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·临床研究·

结直肠癌肝转移差异表达基因与信号通路分析

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[摘 要] **目的:**探讨结直肠癌(colorectal cancer, CRC)肝转移的关键基因和分子机制,为CRC肝转移的治疗提供潜在靶点和生物标志物。**方法:**基于生物信息学方法从GEO数据库下载CRC肝转移基因表达数据集,筛选差异表达基因(differentially expressed gene, DEG),利用DAVID在线工具对DEG进行GO和KEGG富集分析,构建蛋白互作(protein-protein interaction, PPI)网络图,筛选出CRC关键基因并进行预后分析。**结果:**从183例CRC组织标本和39例CRC肝转移组织标本中筛选出321个DEG,其中上调基因153个、下调基因168个。GO和KEGG富集分析结果显示,DEG的功能主要涉及蛋白质激活级联反应、炎症反应、细胞外基质、血小板脱颗粒、补体与凝血级联反应等。PPI网络图筛选出8个CRC关键基因为ALB、APOB、FGA、F2、APOA1、SERPINC1、FGG和AHSG。生存分析发现,SERPINC1、FGG表达高的患者预后不良(均$P<0.05$)。**结论:**DEG的生物学功能和信号通路与CRC肝转移的发生发展相关,8个CRC关键基因可能是CRC肝转移治疗的潜在靶点,SERPINC1、FGG可能成为新的预后标志物。

[关键词] 结直肠癌;肝转移;生物信息学;差异表达基因
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Analysis of differentially expressed genes and signaling pathways in colorectal cancer with liver metastasis

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[Abstract] Objective: To explore the key genes and molecular mechanisms of liver metastasis in colorectal cancer (CRC), and to provide potential targets and biomarkers for the treatment of CRC with liver metastasis. **Methods:** Based on the bioinformatics method, the gene data sets of CRC liver metastasis were downloaded from the GEO database to screen the differentially expressed genes (DEGs); the GO and KEGG enrichment analyses of DEGs were performed by using DAVID online tool, and the protein-protein interaction (PPI) network was constructed to screen out the key genes, and subsequently the prognosis was analyzed. **Results:** A total of 321 DEGs were selected from 183 CRC specimens and 39 liver metastasis specimens, including 153 up-regulated genes and 168 down-regulated genes. The results of enrichment analysis of GO and KEGG showed that the functions of DEGs were mainly related to protein activation cascade, inflammatory response, extracellular matrix, platelet degranulation, complement and coagulation cascade reaction etc. 8 key CRC genes (ALB, APOB, FGA, F2, APOA1, SERPINC1, FGG and AHSG) were screened by PPI network. Survival analysis showed that patients with high expressions of SERPINC1 and FGG had poor prognosis (all $P<0.05$). **Conclusion:** The biological functions and signaling pathways of DEGs are related to the occurrence and development of liver metastasis. The 8 key genes may be the potential therapeutic targets of CRC liver metastasis, and SERPINC1 and FGG may be new prognostic markers.

[Key words] colorectal cancer (CRC); liver metastasis; bioinformatics; differentially expressed genes (DEGs)
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结直肠癌(colorectal cancer,CRC)是全球范围发病率居第3位、病死率居第2位的恶性肿瘤。癌症统计数据[1-3]显示,2018年全球有180万例CRC新发病例和88万例病死病例,中国CRC发病率和病死率的上升速度高于全球水平。晚期CRC发生远处转移以肝转移为主,占比超70%。早期接受CRC根治性切

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除术的患者仍有远处转移的风险，发生肝转移的5年累积率为14.5%，肝转移患者5年生存率低至6.1%，因此CRC肝转移成为重要的预后因素[4]。有研究[5-8]发现，S100P、CD133、LIP-C、APOBEC3G等基因影响CRC肝转移的过程。CRC肝转移过程涉及肿瘤细胞溶解基质、黏附减弱、脱离原发灶、经淋巴管或血管进入肝脏定植增生、形成新生血管等，通过多条信号通路及多个分子的共同参与，过程十分复杂，其分子机制有待深入研究。随着基因芯片技术和生物信息学分析的迅速发展，为恶性肿瘤的发生与进展机制提供了新的研究手段。本研究从整合公共基因芯片数据库（gene expression omnibus，GEO)下载CRC和CRC肝转移组织的基因芯片，通过生物信息学方法分析获得CRC肝转移的差异表达基因（differentially expressed gene, DEG），筛选出CRC的关键基因，对其进行功能、通路、蛋白互作（protein-protein interaction, PPI）网络和预后分析，旨在为CRC肝转移的机制提供新的理论依据。

