各分组之间无统计学差异（P＞0.05）。生存分析显示，AR+组病人在无 DFS 优于 AR-组,OS 无差异。

结论 通过平均 4 年的随访，研究发现,AR 阳性的 TNBC 较 AR 阴性的有更长的 DFS，OS 上两者相似，提示 AR 或许可以成为 TNBC 新的预后指标或治疗靶点。

598. 探讨 2018 ASCO/CAP HER2 检测指南对于 FISH 原可疑阳性病例判读及其预后分析

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目的 通过对比 2013 版乳腺癌 HER2 检测指南与 2018 版更新后指南的差异，探讨 IHC2+，FISH 不确定病例 HER2 的表达与临床病理特征和预后之间的关系。

方法 筛选 2014 年 10 月至 2017 年 10 月期间河北医科大学第四医院术后组织病理学诊断为浸润性乳腺癌（Invasive Breast Cancer，IBC），且术前未接受任何治疗的患者 3483 例。依据 2013 版乳腺癌 HER2 检测指南，通过行荧光原位杂交（Fluorescence in situ hybridization，FISH）检测，确定 HER2 表达为可疑的病例根据 2018 版指南确定为阴性的病例 93 例，收集患者临床病理资料并随访，进一步分析不同指南判读对患者预后生存的影响，比较两版指南的临床意义，并分析 HER2 治疗及其预后的关系。

结果 1.收集符合标准病例 3483 例，男性 11 例，女性 3472 例，年龄 20-78 岁。2013 版判读结果：HER2 阴性 2505 例，阳性 885 例，可疑 93 例。2018 版更新后指南判读结果：HER2 阴性 2601 例，阳性 882 例。其中 2013 版 HER2 检测指南判读结果中 93 例可疑患者指南更新后改为阴性。经统计学分析，两版指南判读结果存在显著差异（$P<0.05$）。2.根据 2013 版指南 FISH 结果中 HER2 信号总数/肿瘤细胞数≥4.0 且＜6.0，HER2/CEP17 比值＜2 的患者，将其判读为可疑，共 93 例。而 2018 版指南将其判读为阴性，93 例患者中行抗 HER2 治疗组 7 例（7.53%），出现复发转移 1 例（1.08%）；未行抗 HER2 治疗组 86 例（92.47%），出现复发转移 3 例（3.23%）。采用 Kaplan-Meier 法和 Log-rank 检验，差异无统计学意义（$\chi2=1.471$，$P=0.225$）。这类患者是否进行抗 HER2 治疗，差异无统计学意义（$P>0.05$）。

结论 2018 版 ASCO/CAP HER2 检测指南对可疑结果进行了重新分类，增加了阴性病例的比例，在临床实践应用中具有更好的适用性。

599. 2013 版及 2018 版 ASCO/CAP 乳腺癌 HER2 检测指南更新对比研究分析

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目的 本研究分别使用 ASCO/CAP 颁布的《2013 版乳腺癌 HER2 检测指南》及《2018 版乳腺癌 HER2 检测指南》对 HER2 结果进行判读，比较两版指南之间的差异，分析存在差异的病例在临床治疗及预后中的区别，比较版指南的适用性。

方法 筛选 2014 年 10 月至 2017 年 10 月期间河北省肿瘤医院术后组织病理学诊断为浸润性乳腺癌（Invasive Breast Cancer，IBC），且术前未接受任何治疗的患者 3483 例，收集患者临床病理资料并随访。其中 HER2 免疫组化结果为 0 或 1+（1385 例）判读为 HER2 阴性，3+（679 例）判读为 HER2 阳性，2+（1419 例）为 HER2 结果不确定，行 FISH 检测以明确其最终表达。研究 2013 版及 2018 版乳腺癌 HER2 检测指南的差异，探讨按照不同标准 HER2 结果存在差异的病例在临床治疗及预后中的区别，比较两版指南的临床意义。

结果 2013 版 HER2 检测指南判读结果中 3 例阳性（HER2 免疫组化为 2+，FISH 结果为 HER2/CEP17 比值≥2.0，HER2 信号总数/肿瘤细胞数＜4.0）及 93 例可疑（HER2 免疫组化为 2+，FISH 结果为 HER2 信号总数/肿瘤细胞数≥4.0 且＜6.0，HER2/CEP17 比值＜2）的患者指南更新后改为阴性。另外，HER2 单探针阳性（HER2/CEP 比值＜2，但 HER2 信号总数/肿瘤细胞数≥6.0）的患者虽被判读为阳性，但更新后指南认为这样的患者不适于抗 HER2 治疗。Kaplan-Meier 生存分析结果显示：HER2 结果由可疑改为阴性的 93 例患者以及 43 例 HER2 单探针阳性的患者，是否进行抗 HER2 治疗，差异无统计学意义（P＞0.05）。

结论 两版乳腺癌 HER2 检测指南判读结果存在显著差异，且更新后判读标准在临床实践中具有更好的适用性。

600. 微小染色体维持蛋白 2 在子宫内膜癌中的表达及意义

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目的 探讨 MCM2 蛋白在子宫内膜癌组织中的表达及意义。

方法 免疫组化组化学方法检测 53 例经手术切除的子宫内膜癌标本中 MCM2 蛋白的表达，统计患者术后免疫组化 ER、PR 结果，分析其表达与患者临床病理特征之间的关系及三者相关性。

结果 子宫内膜癌和正常增生期子宫内膜中该蛋白的表达无显著差异（P>0.05），而子宫内膜癌和正常增生期子宫内膜比正常分泌期子宫内膜中该蛋白的表达更广泛，染色强度也明显增加，具有显著性差异（P<0.01）。MCM2 蛋白的表达与子宫内膜癌患者病理分期、组织分级、淋巴结转移、术后 1 年随访结果相关（P<0.05），与患者年龄无关（P>0.05）。ER、PR 的表达与患者病理分期、组织分级及术后 1 年随访结果相关（P<0.05），与患者年龄、淋巴结转移无关（P>0.05）。MCM2 蛋白阳性表达子宫内膜癌组织中 ER、PR 的阳性表达率为 61.5%、57.7%，MCM2 蛋白与 ER、PR 的表达均无明显相关性（r 值分别为－0.108、－0.117，P 值分别为 0.422、0.405）。

结论 MCM2 蛋白和 ER、PR 在子宫内膜癌组织中的表达均无明显相关，但三者都与子宫内膜

癌的预后相关。检测 MCM2 蛋白和 ER、PR 可分别对子宫内膜癌进行高风险筛选及预后评估有一定意义。

601. 早期卵巢交界性肿瘤行保留生育功能手术的临床分析

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目的 探讨早期（FIGO I期）卵巢交界性肿瘤行保留生育功能手术对生育和预后的影响。

方法 回顾性收集 2009 年 10 月至 2019 年 10 月在南方医科大学附属衡阳医院和铜仁市人民医院行保留生育功能手术的 FIGO I期卵巢交界性肿瘤患者的临床资料。患者年龄为 16～39 岁，平均年龄 26.5 岁。其中浆液性卵巢交界性肿瘤（serous borderline ovarian tumor, S-BOT）18 例，黏液性卵巢交界性肿瘤（mucinous borderline ovarian tumor, M-BOT）10 例，子宫内膜样卵巢交界性肿瘤 2 例。病理检查证实为 BOTs，有强烈保留生育要求的患者及家属在知情同意下选择保留生育功能手术。保留生育功能手术定义为保留子宫及至少一部分卵巢组织，包括单侧附件切除术、一侧附件切除+对侧卵巢肿物剥除术、单侧卵巢肿物剥除术和双侧卵巢肿物剥除术。随访其生存及妊娠情况。

结果 本研究共纳入 30 例卵巢交界性肿瘤患者(Ia 期 18 例，Ic 期 12 例)。30 例均行手术治疗，开腹 24 例，腹腔镜 6 例。30 例患者中 8 例为双侧卵巢受累。保守性手术包括：单侧附件切除术 18 例(60.0%)；单侧卵巢肿物剥除术 4 例(13.3%)；双侧卵巢肿物剥除术 6 例(20.0%)；一侧附件切除+对侧卵巢肿物剥除术 2 例(6.7%)。30 例患者中，病理类型浆液性 18 例，黏液性 10 例，子宫内膜样 2 例。30 例患者术后均有月经复潮，未化疗患者月经在手术后 2～3 个月规律，手术后化疗的 6 例患者均在化疗 1～2 次后停经，在化疗结束后 2～8 个月月经恢复。计划妊娠 22 例，13 例(59.1%)自然妊娠并成功分娩，子代健康无畸形。中位随访时间 42 个月，3 例（10.0%）患者出现复发。随访结束时，所有患者均无瘤生存。

结论 对年轻有强烈生育要求的早期卵巢交界性肿瘤患者行保留生育功能手术是安全而可行的。

602. 术前炎症免疫相关指标与宫颈癌临床病理特征的关系

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目的 探讨宫颈癌患者术前炎症免疫相关指标与临床病理特征的关系，指导临床制订个性化治疗策略,特别是为不能手术的宫颈癌（放化疗、姑息治疗）患者的治疗方案提供参考。

方法 回顾性分析 2017 年 2 月至 2018 年 12 月在云南省肿瘤医院妇瘤科

经病理确诊为宫颈癌初诊行手术治疗的 210 例患者的术前炎症免疫相关指标及临床病理资料，讨论炎症免疫相关指标与宫颈癌临床病理特征的关系。

结果 术前淋巴细胞、单核细胞与宫颈癌的肿瘤大小差异有统计学意义（P＜0.05）；术前 LMR、PLR 与宫颈癌的宫颈间质浸润深度差异有统计学意义（P＜0.05）；术前 SIRI 与宫颈癌的淋巴结转移差异有统计学意义（P＜0.05）；其余各炎症免疫指标与宫颈癌各临床病理特征差异无统计学意义（P＞0.05）。

结论 术前淋巴细胞、单核细胞、LMR、PLR、SIRI 水平与宫颈癌的生物学特征具有相关性。因此建议在宫颈癌的治疗中，应结合炎症免疫相关指标，拟定风险评估方案，制订个性化治疗策略。

603. 阴道微生态与 HPV 感染及宫颈癌临床病理特征的关系

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目的 宫颈癌是常见的妇科恶性肿瘤之一，危及广大妇女身心健康。本研究探讨阴道微生态与人乳头瘤病毒(HPV)感染及宫颈癌患者各临床病理特征的关系。

方法 收集 2017 年 2 月 27 日至 2018 年 12 月 21 日在云南省肿瘤医院妇瘤科经病理确诊为宫颈癌初诊行手术治疗的 210 例患者的阴道微生态、HC2-HPV 检测结果及相关临床资料并进行分析。

结果 HPV 阴性、阳性两组患者之间的阴道微生态各指标比较，差异均无统计学意义（P＞0.05）。不同临床病理特征患者之间的小杆菌含量、 过氧化氢、G+大杆菌（乳杆菌）、球菌、白细胞酯酶、乙酰氨基葡萄糖苷酶含量、乳杆菌分级、Nugent 评分、AV 评分，均差异无统计学意义（P＞0.05）。不同临床分期患者之间白细胞含量、PH 等级、菌群密集度差异有统计学意义（P＜0.05）；不同肿瘤大小患者之间唾液酸苷酶含量差异有统计学意义（P＜0.05）；不同间质浸润深度患者之间 PH 等级差异有统计学意义（P＜0.05）；淋巴结阳性、阴性患者之间白细胞、菌群密集度、菌群多样性、优势菌等级差异有统计学意义（P＜0.05）。

结论 HPV 阴性、阳性两组患者之间的阴道微生态各指标比较，差异均无统计学意义（P＞0.05）。不同临床病理特征患者之间的小杆菌含量、 过氧化氢、G+大杆菌（乳杆菌）、球菌、白细胞酯酶、乙酰氨基葡萄糖苷酶含量、乳杆菌分级、Nugent 评分、AV 评分，均差异无统计学意义（P＞0.05）。不同临床分期患者之间白细胞含量、PH 等级、菌群密集度差异有统计学意义（P＜0.05）；不同肿瘤大小患者之间唾液酸苷酶含量差异有统计学意义（P＜0.05）；不同间质浸润深度患者之间 PH 等级差异有统计学意义（P＜0.05）；淋巴结阳性、阴性患者之间白细胞、菌群密集度、菌群多样性、优势菌等级差异有统计学意义（P＜0.05）。

604. The effect and mechanism of HPV on the malignant transformation to immortalized cervical epithelial cells mediated by Mortalin protein of tumor-derived exosomes

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Objective Tumor formation is an elaborate and complicated long-term process, influenced by many regulatory mechanisms. Clearly, for cervical cancer(CC), it is crucial for the normal cervical epithelium to acquire malignant traits and finally turn into cancer cells. As we all know, HPV and its oncogenic protein E6/E7 are the initiative factors in the development of cervical carcinoma. Yet it still remians unclear about how HPV infection facilitates malignant transformation of surrounding healthy tissues in cancer. Tumor-derived exosomes are emerging mediators to tumorigenesis. Here we explored the mechanisms and pathways that how HPV up-regulated CC-derived exosomal Mortalin to trigger malignant transformation of immortalized cervical epithelial H8 cell-line.

Methods Exosomal different protein profile was screened out by proteomics technology. The CC exosomes were characterized by TEM, western blotting and NTA. The enrichment of Mortalin, CTCF, HPV E6/E7, p53 and Gadd45A were detected using Western blot and qPCR. Subsequently, Dual-Luciferase reporter gene assay was employed to detect whether CTCF was the transcription factor of Mortalin. CC-derived exosomal Mortalin was confirmed that promoted malignant transformation in vitro by migration assay, tube formation assay, wound healing assay, clone assay and EdU staining.Then, exosome injection to subcutaneous implantation mice indicated that CC exosomal Mortalin promoted tumor growth in vivo. Furthermore, the possible downstream target p53-Gadd45A were predicted via transcriptomics. And the impact of p53-Gadd45A on apoptosis and cell cycle were verified by flow cytometry.

Results Using Proteomics, we identified Mortalin, a Heat shock protein, significantly enriched in plasma exosomes of CC patients than those in Cervical Neoplasia (CIN) patients and healthy individuals.The mechanism of HPV regulation to exosomes Mortalin was explored. Mortalin expressed highly not only in HPV infected cervical cancer cell but also in their exosomes. However, HPV E6/E7 loss could reduce both cellular and exosomal Mortalin expression. Zinc finger protein CTCF could be collected in virus proliferation and then released in the period of HPV DNA integration. Interestingly, it was also confirmed as a transcription factor of HSPA9 (Gene of Mortalin) in luciferase assay and could activate cellular Mortalin production. The change of Mortalin in exosomes is consistent with that in cells. Therefore, HPV infection up-regulates the expression of cellular Mortalin by releasing CTCF as a transcription factor and then finally up-regulate the content of exosomal Mortalin.In addition, this study revealed the function and mechanism of Mortalin in CC-derived exosomes on malignant transformation to immortalized cervical epithelial cells H8. Both in

vitro and in vivo data proved that Mortalin in CC-derived exosomes enhanced H8 cells with the ability of proliferation, migration and tube formation, and reduced the level of apoptosis. Reducing Mortalin expression in exosomes could diminish the malignant transformation behavior. In addition, we found p53-Gadd45A changed significantly through transcriptomics. Mortalin in CC-derived exosomes arrested p53 in H8 cells from returning to the nucleus as well as prevented p53-Gadd45A from performing the function of stable cell cycle and DNA repair, contributing to the state of dysfunction and instability of H8 cells and leading to malignant phenotype.

Conclusions Our data demonstrated that HPV E6/E7 inducing CTCF transcription enhancement, tumor-derived exosomal mortalin was up-regulated and released to cervical epithelial cell, ultimately promoting malignant transformation by mortalin-p53-Gadd45A pathway. Our findings signify a brilliant mechanism of exosomal proteins which under the regulation of HPV accelerating carcinogenesis process, providing a new ideas for effective anti-tumor therapies. What's more, the plasma exosomal release of mortalin could potentially be biomarkers for diagnosis and prognosis to cervical cancer in near future.

605. Dysregulation of SPRR3/miR-876-3p axis contributes to tumorigenesis in non-small cell lung cancer

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Objective SPRR3, also known as esophagin, has been shown to be involved in the initiation and progression of numerous types of tumor. However, the biological function of SPRR3 contributes to non-small cell lung cancer (NSCLC) growth and migration is largely unknown.

ethods The expression of SPRR3 and its association with EZH2, miR-876-3p in NSCLC cells were determined by real-time PCR. Protein levels were measured by immunohistochemistry (IHC) and western blot. Cell functions were studied by CCK-8, transwell assay, flow cytometry and dual-luciferase reporter assay. The effect of SPRR3 on tumor growth in-vivo was evaluated in patient derived xenograft (PDX) models.

Results SPRR3 is up-regulated in most NSCLC cell lines and clinical tissues. Also, the correlation between SPRR3 expression and clinical features were significant. Functional studies confirmed that SPRR3 modulates cell proliferation, invasion and cell apoptosis in NSCLC via regulating EZH2, which is a well-known oncogene in NSCLC. Furthermore, SPRR3 is found to be a direct target of miR-876-3p that also plays a suppressor role in NSCLC.

Conclusions The discovery of miR-876-3p/SPRR3/EZH2 signaling cascade exerts important roles in the regulation of NSCLC, suggesting that this pathway can be served as potential therapeutic targets in NSCLC.

606. PD-L1 在肺基底样鳞状细胞癌的表达及预后分

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目的 肺基底样鳞状细胞癌（Basaloid squamous cell carcinoma, BSCC）具有高度侵袭性，其临床病理特征不明确且预后较差，本文通过分析肺 BSCC 的 PD-L1 表达的一致性。并分析 PD-L1 及临床病理特征和治疗方式与患者预后的关系，以期找到影响患者预后的因素。

方法 选取 2012 年 12 月—2017 年 12 月河北医科大学第四医院入院治疗的 BSCC 患者 33 例，免疫组化检测其 PD-L1（SP142、E1L3N、22C3、SP263）的表达情况，相关分析研究不同抗体 PD-L1 表达的一致性。分析患者的临床病理资料，电话随访计算患者的生存时间。生存分析采用 Kaplan-Meier 生存曲线，生存曲线的比较采用 Log-rank 检验，生存时间影响因素分析采用多因素 Cox 风险回归模型。

结果 结果显示，33 例 BSCC 患者中位生存时间为 22 个月，1 年、3 年、5 年生存率为 80.5%、53.9%、39.3%，PD-L1 免疫组化结果 E1L3N，22C3，SP263 对肿瘤细胞染色一致性较高。Kaplan-Meier 单因素分析显示：患者 TNM 分期、胸膜有无受侵及 PDL1 临界值为 50%（E1L3N，22C3，SP263）的表达与 BSCC 患者中位生存时间相关（P<0.05）。而年龄、性别、有无脉管瘤栓、有无气道内播散及术后治疗方式与 BSCC 患者中位生存时间无明显相关（P>0.05）。Cox 比例风险模型多因素分析显示，TNM 分期是影响 BSCC 患者生存时间的独立预后因素（P<0.05）。

结论 PDL1 临界值（E1L3N，22C3，SP263）为 50%更能有效预测肺 BSCC 患者预后。TNM 分期与 BSCC 的预后相关，是影响其生存时间的独立预后因素，应争取早期诊断早期治疗。

607. 食管非鳞状细胞癌组织病理学分析

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目的 食管癌在我国消化道恶性肿瘤中非常常见，其发病率和死亡率分别居的第五位和第四位，而食管少见恶性肿瘤十分罕见，目前综合性报道也比较少，本文通过对 629 例食管少见恶性肿瘤患者的组织病理学特征分析，加深对食管少见恶性肿瘤的了解。

方法 收集河北医科大学第四医院 2003 年 1 月 1 日至 2017 年 12 月 31 日被诊断为食管少见恶性肿瘤的 629 例患者，回顾性分析食管少见肿瘤的好发部位、大体类型、病理分型、TNM 分期等，结果以例数及百分比显示。

结果 629 例食管少见恶性肿瘤均为单发肿瘤，并且均为单一类型，发病率男性多于女性，男女比例 2.5:1。病变位于胸上段 45 例（7.2%），胸中段 402（63.9%），胸下段 182（28.9%）。

大体类型髓质型最多为 284 例（45.2%），其次是溃疡型 147 例（23.4%），腔内型 60 例（9.5%），蕈伞型 48 例（7.6%），缩窄型 17 例（2.7%），类型不确定 73 例（11.6%）。629 例食管少见恶性肿瘤中，有淋巴结转移 295 例（46.9%），无淋巴结转移 334 例（53.1%）。TNM 分期中I期 132 例（21%），II期 199 例（31.6%），III期 223 例（35.5%），IV期 75 例（11.9%）。食管肿瘤分类，小细胞癌最多，为 166 例(26．4％)；其次腺癌，为 126 例(20％)，腺鳞癌 98 例（15.6%），肉瘤样癌 59 例（9.4%），未分化癌 55 例（8.7%），基底细胞样鳞状细胞癌 42 例（6.7%），粘液表皮样癌 39 例（6.2%），腺样囊性癌 26 例（4.1%），大细胞神经内分泌癌 18 例（2.9%）。其中，大体类型肉瘤样癌以腔内型最常见 57.6%（34/59），其余各类型均以髓质型最常见。肿瘤位置腺癌以胸下段常见 70.6%（89/126）,其余多位于胸中段。肉瘤样癌和腺样囊性癌发现时一般分期较早，I期患者分别占 59.3%（35/59）、64.5%（17/26）,淋巴结转移率低,分别为 20.3%（12/59）、17.3%（4/26）。

结论 食管少见肿瘤，男性发病率高于女性，肿瘤位置以胸中段最常见，腺癌以胸下段常见，大体类型以髓质型最常见，其中肉瘤样癌以腔内型最常见。腺样囊性癌和肉瘤样癌分期较早，淋巴结转移率较低。

608. 食管基底样鳞状细胞癌预后分析及与食管鳞状细胞癌对比差异

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目的 食管基底样鳞状细胞癌（BSCC）非常罕见，无明显临床病理特征，且与食管鳞状细胞癌（SCC）不易区分，本文通过分析 BSCC 的临床病理特征与患者预后的关系，以及通过与不同组织学分级的食管鳞状细胞癌对比，分析两者之间的差异。

方法 选取 2010 年 1 月—2013 年 1 月河北医科大学第四医院入院治疗的 BSCC 患者 42 例，同期鳞状细胞癌患者 1341 例，分析患者的临床病理资料，电话随访计算患者的生存时间。生存分析采用 Kaplan-Meier 生存曲线，生存曲线的比较采用 Log-rank 检验，生存时间影响因素分析采用多因素 Cox 风险回归模型。 BSCC 患者与 ESCC 患者的临床病理特征对比采用 X2 检验或 Fisher 确切概率法。

结果 42 例 BSCC 患者 1 年、3 年、5 年生存率为 83.3%、54.8%、35.7%。Kaplan-Meier 单因素分析显示：肿瘤位置和 TNM 分期与 BSCC 患者中位生存时间相关（P<0.05）。而患者年龄、性别、有无脉管瘤栓、神经受侵以及术后治疗方式与中位生存时间无显著相关（P>0.05）。Cox 比例风险模型多因素分析显示，TNM 分期是影响 BSCC 患者生存时间的独立预后因素

（P<0.05）。与食管 SCC 对比，BSCC 患者中位生存时间明显低于高、中分化 SCC 患者（P<0.05），但与中低分化 SCC 患者的无显着差异（P >0.05）。

结论 TNM 分期与 BSCC 的预后相关，是影响其生存时间的独立预后因素，应争取早期诊断早期治疗。BSCC 患者预后较高中分化的 SCC 差，但与低分化的 SCC 相似。

609. 食管小细胞癌的临床病理特征及预后分析

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目的 探讨原发性食管小细胞癌（primary esophageal small cell carcinoma，PESC）的临床病理特征和预后影响因素。

方法 选取河北医科大学第四医院 2003 年 1 月- 2017 年 12 月 PES 手术标本 166 例，其中 120 例有完整的随访资料，免疫组化染色检测 Syn、CgA、CD56 表达情况，分析患者的临床病理特征。电话随访患者的生存时间。采用 Kaplan-Meier 法进行单因素生存分析，生存曲线的比较采用 Log-rank 检验，生存时间影响因素分析采用多因素 Cox 比例风险回归模型。