1　资料与方法

1.1　基因芯片数据的来源

以“colorectal cancer liver metastasis”为关键词，利用美国国家生物技术信息中心（National Center for Biotechnology Information, NCBI）平台提供的GEO数据库进行检索筛选。GEO数据库是一个公开的基因组数据库，包含了整个基因表达数据、芯片和微阵列。从该数据库获得CRC肝转移患者相关基因表达数据集GSE41258[9]（GPL96平台[HG-U133A]Affymetrix Human Genome U133A Array），依据平台中的注释信息，纳入CRC原发灶和肝转移的组织标本，剔除重复标本，获得183例CRC原发灶组织标本和39例肝转移组织标本，患者平均年龄63.5岁。

1.2　DEG的筛选

利用GEO数据库的GEO2R在线工具（http://www.ncbi.nlm.nih.gov/geo/geo2r）筛选DEG。设置筛选条件：(1)校正后P<0.05（adjusted P-values，adj.P）；(2) |log FC|>1(fold change，FC)，同时满足以上2个条件的基因有统计学意义。

1.3　DEG的GO和KEGG富集分析

用于注释、可视化和集成发现的数据库（Database for Annotation, Visualization and Integrated Discovery Database，DAVID）整合了生物数据和分析工具，能够对基因和蛋白质进行功能注释。将筛选的DEG上传至DAVID生物信息数据库（version 6.7，http://david.ncifcrf.gov）进行进行基因本体（gene ontology, GO）和基因组百科全书数据库（Kyoto Encyclopedia of Genes and Genomes，KEGG）分析，以P<0.05表示差异具有统计学意义。

1.4　PPI网络图的构建和基因模块分析

将筛选的DEG上传至检索相互作用基因的搜索工具（Search Tool for the Retrieval of Interacting Genes，STRING）网站（http://string-db.org）绘制出PPI网络图，并采用Cytoscape（version 3.7.1）软件绘制成可视化网络互作图。Cytoscape作为生物信息学软件平台，通过构建PPI网络将分子交互网络可视化。再使用Cytoscape中的插件MCODE（Molecular Complex Detection Technology, version 1.4.2）工具识别可视化网络图中最重要的模块。MCODE选择标准：MCODE scores>5，degree cut-off=2，node score cut-off =0.2，Max depth=100，k-score=2。

1.5　CRC关键基因的筛选和分析

筛选出节点值排名前8位的CRC关键基因，使用Cytoscape中的插件BiNGO（Biological Networks Gene Oncology，version 3.0.3）工具绘制GO富集可视化网络图。利用cBioPortal的Kaplan-Meier曲线对关键基因的总生存期（overall survival，OS）和无进展生存期（progression-free survival，PFS）进行分析，绘制预后曲线图。

2　结　果

2.1　筛选出321个DEG

在GEO数据库GSE41258数据集共纳入符合要求的样本222个（183例CRC组织标本、39例CRC肝转移组织标本）。GEO2R在线工具进行分析，根据设置条件adjusted P-values<0.05和|log FC|>1筛选数据集得到321个DEG，其中上调基因153个、下调基因168个。DEG聚类热图见图1，DEG火山图见图2。

2.2　DEG的GO和KEGG富集分析结果

使用DAVID网站对上传的DEG进行GO和KEGG富集分析，其中GO富集分析将DEG功能注释分为3类：生物过程（biological processes，BP）、细胞组分（cell component，CC）和分子功能（molecular function，MF），部分结果见表1。BP包括蛋白质激活级联反应、炎症反应、细胞外基质、血小板脱颗粒、防御反应；CC包括细胞外间隙、血液微粒、细胞外小泡、细胞外泌体、囊腔、膜结合小泡；MF包括肽酶活性调节、内肽酶抑制剂活性、丝氨酸水解酶活性、丝氨酸内肽酶活性、氧结合。KEGG富集通路分析部分结果见表1，包括补体与凝血级联反应、化学致癌、药物代谢-细胞色素P450、类固醇激素生物合成、亚油酸、朊病毒病、代谢途径等。

2.3 成功构建PPI网络图

使用STRING网站和Cytoscape软件构建的PPI网络图（图3），筛选出的DEG共同构成结构复杂的多中心PPI网络。运用MCODE插件得到可视化网络图中最显著的模块（图4）。