结果 本组患者男性 103 例，女性 63 例。发病部位以胸中段最常见，129 例，其次为胸下段 24 例，胸上段 13 例。肿瘤大体类型仍以髓质型最主，共 74 例。TNM 分期I期 29 例，II期 54 例，III 期 71 例，IV期 12 例。患者淋巴结转移率为 57.2%（95/166）。免疫组化染色显示，166 例 PESC 患者 Syn、CD56、CgA 的阳性率分别为 94.6%（157/166）、91.6%（152/166）、59.6%（99/166）。120 例随访资料完整患者中位生存期 16 个月，1、2、3、5 年生存率分别为 64%、36%、27%、17%。Kaplan-Meier 单因素生存分析显示：患者年龄、Syn 阳性率、肿瘤浸润深度、淋巴结转移、治疗方式、TNM 分期对患者生存率有显著影响（P＜0.05）。Cox 风险模型多因素分析结果显示：模型整体检验有统计学意义，其中患者年龄和治疗方式为 PESC 预后的独立影响因素。

结论 PESC 是一种少见类型的食管癌，需结合组织学形态及免疫组化确诊。其 5 年生存率较低，以手术为主的综合治疗有助于延长患者生存期。

610. PD-L1/2 及错配修复蛋白在食管腺样囊性癌中的表达及其临床病理特征分析

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目的 探讨程序性死亡蛋白配体 1（PD-L1）、PD-L2、错配修复蛋白（MMR）在食管腺样囊性癌（Adenoid cystic carcinoma of the esophagus, ACCE）中的表达及其临床病理特征分析。

法 回顾性分析 53 例食管腺样囊性癌，显微镜下观察其组织形态学，免疫组织化学染色，观察 PD-L1、PD-L2、MMR 的表达情况及其免疫表型特点。使用生存分析评估预后影响因素。

结果 53 例患者，≥50 岁 48 例，<50 岁 5 例；平均年龄 61 岁，中位年龄 63 岁；肿瘤部位：位于食管上段 10 例，食管中段 28 例，食管下段 15 例；大体类型：髓质型 33 例，溃疡型 11 例，蕈伞型 5 例，隆起型 4 例；肿瘤直径：肿瘤直径<2cm 7 例，肿瘤直径 2cm-4cm 31 例，肿瘤直径>4cm 15 例；浸润深度：肿瘤浸润至粘膜下层 27 例，浸润肌层 14 例，浸润纤维膜 12 例；临床分期：I期 33 例，II期 15 例，III期 5 例。淋巴结：有淋巴结转移 8 例，无淋巴结转移 45 例。组织学上，肿瘤具有多种组织学形态，包括筛状、管状和实性型的基底样细胞肿瘤。其中筛状型 30 例，实性型 12 例，管状型 5 例，筛状-实性型 4 例，筛状-管状型 2 例。肿瘤可见脉管和神经侵犯，其中有脉管侵犯 9 例，有神经侵犯 44 例。免疫表型：PD-L1、PD-L2 在 ACCE 中的阳性率分别为 62.3%（33/53）、69.8%（37/53），癌旁食管正常鳞状上皮中的阳性率分别为 33.3%（5/15）、40%（6/15），PD-L1、PD-L2 在 ACCE 中表达明显高于癌旁组织。53 例患者中有 4 例为 MMR 缺陷（MSI）。预后：患者术后平均存活时间 15 个月。术后 1 年总生存率 90.6%（48/53），2 年总生存率 69.8%（37/53），3 年总生存率 28.3%（15/53）。Kaplan-Meier 生存分析结果显示肿瘤直径、临床分期、淋巴结转移、神经侵犯、MSI 与患者预后有关（P＜0.05），多因素 COX 回归结果显示，临床分期是影响患者生存时间的主要因素；PD-L1 的表达与临床分期相关，PD-L2 的表达与淋巴结转移和临床分期相关。

结论 ACCE 中 PD-L1/2 的表达与临床分期和淋巴结转移相关，其有望成为 ACCE 患者免疫治疗的潜在靶点。MSI 是 ACCE 中的一个罕见事件，可能不是预测临床治疗效果的前瞻性生物标志物。临床分期是患者预后的独立影响因素。

611. Cinobufotalin induces apoptosis through the ROS / MAPK and NF–κB pathways in esophageal cancer

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Objective Esophageal cancer is a common malignant tumor of the digestive tract. Since the pathogenesis of this disease is complex and most cases are found in the late stage, chemotherapy is still one of the main treatment methods for this disease, but the effect of chemotherapy is not ideal and the side effects are large. With recent developments in targeted therapy and molecular analysis, targeted therapy has become increasingly more important, perfected and normalized. Numerous active components extracted from traditional Chinese medicinal plants exert multiple pharmacological effects. Traditional Chinese medicinal herbs may be a potential alternative medicine source for treatment, which is the treasure of our country. In recent years, cinobufotalin extracted from Chinese herbal medicine have shown good clinical effects in the treatment of cancer. It is mainly used in the comprehensive treatment of liver cancer, lung cancer and other tumors clinically. Research shows that cinobufotalin could induce the downregulate the anti-apoptotic proteins and upregulate the pro-apoptotic proteins in MDA-MB-231 cells to promote their apoptosis. The effect of cinobufagin on human multiple myeloma U266 cells is related to ros-mediated activation of ERK, JNK, p38 and MAPK, which leads to the activation of caspase-3 in U266 cells. The mitochondrial-mediated apoptotic pathway begins with mitochondrial membrane potential loss, cytochrome c release, the executioner caspase-3 cleavage, and eventually resulting in the formation of apoptotic bodies. JNK, p38, ERK and NF- κB are activated in response to several stress signals and are associated with the induction of apoptosis. It is becoming one of the key targets in screening treatment agents against cancer. However, the effect of cinobufotalin on the proliferation of esophageal cancer and its molecular mechanism have been little studied. The purpose of this study is to explore the effect of cinobufotalin on esophageal cancer kyse-70 cells proliferation and apoptosis, and to further expiore it.

Methods 1. CCK-8, LDH, cloning experiments and EDU assay was used to determine the effects of cinobufotalin on the growth and viability of esophageal cancer cells.2. TUNEL, DAPI, flow cytometric, western blot and qPCR assay was used to verify the apoptosis rate, apoptosis morphology and expression of apoptotic proteins.3. ATP, mitochondrial membrane potential, ROS, GSH and GSSG were measured to study the effect of the drug cinobufotalin on mitochondrial function in esophageal cancer cells.4. The mechanism of apoptosis was further analyzed by Western blot analysis.5. KYSE70 esophageal cancer cells xenograft-bearing nude mice were used to evaluate the therapeutic efficacy.

Results We funod that with the increase of drug concentration, cinobufotalin can significantly inhibit the proliferation of esophageal cancer cells in vitro. Cinobufotalin can induce the apoptosis of kyse-70

in esophageal carcinoma cells, and the apoptosis rate is positively correlated with drug concentration. Moreover cinobufotalin can significantly inhibit ATP production and mitochondrial membrane potential in the mitochondria of esophageal cancer cells, resulting in excessive intracellular ROS accumulation and decreased GSH content. Furthermore, we found that cinobufotalin induces apoptosis by ROS/ MAPK and NF –κB signaling pathway in vitro. And also, cinobufotalin inhibits proliferation of esophageal cancer cells in vivo.

Conclusions In conclusion, Our results show that cinobufotalin induces apoptosis through ROS/MAPK and NF–κB signaling pathway in vitro, which provides theoretical basis for further studies on the application of cinobufotalin in the treatment of esophageal cancer. Other mechanisms by which cinobufotalin affects the growth of esophageal cancer cells have not been proven. In addition, which signal pathways play a role remains to be explored.

612. Ivermectin-induced apoptosis in esophageal squamous cancer cells via ROS/NF-κB mediate Bax/Bcl-2 signaling

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Objective This study aimed to explore the antitumor effects and

mechanisms of ivermectin in Esophageal cancer cells in vitro and in vivo.

Methods The effects of IVM on cell viability and apoptosis rate were determined by MTT assay/colony formation assay and flow cytometry, respectively. In addition, the expression levels of apoptosis-associated proteins were individually examined by western blot analysis . Moreover, cell proliferation and apoptosis analyses were carried out by Ki-67 immunostaining assay. IVM has a potential dosage-dependent inhibition effect on the apoptosis rate of Esophageal cancer cells.

esults 1、IVM has a potential dosage-dependent inhibition effect on the apoptosis rate of Esophageal cancer cells.The mechanism of ivermectin induced apoptosis of esophageal cancer cells is related to inhibit the activation of NF-κB signaling pathway, block the activation of IκBα, while decreasing the phosphorylation of NF-κB p65.

Conclusions In conclusion, the present study demonstrated that the anthelmintic drug IVM exerted its anti-tumor activity by suppressing NF-κB signaling in ESCC cells, regulates the expression of related proteins, inhibits cell proliferation, promotes the apoptosis of esophageal cancer cells, and thus inhibits the tumorigenesis .

613. Foxq1 促进结肠癌生长及肝脏转移的作用及机制

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目的 肿瘤远处转移的机制一直是基础研究领域的世界性难题，阐明结直肠癌肝脏转移的机制尤为重要。

方法 在数据库中筛选影响结直肠癌生存预后的基因，并在临床标本中进行验证。随后，在体内外实验中论证靶基因促进结直肠癌生长及肝脏转移的作用。最后在 GEO 芯片数据中进一步筛选调控靶蛋白的基因。

结果 通过对 Oncomine 和 TCGA 数据库的挖掘，我们发现，与正常结肠组织相比，Foxq1 在结肠癌中表达明显升高，少数结直肠癌患者伴有 Foxq1 突变。采用免疫组化方法检测结直癌组织芯片（N=100）Foxq1 蛋白的表达，结果显示 Foxq1 高表达与结肠癌患者生存时间缩短显著相关。在体外克隆形成实验中，干扰结肠癌细胞 Foxq1 显著减少克隆形成数目。应用 HCT116 细胞建立结肠癌皮下成瘤（裸鼠）模型，进一步证明沉默 Foxq1 可以显著减慢肿瘤的生长。在原位盲肠肿瘤模型中，非 HCT116 干细胞模型仍未能观察到肝转移；同 HCT116 干细胞模型相比，沉默 Foxq1 的 HCT116 干细胞可显著减少原位种植结肠癌导致的肝转移。深入分析 Foxq1 干扰后的 GEO 芯片数据，寻找 Foxq1 干扰后结肠癌细胞与未干扰的结肠癌细胞对比的差异基因，以及与耐奥沙利铂的结肠癌细胞的差异基因，并与 Foxq1 干扰的结肠癌细胞做共有差异分析。最终，发现了 2 个共有差异基因（NDRG1，PPP2CA）潜在参与了 Foxq1 调控结肠癌生物学行为的作用。

结论 Foxq1 促进结直肠癌的生长，与患者的不良预后相关，且潜在经调控相关基因（NDRG1，PPP2CA）促进结直肠癌干细胞肝脏转移。

614. 白细胞介素 6 在结直肠癌患者中的表达及与肿瘤疗效关系

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目的 探讨人白细胞介素 6（Interleukin-6，IL-6）在结直肠癌患中的表达及意义。

方法 收集 132 例首诊结直肠癌患者（CRC）、34 例肠道良性疾病患者(CBD)及 84 例表观健康体检者(HC)血清,采用电化学发光双抗体夹心免疫分析法（ECLIA）检测血清中白细胞介素 6（IL-6）及癌胚抗原（CEA）含量，分析 IL-6 水平与结直肠癌患者临床病理特征的相关性；应用受试者工作特性曲线（ROC）和二元 Logistic 法回归分析 IL-6 和 CEA 两指标对结直肠癌的诊断价值；对随访资料完整的 120 例结直肠癌患者动态观察治疗前后血清 IL-6 和 CEA 水平，