图1 DEG聚类热图

Fig.1 DEG clustering heat map

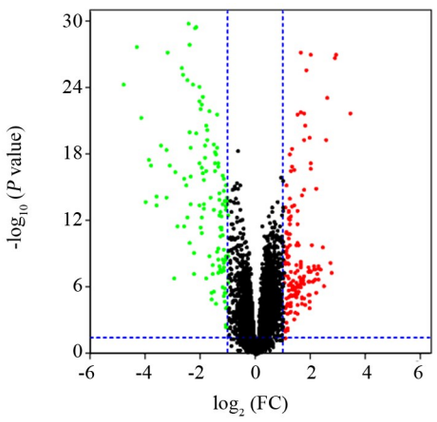


图2 DEG火山图

Fig. 2 The volcano map of DEGs

2.4 筛选出CRC的8个关键基因

通过MCODE插件得到DEG的节点度，选取节点度排名前8的关键基因，分别是ALB(degree=92)、APOB(degree=65)、FGA(degree=62)、F2(degree=61)、APOA1(degree=60)、SERPINC1(degree=58)、FGG(degree=56)、AHSG(degree=55)。使用BiNGO插件绘制GO富集可视化网络图（图5），发现关键基因的功能相互作用。通过Kaplan-Meier曲线对关键基因进行预后OS分析结果（图6）显示，SERPINC1高表达组的OS明显短于低表达组（P<0.05），FGG高表达组的PFS明显短于低表达组（P<0.05），提示两基因在CRC肝转移整体生存时间上可能发挥着一定的作用。

3 讨 论

CRC肝转移患者5年OS率极低，肝切除术为目前最有效的治疗方式，然而术后仍有2/3的患者复发，早期发现对CRC的治疗具有重要意义，因此CRC肝转移相关生物标志物、信号通路、分子机制亟待深入研究。近年来开展了多项关于CRC发生与转移的分子机制研究，发现KRAS、p53、SMAD4和BRAF突变在CRC转移中发挥重要作用[10]；KRAS突变通过上调TGF-β信号转导促使CRC侵袭与转移[11]；CXCR4和CCR6与CRC肝转移过程密切相关[12]，肝转移的分子机制尚需进一步明确。生物信息学方法可以帮助分析CRC肝转移基因层面的变化，以期发现潜在的基因靶点和生物标志物。

本研究基于GEO数据库对数据集GSE41258的

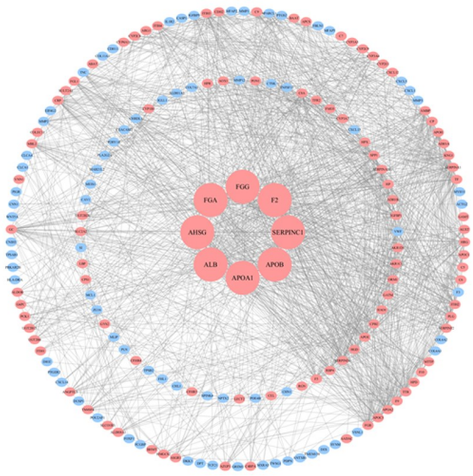
组织标本进行筛选，运用GEO2R对纳入的222例组织标本进行分析，共获得321个DEG，包括上调基因153个、下调基因168个。通过GO和KEGG富集分析，DEG的功能主要富集在蛋白质激活级联反应、炎症反应、细胞外基质、血小板脱颗粒、补体与凝血级联等。在CRC肝转移的过程，如KRAS/BRAF/ERK、Wnt/β-catenin等信号通路发生级联反应，通过复杂的生物学过程完成细胞增殖、迁移[13]。TNF-α、IL-6、TGF-β和IL-10等炎性介质引起肿瘤微环境的炎症反应，参与上皮间质转化（epithelial-mesenchymal transition，EMT）、血管形成及肝转移过程[14-15]。有研究[16]发现，癌胚抗原可作为促炎剂促进分泌以上细胞因子，以保护CRC细胞免受活性氧自由基的杀伤作用，并顺利在肝内定植完成转移。CRC细胞与细胞外基质相互作用，受蛋白酶影响肿瘤细胞的黏附性降低，从而引起远处转移的发生，细胞外基质中成分的改变如PAD4、TIMP-1等促进了肝转移的过程[17]。凝血过程通过血小板脱颗粒，释放各类生长因子，抑制NK细胞和募集巨噬细胞，促进CRC的血行播散[18]。已有研究[19,20]表明，补体可通过修饰细胞膜引起凝血级联的过度活化，凝血的过度激活形成高凝状态和缺氧环境，对肿瘤的进展起着关键的作用。

表1 DEG的GO和KEGG富集分析部分结果

Tab.1 Partial results of GO and KEGG enrichment analysis of DEGs

Classification	Serial number	Function	Count	*P*
BP	GO:0072376	Protein activation cascade	27	7.97E-24
	GO:0002526	Acute inflammatory response	25	8.38E-22
	GO:0006954	Inflammatory response	39	2.93E-17
	GO:0030198	Extracellular matrix organization	29	1.34E-16
	GO:0006953	Acute-phase response	15	1.41E-16
	GO:0043062	Extracellular structure organization	29	1.45E-16
	GO:0002576	Platelet degranulation	19	2.39E-16
	GO:0006952	Defense response	57	1.02E-15
	GO:0032101	Regulation of response to external stimulus	39	1.99E-15
	GO:0009605	Response to external stimulus	66	6.63E-15
CC	GO:0005615	Extracellular space	89	1.93E-38
	GO:0072562	Blood microparticle	38	1.01E-36
	GO:0005576	Extracellular region	144	1.06E-34
	GO:0044421	Extracellular region part	128	5.84E-31
	GO:1903561	Extracellular vesicle	99	2.81E-23
	GO:0043230	Extracellular organelle	99	2.88E-23
	GO:0070062	Extracellular exosome	98	8.54E-23
	GO:0060205	Cytoplasmic membrane-bounded vesicle lumen	24	4.68E-22
	GO:0031983	Vesicle lumen	24	5.91E-22
	GO:0031988	Membrane-bounded vesicle	106	2.71E-19
MF	GO:0061134	Peptidase regulator activity	21	8.21E-13
	GO:0004866	Endopeptidase inhibitor activity	18	1.47E-11
	GO:0004857	Enzyme inhibitor activity	25	1.67E-11
	GO:0061135	Endopeptidase regulator activity	18	2.53E-11
	GO:0030414	Peptidase inhibitor activity	18	3.29E-11
	GO:0004867	Serine-type endopeptidase inhibitor activity	14	7.43E-11
	GO:0017171	Serine hydrolase activity	21	9.46E-11
	GO:0004252	Serine-type endopeptidase activity	20	1.03E-10
	GO:0008236	Serine-type peptidase activity	20	5.71E-10
	GO:0004175	Endopeptidase activity	25	2.26E-09
KEGG	hsa04610	Complement and coagulation cascades	23	4.55E-23
	hsa05204	Chemical carcinogenesis	15	4.54E-11
	hsa00982	Drug metabolism - cytochrome P450	13	1.08E-09
	hsa00980	Metabolism of xenobiotics by cytochrome P450	13	3.00E-09
	hsa00830	Retinol metabolism	11	9.63E-08
	hsa00140	Steroid hormone biosynthesis	10	4.63E-07
	hsa00350	Tyrosine metabolism	6	2.82E-04
	hsa00591	Linoleic acid metabolism	5	1.36×10^{-3}
	hsa01100	Metabolic pathways	34	3.18×10^{-3}

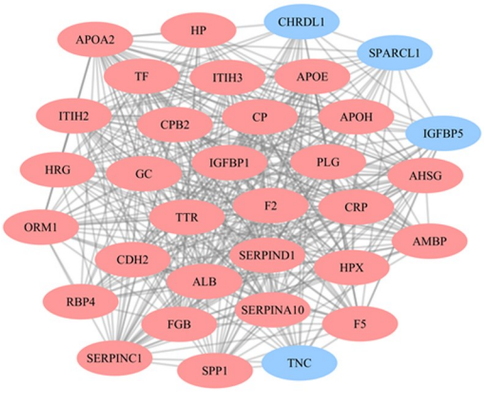
BP: Biological processes; CC: Cell component; MF: Molecular function