分析两指标与肿瘤疗效的关系。

结果 结直肠癌患者血清 IL-6 水平显著高于肠道良性疾病组(P<0.01)和健康对照组(P<0.01)，结直肠癌患者血清 CEA 水平显著高于肠道良性疾病组(P<0.05)和健康对照组(P<0.01),差异均有统计学意义。CRC 患者血清 IL-6 水平与肿瘤直径、分化程度、组织类型、淋巴结转移、远处转移、TNM 分期均显著相关(P<0.05)，而与年龄、性别及肿瘤发生部位无明显相关。IL-6 诊断结直肠癌的灵敏度（72.7%）和准确性（78.6%）均高于 CEA(分别为 68.2%和 77.9%，特异性（85.2%）低于 CEA（88.9%），两指标联合检测能够提高灵敏度（97.2%）和准确性（85.6%）。结直肠癌肿瘤控制组(CR+PR+SD)治疗后两指标均较治疗前有显著下降(P<0.05)，差异有统计学意义，而肿瘤进展组(PD)治疗后两指标均未显著下降(P>0.05)。

结论 IL-6 和 CEA 两指标联合检测有助于结直肠癌的诊断和疗效观察。

615. IgG4 相关硬化性疾病 48 例临床特征分析

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目的 析 48 例 IgG4 相关硬化性疾病（IgG-4 related sclerosing disease）患者的临床病理特征，旨在加深对该病的认识，提高对本病的诊治水平。

方法 收集 2015 年 1 月-2018 年 10 月病理诊断为 IgG4 相关硬化性疾病患者 48 例。分析患者基线特征、临床表现、实验室检查及治疗情况。

结果 48 例患者中男性 23 例(47.9%)，女性 25 例(52.1%)，发病年龄 21-81 岁(50.3±12.6)岁。最常受累器官为颌下腺 20 例(41.7%)和淋巴结肿大 11 例(22.9%)，肺 6 例(12.5%)，甲状腺 4 例(8.3%)，其次常见为颈部、牙龈、胰腺、面部、耳后、腮腺、腹部以及泪腺。3 个及以上器官受累的患者 14 例(29.2%)，2 个器官受累患者 19 例(39.6%)，15 例(31.2%)患者单个器官受累。血 IgG4（8.37 ± 7.26）g/L，11 例患者不升高。48 例全部行病理检查，镜下淋巴浆细胞纤维化明显，个别病例可见嗜酸性粒细胞浸润，IgG4+细胞均＞10 个/HP，IgG4+/IgG+细胞比例均＞超过 40%。大部分患者用糖皮质激素治疗，且治疗后好转或者病情稳定。

结论 IgG4 相关硬化性疾病是一种累及一个或多器官的免疫介导相关的慢性炎性伴有纤维化疾病，最长受累器官是颌下腺及淋巴结，易误诊为肿瘤，病理是诊断的重要手段之一，需要结合临床特征。对本病的早期正确诊断需要各科医师提高对其正确认识。

616. 鼻咽癌中 GLI3 基因转录失活机制及其作用的研究

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目的 研究鼻咽癌(nasopharyngeal carcinoma，NPC)细胞 Hedgehog 信号通路成员 GLI3 转录因子甲基化及去甲基化干预对细胞恶性生物学行为的影响，探讨 NPC 发生的可能机制及治疗策略。

方法 采用亚硫酸氢盐修饰后测序法（Bisulfite sequencing PCR, BSP）测定 NPC 组织及癌细胞系（C666-1、CNE1、CNE2）中 GLI3 甲基化程度，选出 GLI3 甲基化水平较高的两种 NPC 细胞（即 C666-1 和 CNE1 细胞）进行后续实验。首先使用去甲基化药物 5-Aza-dC 进行干预，采用 CCK8 实验、细胞划痕实验、Transwell 实验检测 C666-1 和 CNE1 细胞去甲基化前后细胞增殖、迁移、侵袭能力。应用 qRT-PCR 和 Western-blot 检测并比较去甲基化药物作用后细胞表达 GLI3 mRNA 和蛋白水平的变化。

结果 4 例鼻咽癌组织中 GLI3 基因启动子甲基化水平分别为 16.5%、16.5%、31.8%、58.8%，呈中低水平甲基化；三种鼻咽癌细胞中 GLI3 甲基化比率分别为 44.7%（CNE1）、43.1%（CNE2）、70.6%（C666-1）；筛选出 GLI3 甲基化水平较高的 C666-1 和 CNE1 细胞进行后续实验；CCK8 实验、划痕实验和 Transwell 实验结果显示 C666-1 和 CNE1 细胞的增殖、迁移和侵袭能力随着去甲基化药物 5-Aza-dC 浓度的增加而降低（均为 $P<0.01$）。并观察到 C666-1 和 CNE1 细胞对 GLI3 mRNA 和蛋白表达随着去甲基化药物浓度增加而呈上升趋势（均为 $P<0.01$）。

结论 GLI3 甲基化是鼻咽癌中 Hedgehog 信号通路异常激活的重要机制之一，GLI3 可作为鼻咽癌治疗的潜在新靶点。

617. 阻断 Hedgehog 信号通路对鼻咽癌 CNE2 细胞增殖及凋亡影响

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目的 我们前期的研究与国外同道的实验均证实鼻咽癌中存在 HH 通路的异常激活，然而，尚缺乏关于通过阻断 HH 信号通路治疗鼻咽癌的基础及临床研究报道。为取得从基础到临床具有参考价值的依据，本研究通过体外细胞试验，观察阻断 HH 信号通路对鼻咽癌细胞增殖及凋亡的影响。

方法 使用不同浓度的 GLI1、GLI2 特异性抑制剂 GANT61 作用于鼻咽癌 CNE2 细胞，倒置显微镜下观察细胞形态的变化；采用 CCK-8 法检测细胞增殖的抑制状态；借助 Annexin V-

FITC/PI 双染流式细胞术检测该制剂对细胞凋亡的影响；基于 RT-PCR 和 Western blot 分别检测 CNE2 细胞中 GLI1、GLI2 和 GLI3 mRNA 及蛋白表达水平。

结果 经 GANT61 作用后，细胞形态明显改变、活力明显下降；GANT61 显著抑制 CNE2 细胞的增殖和促进凋亡（P<0.05）。进一步观察到，该抑制剂干预后细胞对 GLI1、GLI2、GLI3 mRNA 及其蛋白的表达均明显下调（P<0.05）。

结论 Hh 信号通路是维持鼻咽癌细胞生长所必须。GANT61 能显著抑制 CNE2 细胞的增殖和促进其凋亡,其机理与该制剂靶向阻遏 GLI 家族蛋白的表达有关。

618. lncRNA AFAP1-AS1 is a critical regulator of nasopharyngeal carcinoma tumorigenicity

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bjective The long noncoding RNA (lncRNA) AFAP1-AS1 is a critical player in various cancers. However, the clinical value and functional mechanisms of AFAP1-AS1 during the tumorigenicity of nasopharyngeal carcinoma (NPC) remain unclear.

Methods Here, we reveal that AFAP1-AS1 is upregulated in NPC and is a poor prognostic indicator for NPC survival. AFAP1-AS1 was required for NPC proliferation in vitro and tumorigenicity in vivo. Mechanistic investigations suggest that AFAP1-AS1 binds to KAT2B and promotes its acetyltransferase activation at two residues (E570/D610). KAT2B promotes H3K14 acetylation and binding to the Bromo domain of TIF1α. Consequently, TIF1α acts as a nuclear transcriptional co-activator of RBM3 transcription, leading to YAP mRNA stability and enhanced NPC tumorigenicity.

Results Our findings suggest that AFAP1-AS1 functions as an oncogenic biomarker and promotes NPC tumorigenicity through enhanced KAT2B acetyltransferase activation and YAP mRNA stabilization.

Conclusions AFAP1-AS1 enhances KAT2B acetyltransferase activation, which upregulates H3K14ac activity against TIF1α, resulting in enhanced RBM3 transcription and subsequent stability of YAP mRNA inducing AFAP1-AS1-driven NPC tumorigenicity.

619. Identification of prognostic chromatin-remodeling genes in clear cell renal cell carcinoma

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Objective Chromatin remodeling genes are groups of genes that could translate into chromatin remodeler, involving in the processes of changing nucleosomes structures and covalently modifying histones to further promote or suppress transcription. Aberrant expressions of some chromatin remodeling genes have been found associated with tumorigenesis and tumor progression. The roles of chromatin remodeling genes remain unclear to be explored in ccRCC.

Methods Two subgroups of patients with distinct survival outcome in TCGA-ccRCC were identified based on 86 chromatin remodeling genes and k-means consensus clustering. Random forest algorithm was used to selected characterized chromatin remodeling genes that contributed most in classifying above two subgroups and the risk model was evaluated by time-dependent ROC curve. GSEA was used to annotate the characterized genes. With iRegulon plugin embedded in Cytoscape and String database, putative transcription factors of target genes were predicted and the regulator interactive network was generated.

Results Survival analysis, univariate and multivariate cox regression discovered that subgroups based on the differential expression of 86 chromatin remodeling genes was an independent prognostic factor in ccRCC. After assessing the importance of each features and calculating the model accuracy, three chromatin remodeling genes: CNOT1, SIN3A and BPTF were identified by multiple cross-validation of random forest. Survival analysis suggested that high expression of CNOT1, SIN3A and BPTF were significant associated with better prognosis in ccRCC and their expressions were found significantly decreased in late stage and poor differentiated tumor. GO and KEGG annotation indicated genes related to CNOT1, SIN3A and BPTF (Pearson $r>0.5$, $p<0.001$) were enriched in the process utilizing autophagic mechanisms and ubiquitin-mediated proteolysis. 92% of their overlapping correlated genes (Pearson $r>0.6$, $p<0.001$) were significant good prognostic predictors in ccRCC and were associated with ubiquitination pathway. According to iRegulon, YY1 was predicted as one of the top 20 downstream transcriptional factor of BPTF. String database discovered a co-expression relationship between BPTF, SIN3A and YY1 with SIN3A acting as the crosslinking bridge. By motif mapping, ChIP-seq track signal comparison and Pearson correlative analysis, YY1 was identified as the putative transcriptional factor of CNOT1, SIN3A and BPTF overlapping correlated genes. KEGG analysis found that YY1 was also enriched in ubiquitin proteolysis and high expression of YY1 indicated good prognosis in ccRCC. Time-dependent ROC curve suggested that the combination of CNOT1, SIN3A, BPTF, YY1 and tumor stage has better risk-prediction performance than tumor stage only, especially for long-term survival. Although high correlation between CNOT1, SIN3A, BPTF and YY1 were

shown in pan-cancer, their distinct prognostic values were only found in ccRCC in GEPIA analysis.

Conclusions Our research first identified three chromatin remodeling genes CNOT1, SIN3A and BPTF which were significantly associated with good prognosis in ccRCC. Putative transcriptional factor YY1 was predicted and the gene network involved in ubiquitin-mediated proteolysis process deserved further mechanism study. CNOT1, SIN3A and BPTF may be potential prognostic biomarkers in ccRCC patients.