Red: Up-regulated genes; Blue: Down-regulated genes

图3 DEG的PPI网络图

Fig.3 PPI network of DEGs



Red: Up-regulated genes; Blue: Down-regulated genes

图4 最显著模块的PPI网络图

Fig.4 PPI network of the most significant modules

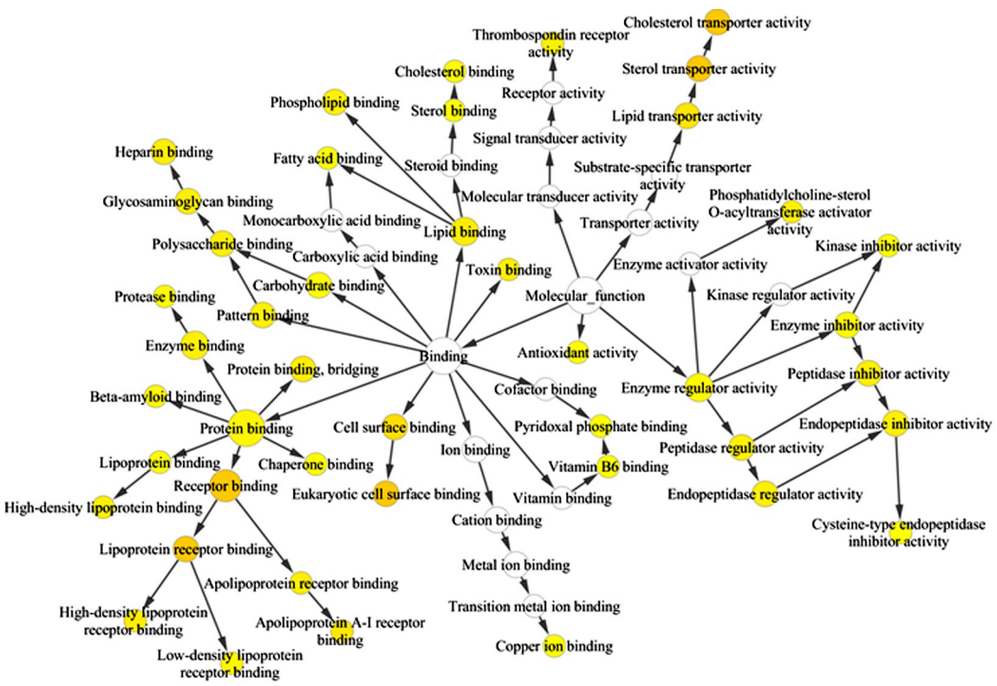
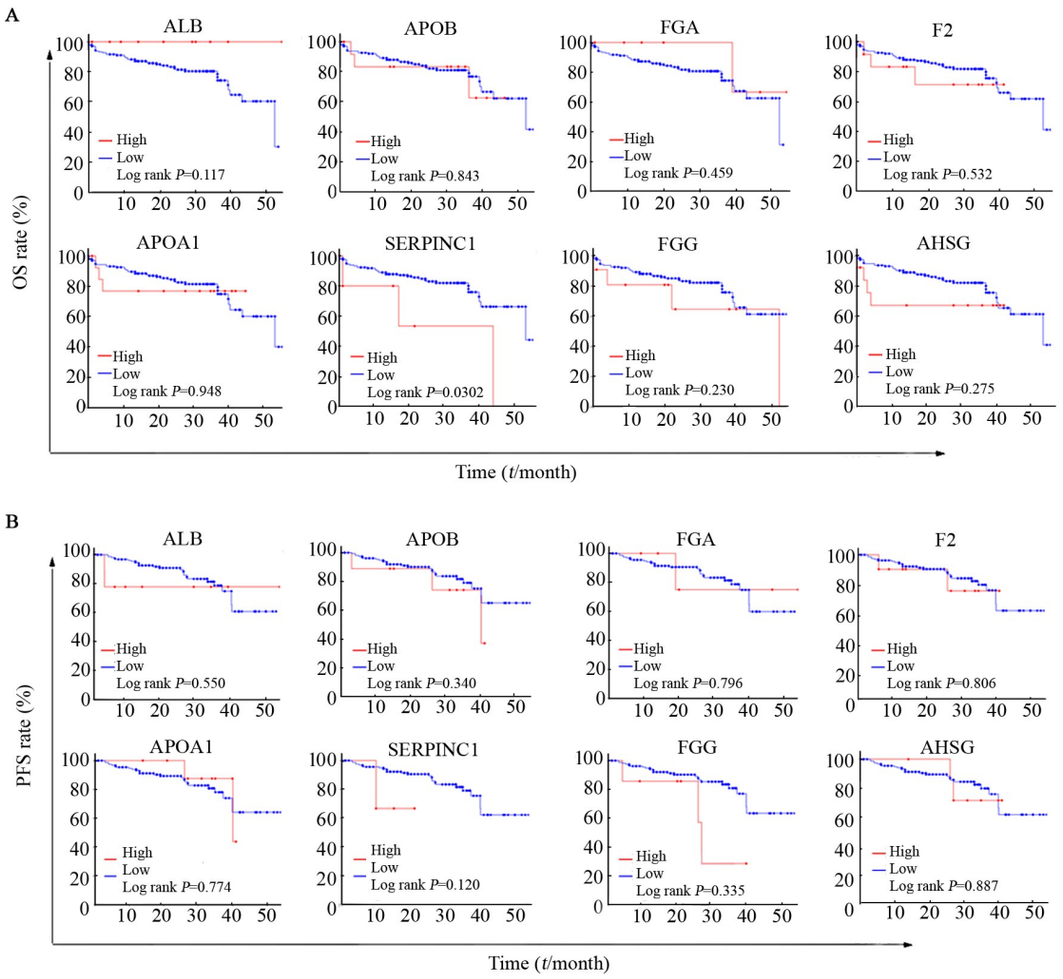