620. 治疗前炎症复合指标在老年晚期非小细胞肺癌预后评估的价值

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陕西省肿瘤医院

目的 评估治疗前粒淋比 (Neutrophil-lymphocyte ratio，NLR) 、血小板/淋巴细胞比值 (Platelet-lymphocyte ratio，PLR)、系统免疫炎症指数(Systemic immune-inflammation index，SII)在老年晚期非小细胞肺癌 (Non-small cell lung cancer, NSCLC) 患者预后评估中的价值。

方法 回顾性分析 2016 年 1 月至 2017 年 12 月在陕西省肿瘤医院就诊且明确诊断为原发性晚期 NSCLC 的 164 例老年患者（≥65 岁）的临床资料, 根据受试者工作特征曲线 (Receiver operating characteristic curve，ROC) 确定炎症复合指标（NLR、PLR、SII）预测患者总生存期（overall survival, OS）的最佳临界值，根据临界值将患者分为低组和高组，分析以上炎症指标与患者预后的相关性。

结果 确定炎症复合指标（NLR、PLR、SII）的最佳临界值分别为 3.5、248.9、1276.8。单因素生存分析显示治疗前合并恶性胸腔积液、肿瘤分化程度、NLR、PLR、SII 与老年晚期 NSCLC 患者的预后显著相关， P 值分别为 0.019、＜0.001、＜0.001、＜0.001、＜0.001。多因素生存分析显示恶性胸腔积液(HR=1.605，95%CI：1.1-2.343；P=0.014)、肿瘤分化程度(HR=1.78，95%CI ： 1.209-2.62 ； P=0.004) 、 NLR(HR=1.941 ， 95%CI ： 1.247-3.021 ； P=0.003) 、PLR(HR=1.698，95%CI：1.032-2.795；P=0.037)是影响老年晚期 NSCLC 患者 OS 的独立危险因素。

结论 炎症复合指标（NRL、PLR、SII）有望成为评估老年晚期 NSCLC 患者预后的有效指标，与预后呈负相关，治疗前水平越高，预后越差；尤其治疗前外周血 NLR 和 PLR 检测对评估老年晚期 NSCLC 患者的预后具有较高的价值。

621. 49 例肿瘤遗传咨询案例的总结分析

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目的 通过分析来我院进行肿瘤遗传咨询的案例，总结其特点和存在的普遍性问题，以便后续工作开展，亦望能引起同仁关注，共寻解决之道。

方法 回顾我院肿瘤遗传咨询门诊接诊的 49 例咨询案例，所有案例未进行倾向性筛选。从咨询者来源、构成、主要相关癌种、是否有明显家族史、来咨询前是否已行基因检测、已行基因检测是否必要且合理等方面，对案例进行分类统计分析，挖掘其特点。

结果 1. 49 个案例中来自临床推荐的有 27 例（癌症患者 26 例，血亲 1 例），自主前来咨询的有 22 例（癌症患者 1 例，血亲 21 例），二者在患者和血亲的构成比例上有显著差异，p=0.000。2.在所有 27 例癌症患者中，有 26 例接受了遗传性肿瘤基因检测，其中 7 例无明显家族史患者中有 1 例卵巢癌患者检出胚系突变（14.29%），19 例有明显家族史患者中有 13 例检出胚系突变（68.42%），后者检出率显著高于前者，p=0.026。3.49 个案例中 34 例在前来遗传咨询前已行基因检测（患者 24 例，近血亲 10 例），15 例遗传咨询前未行基因检测（患者 3 例，近血亲 12 例），二者在患者和血亲的构成上有显著差异，p=0.001；而在 34 例咨询前基因检测的案例中，有 9 例（26.47%，患者 7 例，近血亲 2 例）接受了不必要或不合适的基因检测。4.在咨询前未行基因检测的 15 例中，符合临床遗传性肿瘤基因检测条件的有 13 例，其中 8 例接受基因检测，而未接受基因检测的 5 例主要原因为经济因素和心理因素。5.49 个案例中妇科/乳腺肿瘤相关案例共计 45 例（91.84%），其余肺癌、直肠癌、食管癌、视网膜母细胞瘤各 1 例。

结论 1.肿瘤患者近血亲的自主咨询需求显著高于患者本身，而前来咨询的患者主要来自临床推荐。2.有家族史者胚系突变检出率显著高于无家族史者，在行遗传性肿瘤基因检测前对咨询者进行家系评估具有重要意义，有助于基因检测的合理使用。3.大部分案例（69.39%）在咨询前已经进行了遗传性肿瘤基因检测，而未经严格评估便进行基因检测具有很大的盲目性，存在较高比例（26.47%）的不必要或不合适的检测案例，这一现象在肿瘤患者中更为突出。4.经济因素和心理因素是限制符合临床检测条件者进行遗传性肿瘤基因检测的主要原因。5.自主来询者和临床医生对妇科/乳腺相关肿瘤的遗传风险重视程度均显著高于其它肿瘤，需加强宣教导向，提高对其它肿瘤遗传风险的重视程度。

622. 243 例多原发恶性肿瘤临床分析

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目的 分析多原发恶性肿瘤可能的发病因素、总结临床特点、治疗手段及预后情况。

方法 收集成都中医药大学第二临床学院（成都市第五人民医院）2003 年 2 月-2019 年 10 月多原发恶性肿瘤患者病历资料，回顾性分析 243 例多原发恶性肿瘤患者的年龄、性别、肿瘤部位、治疗手段以及患者个人史及既往史的相关特点(吸烟史、饮酒史、高血压、糖尿病及肿瘤家族史)。

结果 (1)男女比例相近;(2)发病年龄为 32~93 岁，中位年龄 65 岁;(3)双原发恶性肿瘤 233 例，三原发恶性肿瘤 9 例，四原发恶性肿瘤 1 例;(4)首发恶性肿瘤以消化系统（肠道）最多，第二原发恶性肿瘤也以消化系统（肠道）居多。

结论 多原发恶性肿瘤的治疗目前尚缺乏标准的诊治指南，现有文献大多提出需要根据肿瘤的部位、病理、肿瘤分期及患者的一般情况等因素综合考虑，选择手术切除与放化疗结合的根治性治疗手段，也可根据患者的具体情况在术前或术后采用辅助放化疗的方式。如果患者已失去手术机会，则应该根据具体的病情，采用放化疗、靶向治疗、免疫治疗、中西医结合等综合治疗的手段。通过回顾性分析提高对多原发恶性肿瘤的认识，指导医务工作者开展多原发恶性肿瘤的早筛、早诊治工作，以期提高疾病诊断率，提高患者总生存时间，改善患者预后。

623. 肿瘤患者念珠菌感染的危险因素及药敏分析

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福建省肿瘤医院

目的 分析福建省肿瘤医院肿瘤患者念珠菌感染的临床特点、流行病学特征及导致感染发生的可能危险因素，为临床念珠菌感染的预防和诊疗提供参考依据。

方法 回顾性分析我院 2015-2017 年恶性肿瘤患者念珠菌感染的 60 例临床资料，对可能的危险因素进行单因素及多因素 logistic 回归分析，估计各危险因素的 OR 值并统计病原菌药敏试验结果作进一步分析。

结果 在念珠菌感染中，根据单因素卡方检验分析结果显示，应用广谱抗生素、住院天数（≥14 天）、术后引流管留置数量（≥4 个）及天数（≥7 天）、放化疗和是侵入性操作是发生念珠菌感染的危险因素（P＜0.05）。Logistic 分析中，应用广谱抗生素、术后引流管留置天数（≥7 天）、住院天数（≥14 天）和侵入性操作的 OR 值分别为 11.177、1.925、15.154、4.613 均是发生感染的独立危险因素（P＜0.05）。白色念珠菌仍是最主要的病原菌（73%），常见真菌对常见抗真菌药物的敏感性由高到低依次为：两性霉素 B,5-氟胞嘧啶，伊曲康唑，伏立康唑，氟康

唑。

结论 肿瘤患者住院治疗的周期长，放化疗，术后引流管插管数量多时间长，侵入性操作，术后广谱抗生素应用不规范等是引起念珠菌感染危险因素，临床应对存在危险因素的患者重点预防感染并掌握引起真菌感染病原菌的分布及耐药性，同时合理应用抗真菌药物以及同时注意及时送检合格标本。

624. Effect of intervention model based on empowerment theory on self-efficacy and self-acceptance in patients with permanent enterostomy

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bjective To investigate the effect of intervention model based on empowerment theory on self-efficacy and self-acceptance in patients with permanent enterostomy.

Methods 120 colorectal cancer patients undergoing permanent enterostomy operation were selected in two intestinal departments, which were divided into control group and experimental group by drawing lots, each choosing 60 cases. The control group was given conventional nursing care while the experimental group was given intervention based on the empowerment theory. The contents include: identifying the current problems of patients, encouraging patients to express their feelings, working with patients to set short-term and long-term goals, and formulating implementation plans, etc. Stoma Self Efficacy Scale（SSES）and Self-Acceptance Questionnaire（SAQ） were used to assess the patients.

Results After intervention， the total score of SSES and SAQ of the experimental group were higher than those of the control group（P＜ 0.05）

Conclusions The intervention based on empowerment theory can improve the self-efficacy and self-acceptance level of patients with permanent enterostomy.

625. 癌症化疗患者脱发的护理效果观察

曲丽丽

辽宁省肿瘤医院

目的 探讨癌症化疗患者脱发的护理效果观察。

方法 化疗脱发可以改变人的自我形象降低人的生存质量，随着化疗新药的不断问世，应用化疗药后患者的脱发问题日渐严峻。我院设立癌症相关性脱发学术组，评估患者后采取相应护理干预，告知其如何采取措施来减轻脱发、保护头发、促进脱掉的头发再生。根据 WHO 毒性反

应分级标准将脱发分为 5 级；分别是 0、I、II、III、IV度，现将我科室 2019 年 1 月-2019 年 6 月期间化疗患者进行回顾性研究，取化疗患者样本共 30 例，进行健康教育后，经评估 0 度脱发患者共 6 例，I度脱发患者共 7 例，II度脱发患者共 11 例，III度脱发患者共 6 例，IV度脱发患者共 0 例，III度以上的脱发患者予以上报学术组，请专项小组人员制定完善的护理计划，延缓脱发的进一步发展。

结果 经过护理干预，脱发人数仍占化疗总人数的 80%，可见化疗药物对头发的损伤极大。

结论 化疗患者脱发问题通过目前护理措施可以有所干预，但却不能明显改善，针对化疗患者脱发问题，目前临床上并没有很好的解决措施，脱发问题应该引起各位医护同仁的重视，在为患者治疗癌症的同时也应该解决化疗药物引起的脱发问题，减轻肿瘤患者身心痛苦，改善其生存质量，关注脱发，重拾美丽。

626. Accurate prediction of hierarchy prognosis integrated of clinical and molecular characteristic in colon cancer

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Objective The difference of prognosis for colon cancer is associated with complicated factors. This increases the accurate assessment of prognosis and decision-making in clinical practice.A series of prediction models based on machine learning and statistical method were exploited to screen potential factors for survival probability in colon cancer.

Methods The clinical characteristics of 161,694 colon cancer patients who were treated with adenocarcinoma and have received surgery were obtained, which was taken advantage of SEER from April 2000 to April 31, 2013.We also collected clinical and four types molecular datasets from the TCGA, including mRNA、lncRNA、miRNA and DNA methylation profile. We employed machine learning and statistical methods such as Lasso cox to screen potential factors for survival probability in colon cancer.The classier AUC,survivalROC,nomogram and Kaplan-Meier survival curve were displayed the results of different follow-up time.

Results We developed a series of prediction model for colon cancer stratified survival time. The classifiers AUC values of the models were achieved to 0.935(95%CI, 0.857-0.985), 0.919(95%CI, 0.87-0.962), 0.873(95%CI, 0.793-0.932) for different survival time which were respectively derived 8/9/4 features consisting of combination clinical factors and a group of molecular features. In the feature sets, molecular risk score was the best factor for survival assessment, which of them the top one were ranked as DNA methylation on cg01515427, cg03024587 and cg04067612, respectively. T4&poorly differentiated or undifferentiated was the best clinical factor for one year, and M0 was for

three and five years overall lifetime. According to the combination of clinical factors and molecular features, we provided the guidelines by nomograms to predict the rate of survival for different follow-up time.

Conclusions This study established objective criteria for clinicians to evaluate the survival of colon cancer patients after surgery from multidimensional and complex patient information. The analysis strategy of the partition of survival time have pertinence up to diverse patients.

627. A novel NGS-based approach for concurrent detection of mitochondrial DNA copy number and mutation

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Fourth Military Medical University

Objective Numerous studies have identified essential contributions of altered mitochondrial DNA (mtDNA) copy number and mutation in many common disorders including cancer.To date, capture-basednext-generation sequencing (NGS) has been widely applied to detect mtDNA mutation, whereas lacks abilityin assessing mtDNA copy number.Current strategy for quantifying mtDNA copy number mainly relies on quantitative PCR (qPCR), which is limited in degraded samples.

Methods Here, we developed anovel capture-based NGS approach using both mtDNA and nuclear DNA (nDNA) probes to capture target fragments, enabling simultaneous detection of mtDNA mutation and copy number in different sample types.