图5 CRC关键基因的GO可视化网络（MF网络图）

Fig.5 Go visualization network of key genes (MF network diagram)

依据Cytoscape软件获得节点度前8位的CRC关键基因是ALB、APOB、FGA、F2、APOA1、SERPINC1、FGG和AHSG，可能影响CRC肝转移的发展进程。ALB是由肝产生的血清白蛋白，具有肝特异性，研究[21]发现CRP/ALB比值可以反映肿瘤在微环境中侵袭或扩张引起炎症反应的情况，并成为CRC肝转移术后的预后指标。APOB与APOA1为不同表型的载脂蛋白，分别与低密度脂蛋白和高密度脂蛋白的代谢和功能相关，参与胆固醇的运输。尽管APOB与CRC的转移机制尚未完全清晰，但通过临床数据发现CRC的风险与APOB水平呈正相关，对APOB表达进行测定，发现在CRC肝转移患者中明显增加[22]。APOA1的水平则与CRC的风险呈负相关，且与预后相关[23]。但对CRC肝转移患者亦有报道APOA1表达上调[24]。FGA基因编码纤维蛋白原（fibrinogen，FG）的Aα多肽链，FGG基因编码FG的γ多肽链，研究发现FG在CRC血管生成中发挥作用，促进肿瘤进展[25]，新生血管为CRC肝转移进展的助力因素，同时本研究发现FGG与PFS存在负相关性。此外，FG-ALB比值（FARI）可作为CRC肝转移手术预后的独立预测指标，肝转移患者的纤溶水平更高，与术后复发相关[26-27]。F2为叉头框转录因子F2（forkhead box F2，FOXF2），是调控细胞外基质合成和EMT的关键转录因子，miR-182/FOXF2可能参与调节细胞外基质重

构，促进CRC浸润和转移[28]。Kaplan-Meier曲线分析发现，SERPINC1高表达与患者预后不良相关。SERPINC1基因编码丝氨酸蛋白酶抑制剂，调节凝血、补体激活、炎症反应等过程，在CRC发生和进展过程中发挥潜在作用[29]，这与本研究分析结果一致。AHSG基因编码Fetuin-A蛋白，亦称α2-Heremans-Schmid糖蛋白（由肝合成），可以抑制胰岛素发挥作用，而高胰岛素血症会增加CRC风险。研究[30]发现，Fetuin-A与CRC风险存在一定的正相关关系。Fetuin-A通过触发外泌体介导肿瘤细胞黏附和扩散，在肿瘤的进展中发挥作用[44]。



A: OS analysis; B: PFS analysis

图6 关键基因对CRC患者的预后影响分析

Fig.6 Analysis of the effect of key genes on prognosis of CRC patients

综上所述，本研究基于生物信息学技术深入挖掘CRC肝转移的DEG及关键基因，探究其生物功能和信号通路，预测CRC关键基因可能通过复杂的基因网络调控在CRC肝转移过程中发挥作用，有望成为CRC肝转移治疗的新的分子靶点。本研究预计为CRC肝转移的精准治疗提供新的方向和思路，但研究仍有不足之处，关键基因对CRC肝转移的作用结果仍需进一步实验验证。

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