Results We first evaluated the impacts of selecting reference genes on mtDNA copy number calculation, and finally selected 3 nuclear DNA fragment of 4000bp as internal reference for detection. Then, we verified the effective application of this approach in DNA samples of formalin-fixed, paraffin embedded (FFPE)specimens andbody fluids,indicating the widespread applicability.Importantly, our approach exhibited more accurate and stable results in detecting mtDNA copy number compared with qPCR in degraded DNA samples. Moreover, our data indicated this approach had good reproducibility in detecting both mtDNA copy number and mutation among three sample types.

Conclusions Altogether, we have developed a versatile and cost-effective capture-based NGS approach for concurrent detection of mtDNA copy number and mutation, which can find numerous applications in research and diagnosis.

628. A screening review of recent advance of pre-clinical research setting

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Purpose: To make a preliminary analysis of recent advance of patient-derived models occupying in malignant tumor research.

Method: Sequencing review of literatures published between the year 2018 to 2020 focused on pre-clinical cancer models in vivo and in vitro has made.

Results:1.Patient-derived xenograft and Patient-derived organoids

Malignant tumors remain major threat to mortality and morbidity globally, despite intense research. Patient-derived xenograft (PDX) models, through which tumor biopsies from patients are injected into an animal, had been developed into a vitally important research tool in vivo, thus improve the predictive capacity of preclinical models in cancer stem cell isolating and investigating, molecular mechanism exploring, drug testing, biological research of enormous solid tumors, such as breast cancer, colon cancer, lung cancer, et al . The advantages of this whole animal models had been demonstrated to include the ability to mimic a systemic response of certain drugs, the ability to model metastasis and the maintenance and/or development of an intact tumor microenvironment. Hence, recent observations have called into questions to the clinical relevance. An increasing number of reseach findings give demonstration that patient-derived-organoids (PDO), besides PDX, also play important roles as pre-clinical platforms for drug testing and evaluation , biomarker identification, biological characteristics research, thus opening a door for personalized therapy. For PDO, while compared with PDX, it can be easily preserved, fast resuscitated, indefinitely passed , and mechanically cultured on a chip for high/low-throughout drug screening. Organoid-on-a-chip produced the components of vascularized tissue, lymphatic vessels, and immune system. It also simulated the characteristics of micro-circulation . Moreover, it could mechanize the cultivation of tumor organoids and complete the drug screening of tumor, which could save the human resources and reduce human operational error. Besides, if a patient had multiple tumors or metastasis tumors, the chip could complete the culture of multi-site tumor organoids. Therefore, organoid-on-a-chip had a perspective application for the frontier of biomedical research and shortens the distance to precision therapy.

2. PDX-derived organoids:ancer drug development. In order to gain access to an expanded repertoire of cancer indications, mutational, and pharmacological profiles, cancer drug can be searched through PDX-derived organoids (PDXO), which can be developed using protocols similar to PDO. Briefly, PDXO are in vitro models derived from paired in vivo patient-derived xenografts, which can be extensively collected and well-characterized. Matched in vitro PDXO and in vivo PDX

model pairs provide a unique pre-clinical workflow with improved predictivity and a more rapid and informed study transition to accelerate drug discovery programs. For both models, since originally derived from cancer tissues of patients, cancer stem cells (CSCs) are preserved and give rise to cancers similar to tissues from patients. When compared with other in vitro models of 2D and 3D, PDXO models also retain key genomic and phenotypic molecular features from originally tumor tissues derived from patients, and preserve the histopathological features of patients, so as to the corresponding in vivo PDX tumor, thus providing an easily scalable in vitro system for large scale screens to obtain initial drug sensitivity data. In conclusion, to give a deep insight of this PDX-derived organoids can lead to potential findings to dramatically improve pre-clinical predictivity and investigation.

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肿瘤标志物解决方案

加速进展 - 基于高分辨质谱的多组学分析方法

肿瘤标志物在癌症早期诊断、疾病分析、药物靶点及预后评估等方面具有重要作用。传统生化、免疫方法，由于特异性不高，敏感性不强，针对每个标志物的开发成本高、难以实现高通量分析等原因，对于大规模临床验证仍显露出极大局限性。近年来，随着组学技术的不断发展，基于高分辨质谱的组学分析技术在肿瘤标志物筛选与验证方面显露出快速、高通量、特异性强等独到优势，是适应于未来瘤标志物发现、大规模验证等发展趋势的新型方式。

赛默飞基于组学金标准 -Orbitrap 的超高分辨质谱解决方案，能够多维度、多角度助力肿瘤标志物的发现、验证和临床转化。

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病人精准分型

高特异性、精准定量
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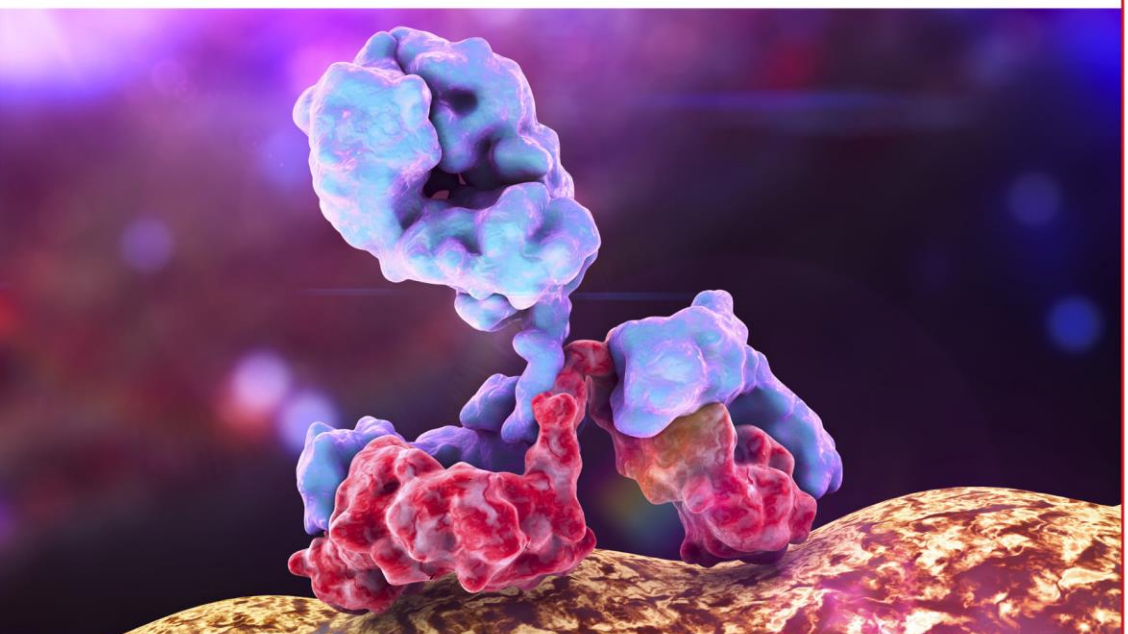

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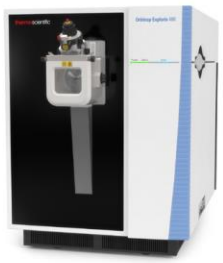

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前列腺特异性抗原同源异构体测定试剂盒 p2PSA 和前列腺健康指数 *phi*

2008-2013 年中国前列腺癌联盟医院新诊断的前列腺癌患者中，局部进展性和转移性占 58%[1]，而美国 2005-2011 年前列腺癌患者中区域和远处转移的仅占 16%[2]，中国前列腺癌患者面临着发现晚、预后差的危局。

为了契合前列腺癌早发现、早治疗、改善预后的需求，贝克曼库尔特研发了 p2PSA 试剂盒，并推出了前列腺健康指数 *phi*（prostate health index，*phi*）多参数风险预测模型，由 PSA、fPSA 和 p2PSA 三个指标通过特定公式计算得出，研究表明 *phi* 值越高，前列腺癌风险越大。

精准诊断

phi 支持前列腺癌精准诊断，避免不必要前列腺活检穿刺，减轻患者痛苦和负担

抗体专利

phi 的前列腺癌特异性和诊断准确度均高于传统指标，是前列腺癌的新型血清标志物

（专利号：US patents: US 7288636 and US7659073）

合作共赢

与多家医院合作建立中国人群参考范围和医学决定值

健康理念

phi 简单、快速、成本低廉，提供前列腺癌的筛查、临床诊疗全病程管理

历史传承

贝克曼库尔特PSA&fPSA可以溯源至Hybritech标准，品质久经验证，拥有临床认可“金标准”

继承优化

phi 是对PSA Hybritech标准的传承延续，是对于中国目前前列腺癌现有诊断方法的有效补充和完善，将成为前列腺癌精准诊疗的新趋势

参考文献：

1. 中国前列腺癌联盟成员医院前列腺穿刺活检现状的调查报告 . 中华泌尿外科杂志 , 2015.36.05:342-345
2. Cancer Statistics, 2016. CA CANCER J CLIN 2016;66:7-30

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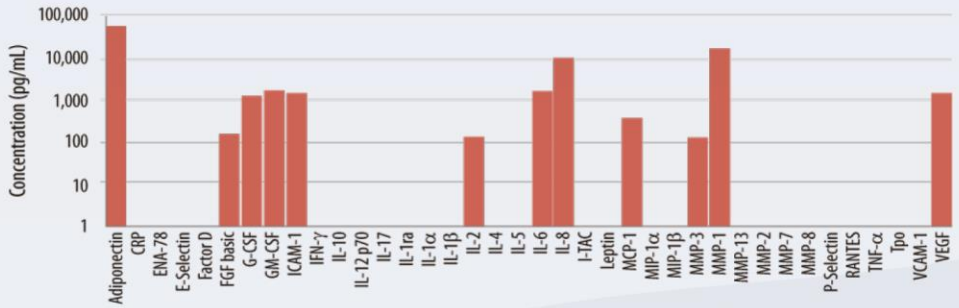
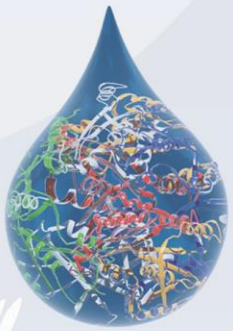
- 仅需 **25 µL** 样本，同时检测 **80** 个样本
- 经过金标准 **ELISA 试剂盒** 相关性验证
- **5 小时**呈现 基于标准曲线定量结果



图示： 人乳腺癌细胞 MDA-MB-231 中 38 种生物标志物水平 （货号：LXSAHM ）

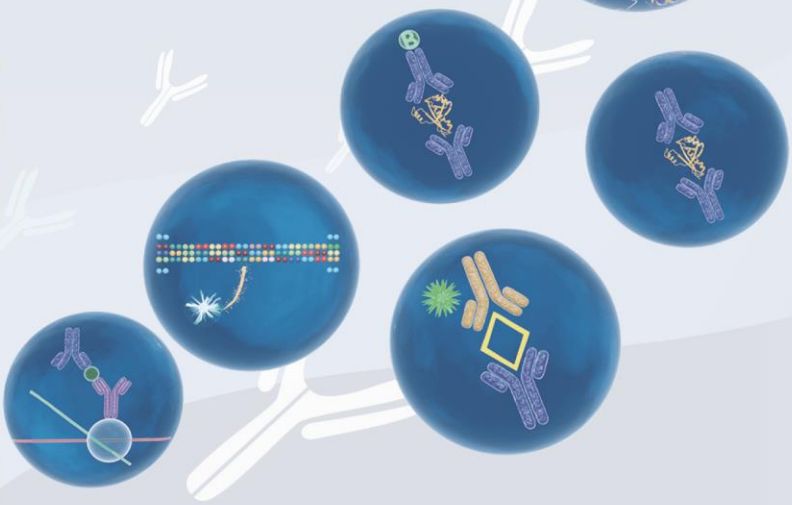


主要应用领域：

肿瘤标志物	心血管疾病	免疫检查点
感染	肾损伤标志物	败血症

适用样本：

细胞培养上清	血清、血浆	尿液
乳汁	唾液、房水、泪液	组织裂解液等



Luminex 多因子检测技术作为重要的生物标志物分析方法，在节约时间、样本及经费方面相较传统单因子定量检测方法具独特优势。

Bio-Techne 的 Luminex 检测试剂盒同时经过近 300 种缓冲液的筛选优化，作为金标准 Quantikine 试剂盒的延伸，在检测稳定性、定量准确性上一直受到国内外重点药企、CRO 公司青睐。 并在 Nature Medicine 等权威杂志有多篇应用文献发表，也已成为高校及医院科研首选的多因子筛选及验证品牌。

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全自动生化分析仪 Alinity c	国械注进20182400028	Abbott Gmbh & Co.KG
全自动化学发光免疫分析仪	国械注进20183400031	Abbott Gmbh & Co.KG

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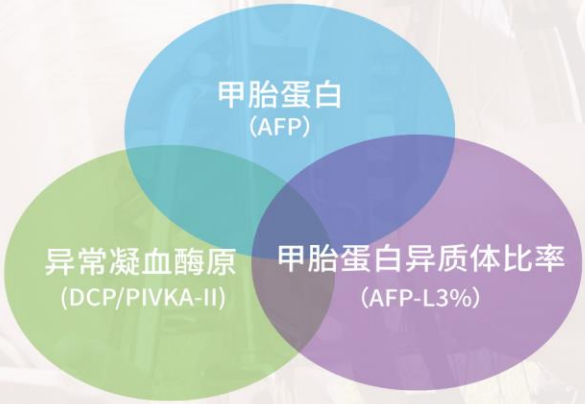
- 《慢性乙型肝炎防治指南(2019年版)》
- 《原发性肝癌诊疗规范(2019)》
- 《EASL临床实践指南:肝细胞癌的管理(2018)》
- 《APASL亚太临床实践指南:肝细胞癌的管理(2017)》



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由金域医学自主研发设计，拥有多项国家计算机软件著作权，以金域病理医生集团为后盾，为开展远程病理各项服务提供强大的信息技术平台支持和人员保障。以该平台为基础，金域构建覆盖全国的远程病理会诊网络及大数据平台。

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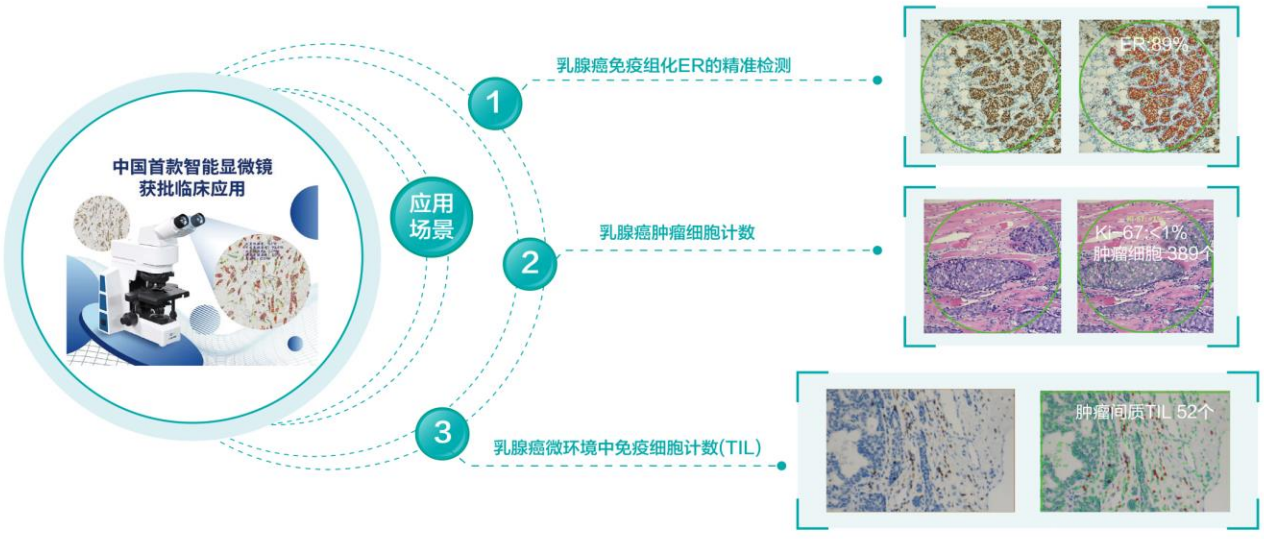

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- 可开展 **2700** 余项检测项目
- 服务 **23000** 多家医疗机构

- 超过 **2300** 个冷链物流网点
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- 年检测标本量超 **7000** 万例

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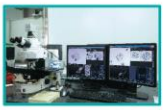

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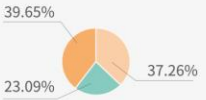
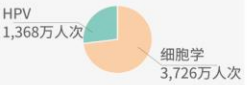
罕见病阳性样本数	宫颈癌筛查人次	25-羟基维生素D累计检测标本	遗传代谢病质谱检测数据	肾脏病理累计诊断标本
70,000⁺例	50,940,000⁺例	3,020,000⁺例	1,858,000⁺例	246,600⁺例

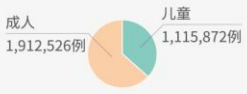


- 基因及基因组技术检出的阳性标本量占比37.26%
- 色谱质谱及酶学方法检出的阳性标本量占比23.09%
- 自身免疫性疾病阳性标本量占比39.65%

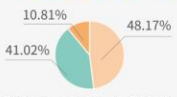
检出宫颈癌及癌前病变病例超**15**万例
助力国家“两癌”早筛早诊早治的方针



宫颈癌检出率 0.02%
癌前病变检出率 0.38%
HPV阳性率 14.36%

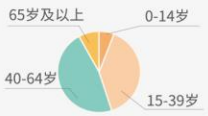


- 成人：1,912,526例
- 儿童：1,115,872例



氨基酸代谢病、有机酸血症、脂肪酸氧化代谢病
分别检出的阳性病例占总阳性病例的比例

- 氨基酸代谢病共检出2,991例，阳性检出率为1.61‰
- 有机酸血症共检出2,547例，阳性检出率为1.37‰
- 脂肪酸氧化代谢病共检出671例，阳性检出率为0.36‰



- 0-14岁：6%
- 15-39岁：39%
- 40-64岁：47%
- 65岁及以上：8%

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——— 格物致知，识微通元

公司介绍

新格元生物科技有限公司致力于将突破性的单细胞分析技术应用于科学研究、临床检测、健康管理和药物开发领域。公司拥有自主知识产权的 GEXSCOPE®单细胞技术平台，并推出了全球首家一站式，全方位的单细胞解决方案—— Singleron 单细胞系统，为单细胞分析技术在临床检测上的应用扫除了障碍。

自主知识产权　　全流程产品提供　　临床应用开发

公司业务

单细胞测序产品

SynEcoSys™
单细胞数据库

CeleScope™
数据分析软件

GEXSCOPE®
海量单细胞测序试剂盒

Singleron Matrix™
单细胞测序文库构建系统

单细胞测序服务

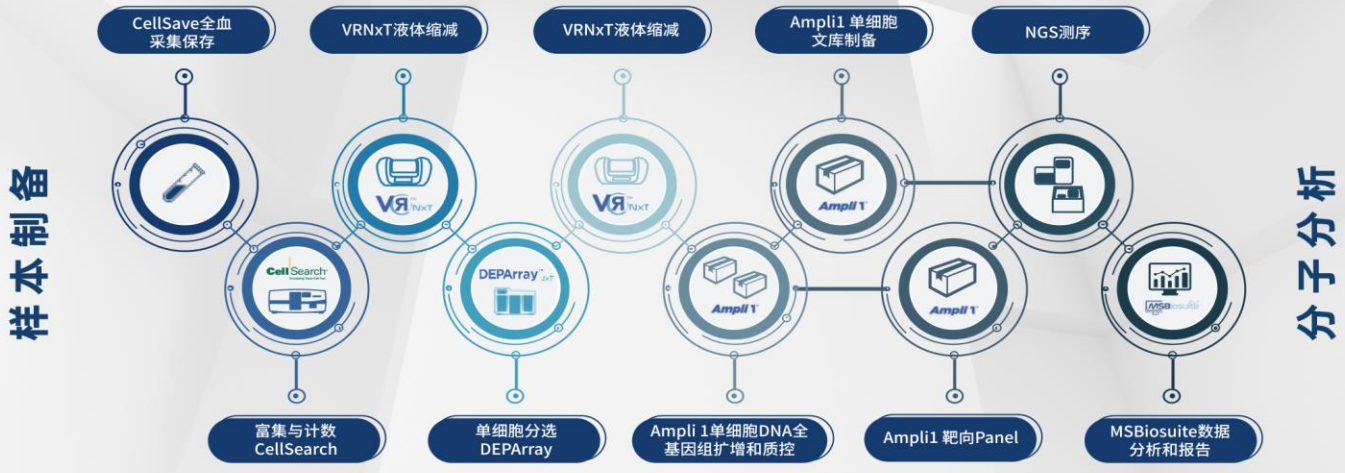
- 单细胞转录组测序
- 单细胞核转录组测序
- 单细胞免疫组库测序
- 空间转录组测序
- 单细胞ATAC测序
- 单细胞测序多组学联合分析
- 单细胞CRISPR测序分析

欢迎莅临新格元生物科技有限公司展位交流学习(展位号B9)

MENARINI
silicon biosystems

美纳里尼硅生物系统(Menarini Silicon Biosystems)是一家总部位于意大利博洛尼亚和美国宾夕法尼亚州亨廷顿谷(Huntington Valley)的生物技术公司,是美纳里尼制药集团(Menarini Group)的一部分。美纳里尼集团成立于1886年,在全球拥有1万7千名员工的国际性私有企业,2019年位居世界药企前50强中的第39位。美纳里尼集团于2013年收购硅生物系统(Silicon Biosystems) 成立美纳里尼硅生物系统公司,在欧洲、美洲和亚洲拥有三个运营中心。中国办公室位于上海市。

作为循环肿瘤细胞(CTC)行业的领导者,美纳里尼硅生物系统收购并结合了作为循环肿瘤细胞行业金标准也是唯一被中国药监局获批三类IVD产品的循环肿瘤细胞(CTC)检测设备与试剂:CellSearch 循环上皮细胞检测系统,联合完全自主创新且技术领先的DEPArray NxT (RUO)单细胞分离系统和下游单细胞测序Ampli1系列RUO产品,提供了CTC从计数、分型、单细胞精度分离、单细胞测序的全流程全覆盖检测平台。近年来为临床和科研端提供了强有力的技术支持,服务患者和临床医生及科研人员。CellSearch与DEPArray在液体活检领域各发表SCI文章超600篇和70篇。2019至2020年间,多项大型临床试验已顺利完成,部分重磅临床研究成果已在Nature Medicine (影响因子:36.1)、JAMA Oncology (影响因子:24.8)等顶尖期刊中发表。



美纳里尼硅生物系统循环肿瘤细胞(CTC)全流程分析平台

B61、B62 (签到处正对面)

详情请查阅:
http://www.siliconbiosystems.com/publications;
http://www.cellsearchctc.com/

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液体活检技术领导者

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- CTC-PCR检测系统
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实验成本，行业最低

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实验结果与临床一致性高

实验操作简单
机械化程度高，仪器自动生成微滴，需微滴转移

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Email：enquiry@cellomicsbio.com
http://www.cellomicsbio.com
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化疗药物疗效评估	109个化疗基因，评估23种化疗药物疗效及毒副风险
靶向治疗疗效预估	新增32个基因，总计106个靶向药物相关基因，解读80种获批靶药（新增10种）、多个临床试验靶药 74个基因全外覆盖，103个基因重要内含子覆盖，27个融合Partner，22个靶向药物相关HRR基因，全面提高各类罕见突变检出率
免疫治疗疗效预估	新增11个相关指标，总计41个免疫用药biomarker，预测11种免疫用药敏感性及风险性
肿瘤易感胚系检测	22个基因胚系解读，覆盖重要遗传因素
DNA修复通路	102个DDR基因

725基因内含子覆盖

2.31Mb

445基因全外显子覆盖

1267基因

深圳裕策生物科技有限公司

服务电话：400-9958-139　网址：www.yucebio.com　客服邮箱：service@yucebio.com

总部地址：深圳市盐田区大百汇中心　医学检验所地址：深圳市大鹏新区生命科学产业园A28栋2楼

扫码关注微信公众号

华大数极介绍

华大数极生物科技（深圳）有限公司（以下简称华大数极）创立于2019年，是华大基因旗下专注于癌症早筛业务和数极服务的子公司，致力于提供精准、普惠的癌症筛查检测和健康服务。

Envelope Health Ltd, established in 2019 as a subsidiary of BGI, focuses on cancer early detection and related data service. Our mission is to provide affordable solutions for cancer diagnosis and screening.

让癌症早筛人人可及

Precision Early Cancer Detection for Everyone

华常康

无创肠癌筛查基因检测
non-invasive stool DNA test for CRC

取样便捷
可居家自采样
只需采集5g粪便
全程只需要10min

准确性好
腺瘤灵敏度65%
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特异性89%

无创无忧
弥补肠镜不足
安全无创无痛
人群接受程度高

使用人群广
高危人群和关心肠道健康的非高危人群均可检测

华甘宁

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non-invasive cfDNA test for HCC

取样简单
一管血10ml

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多基因检测
25个肝癌特异性基因的甲基化状态

性能优异
特异性93.7%
I 期前灵敏度91.8%

扫码了解更多

mindray 迈瑞

生 命 科 技 如 此 亲 近

试剂菜单

肿瘤标志物	甲状腺功能	性激素	生长激素	传染病	唐筛	心肌
AFP	FT3	TotalβHCG	GH*	HBsAg	PAPP-A*	TnI
CEA	FT4	LH	IGF-1*	Anti-HBs	Free β-HCG*	CK-MB
CA125	T3	FSH		HBeAg	AFP	MYO
CA15-3	T4	PRL		Anti-HBe		BNP
CA19-9	TSH(第三代)	TESTO		Anti-HBc		
TPSA	Anti-TG	PROG		HIV Ag/Ab(第四代)		
FPSA	TG	E2		Anti-TP		
FERR	Anti-TPO	E3		Anti-HCV		
CA72-4	rT3	Free testosterone*		HBeAg quantitative*		
NSE	TRAB*	17-OH PROG*		Anti-HBc IgM*		
Cyfra 21-1		SHBG*				
PG I		AMH*				
PG II						
TG						
CT						
SCCA						
HE4						
ProGRP						
CA50						
CA242						

激素类	糖尿病	骨代谢	贫血	肝纤	炎症	高血压	TORCH
Cortisol	Insulin	PTH(第二代)	Folate	LN	PCT	Renin	Toxo IgG*
ACTH	C-Peptide	CT	RBC Folate	HA		ALD	Toxo IgM*
DHEA-S		VD-T	VB12	PIIINP		ACTH	Rubella IgG*
			FERR	C IV		Cortisol	Rubella IgM*
							CMV IgG*
							CMV IgM*
							HSV-1/2 IgG*
							HSV-1/2 IgM*
							HSV-1 IgG*
							HSV-2 IgG*

*试剂注册中

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级联拓展

CL-6000i

CL-6000i*2(免疫互联拓展)

CL-6000i+BS-2000（生化免疫级联拓展）

CL-6000i模块化的设计，可与同型号仪器、BS-2000、BS-800仪器任意组合，具有自由的拓展互联功能。与同型号免疫互联拓展，实现速度扩展，组成全自动化学发光免疫流水线；与迈瑞生化高端产品实现功能拓展，组建生化–免疫血清工作站；同时CL-6000i可兼容后续实验室自动化前后处理系统

蔡司 CTC 循环肿瘤细胞全自动成像

创新解决方案

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Seeing beyond

- 全自动 CTC 扫描分析
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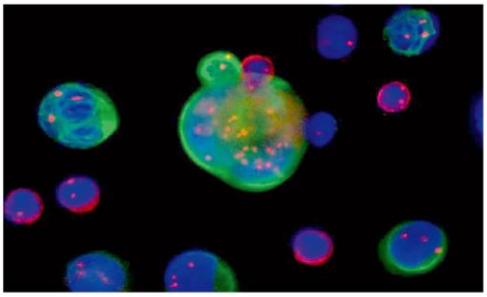
- 20~40 分钟完成一次扫描分析
- 兼容各种 CTC 试剂
- CFDA 认证技术



循环肿瘤细胞 (CTC) 液体活检

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中国目前首个且唯一获批尿路上皮癌适应症的PD-1单抗

百泽安®获领域两大权威指南推荐

CUA 2019版
《膀胱癌诊断治疗指南》[2]

唯一
获推荐的国产
PD-1单抗

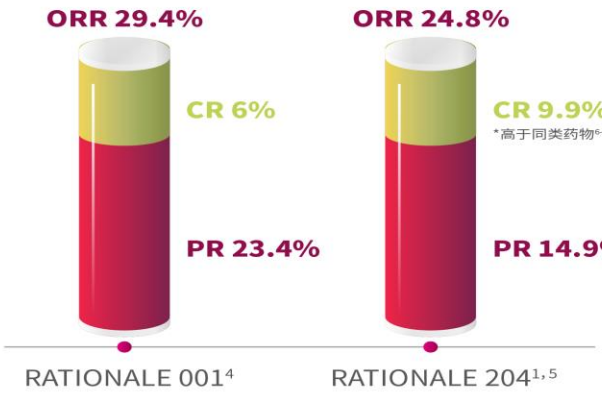
CSCO 2020版
《尿路上皮癌诊疗指南》[3]

首位
推荐用于转移性
UC患者二线治疗*
*首位推荐：替雷利珠单抗列于免疫治疗推荐同类药物首位

百泽安®用于晚期UC患者疗效和安全性良好

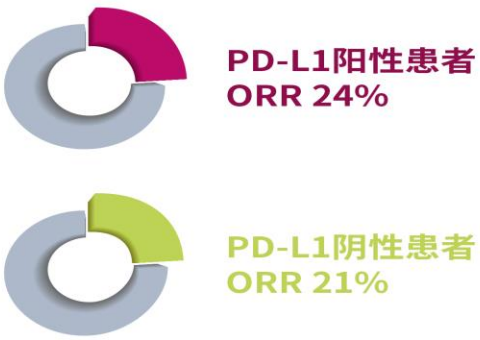
多项临床研究证据

注册研究入组人群贴近中国真实世界晚期UC患者，可更好指导临床实践



全人群均可获益

替雷利珠单抗用于晚期UC患者二线治疗的汇总分析表明，无论PD-L1表达状态，患者均可获益[5]



安全性良好： 大多数治疗相关不良事件（TRAEs）≤2级，且3级以上免疫相关不良事件（irAE）的发生率均小于5%[5]

1. 替雷利珠单抗注射液说明书 2. CUA 2019版《膀胱癌诊断治疗指南》 3. CSCO 2020《尿路上皮癌诊疗指南》 4. Poster Number: 76P, European Society for Medical Oncology-Immuno Oncology Congress 13-16 December 2018, Geneva, Switzerland 5. Poster Number: 920P European Society for Medical Oncology Congress September 27-October 1, 2019, Barcelona, Spain. 6. Bellmunt J, et al. N Engl J Med. 2017 Mar 16;376(11):1015-1026. 7. Sharma P, et al. Lancet Oncol. 2017 Mar;18(3):312-322. 8. Powles T, et al. Lancet. 2018 Feb 24;391(10122):748-757. 9. Powles T, et al. JAMA Oncol. 2017 Sep 14;3(9):e172411. 10. 2020 ASCO GU. Abstract 451

仅供医疗卫生专业人士参考使用
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ORIOMICS
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紧贴时代需求、立足临床痛点、专研前沿技术、引领早诊早筛

专研 + 创新 = 高品质

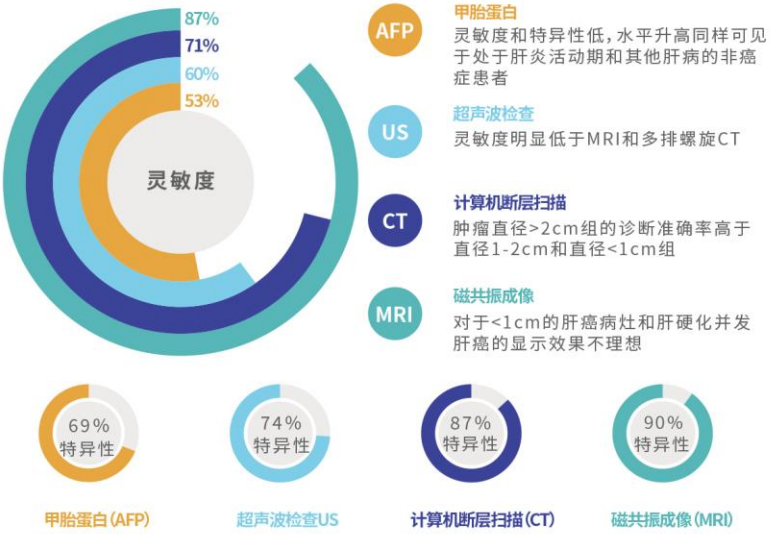
创新：独创的双层机器分析核心算法

全面：精选200个基因，6000个甲基化位点，同时检测ctDNA甲基化水平、甲基化状态和基因组拷贝数变异（CNV）

精准：I期肝癌检测特异性＞90%，敏感性＞90%

无创：仅需10ml外周血

现阶段用于肝癌诊断的影像学和血清学方法由于灵敏度和特异性不足，难以进行有效的肝癌早期诊断。



需求 + 技术 = 好产品

确诊不易 --- 肝癌早诊新选择

肝结节占位直径>2cm，影像学不典型

肝结节占位直径>2cm，影像学不典型，穿刺结果不明确

肝结节占位直径≤2cm，影像学不典型或两项结果不一致

无结节，影像学结果与AFP检测结果不一致

预防更难 --- 肝癌早筛新机遇

乙型肝炎病毒（HBV）感染

任何原因引起的肝硬化患者

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年龄超过40岁的男性

典型案例：

崔XX(HC-275)，女，55岁，首次诊断为乙肝伴肝硬化，使用利为康检测多个指标呈肿瘤特征，最后风险评分为9分，属于高风险。首诊三月后复查，确诊为肝细胞性肝癌。

翱锐生物成立于2016年,专注于肿瘤无创早筛和癌症精准诊断。公司依托强大的生物技术信息分析团队，采取无创液体活检技术，结合独创的双层机器分析核心算法，针对早期肝癌病人的拷贝数变异及肿瘤甲基化特征在全基因组的水平上进行分析比对，已成功研发出高灵敏度、高特异性的肝癌早筛产品-利为康。公司准确把握肿瘤精准治疗与全程管理的大趋势，通过持续的技术创新与优化，拓展肿瘤诊断全流程产品的研发，包括早期筛查，辅助诊断，用药指导，疗效评估，治疗监测，复发耐药检测、预后监测等。

MSD
增辉生命

可瑞达®
(帕博利珠单抗注射液) 100mg

创肺凡 钥启新生

可瑞达®
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已获国家药品监督管理局批准
3*个晚期一线非小细胞肺癌适应症#

* 联合化疗适用于转移性非鳞状NSCLC一线治疗
联合化疗适用于转移性鳞状NSCLC一线治疗
单药适用于PD-L1阳性的局部晚期或转移性NSCLC一线治疗

国家药品监督管理局批准的帕博利珠单抗的非小细胞肺癌适应症为：

帕博利珠单抗联合培美曲塞和铂类化疗适用于表皮生长因子受体(EGFR)基因突变阴性和间变性淋巴瘤激酶(ALK)阴性的转移性非鳞状非小细胞肺癌(NSCLC)的一线治疗。

帕博利珠单抗联合卡铂和紫杉醇适用于转移性鳞状非小细胞肺癌(NSCLC)患者的一线治疗。

帕博利珠单抗适用于由国家药品监督管理局批准的检测评估为PD-L1肿瘤比例分数(TPS)≥1%的表皮生长因子受体(EGFR)基因突变阴性和间变性淋巴瘤激酶(ALK)阴性的局部晚期或转移性非小细胞肺癌一线单药治疗。

PD-L1：程序性死亡配体

09-2022-CN-KEY-03266

Gene+吉因加
基因科技 维护健康

18万+
检测样本数

124+
SCI文章发表

200+
合作科研项目

170+
重点合作医院

1000+
累计影响因子

23家
制药企业合作伙伴

数据统计至2020.10

吉因加 肿瘤用药伴随检测系列产品

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