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miR-129-5p调控的COL1A1作为胃癌潜在治疗靶点的生物信息学分析

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摘要：目的 应用生物信息学技术探索胃癌发病机制，为胃癌的防治提供生物信息学依据。**方法** 用GEO2R在线工具分析GSE79973中胃癌组织和正常胃黏膜组织的差异表达基因（Differentially expressed genes, DEGs），通过DAVID数据库对DEGs进行GO分析和KEGG通路富集分析，然后通过STRING数据库构建蛋白质相互作用网络，用Cytoscape软件进行关键基因（Hub基因）筛选和功能模块分析，并在GEPIA数据库对Hub基因进行验证，用Target Scan数据库预测调控靶基因的microRNAs，并用OncomiR分析microRNAs在胃癌组织中的表达及其与生存预后的关系。**结果** 共筛选出181个在胃癌中差异表达的基因。蛋白质互作网络筛选出10个Hub基因。DEGs功能分析主要涉及蛋白质消化吸收、PI3K-Akt信号通路、ECM-受体相互作用、血小板激活信号通路。GEPIA数据库验证显示COL1A1在胃癌组织中高表达，并和胃癌患者的不良预后有关。miR-129-5p与COL1A1 mRNA的3'UTR结合。与正常组织相比，miR-129-5p在胃癌组织中表达明显下调，且与胃癌患者预后具有一定相关性。**结论** miR-129-5p调控的COL1A1是胃癌潜在的治疗靶点。
关键词：胃癌；差异表达基因；COL1A1；miR-129-5p；生物信息学分析

Bioinformatics analysis of COL1A1 regulated by miR-129-5p as a potential therapeutic target for gastric cancer

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Abstract: Objective To explore the pathogenesis of gastric cancer through a bioinformatic approach to provide evidence for the prevention and treatment of gastric cancer. **Methods** The differentially expressed genes (DEGs) in gastric cancer and normal gastric mucosa in GSE79973 dataset were analyzed using GEO2R online tool. GO analysis and KEGG pathway enrichment analysis of the DEGs in DAVID database were performed. The protein interaction network was constructed using STRING database, and the key genes (Hub genes) were screened and their functional modules were analyzed using Cytoscape software. The GEPIA database was used to validate the Hub genes, and the Target Scan database was used to predict the microRNAs that regulate the target genes; OncomiR was used to analyze the expressions of the microRNAs in gastric cancer tissues and their relationship with the survival outcomes of the patients. **Results** A total of 181 DEGs were identified in gastric cancer, and 10 hub genes were screened by the protein-protein interaction network. Functional analysis showed that these DEGs were involved mainly in protein digestion and absorption, PI3K-Akt signaling pathway, ECM-receptor interaction and platelet activation signal pathway. GEPIA database validation showed that COL1A1 was highly expressed in gastric cancer tissues and was associated with a poor prognosis of patients with gastric cancer. MiR-129-5p was found to bind to the 3'UTR of COL1A1 mRNA, and compared with that in normal tissues, miR-129-5p expression was obviously down-regulated in gastric cancer tissues, and was correlated with the prognosis of the patients. **Conclusion** COL1A1 under regulation by MiR-129-5p is a potential therapeutic target for gastric cancer.
Keywords: gastric cancer; differentially expressed genes; COL1A1; miR-129-5p; bioinformatic analysis

胃癌是我国第2大肿瘤[1]，5年生存率全球仅为10%[2]，其高发病率和高死亡率严重威胁着人类健康，随着诊疗技术的发展，胃癌的发病率和死亡率在一些发达国家有稳步下降的趋势[3]，然而，亚洲仍有很高的发病率[4]，因此，深入探究胃癌的发病机制及新的治疗方法就显得尤为重要。近年来，大量生物标志物已应用于胃癌的早期诊断[5-6]，然而，这些生物标志物并没有被很好的整合，并且，这些生物标志物可在多种肿瘤中被检测到[7-8]，因此，对胃癌诊断和治疗的特异性靶点还需要进行深入的研究。

COL1A1是胶原家族的重要成员，被认为与癌症发生有关，COL1A1的异常表达在多种癌症中均有报道[9-11]。此外，Zang等[12]发现COL1A1在胃癌中存在差异表达，但COL1A1在胃癌中的临床意义仍不清楚。基因表达谱（GEO）数据库为癌症相关基因表达谱的生物信息学挖掘提供了可能[13]。本研究通过生物信息学方法筛选出胃癌芯片数据GSE79973中胃癌组织和正常胃黏膜组织的DEGs，对DEGs进行GO分析和KEGG通路富

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集分析，然后通过构建蛋白质-蛋白质相互作用（PPI）网络，筛选出Hub基因并验证，同时预测调控COL1A1的miRNAs，旨在为胃癌分子机制的进一步研究提供生物信息学依据，也为我们进行基因个体化治疗提供新的途径。

1 材料和方法

1.1 芯片数据来源

本研究从GEO (https://www.ncbi.nlm.nih.gov/geo/) 数据库下载基因芯片数据集GSE79973，芯片总共包含20例样本，其中10例正常胃黏膜组织和10例胃腺癌组织样本，其芯片平台是GPL570[HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array，表达数据为expression profiling by array，种属为Homo sapiens。

1.2 数据处理

用GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/)[14]在线工具分析胃癌样本与正常样本基因数据。将胃癌组织芯片GSE79973矩阵数据的探针名转化为基因名，对原始数据进行去重等处理后，以|logFC|>2且P<0.01的标准筛选出DEGs，用SangerBox软件绘制火山图。

1.3 DEGs的富集分析

为深入了解这些DEGs，我们用DAVID (the Database for Annotation, Visualization and Integrated Discovery，http://david.abcc.ncifcrf.gov/)在线分析数据库[15]对DEGs进行GO和KEGG通路富集分析[16-17]，以P<0.05为差异有统计学意义。

1.4 PPI网络构建和关键基因筛选

通过在线分析网站STRING (Search Tool for the Rtrieval of Interacting Genes, https://string-db.org/)[18]得到DEGs的蛋白互作网络，以TSV格式导出，将所得源文件导入Cytoscape[19]进行可视化分析，用插件cytoHubba进行Hub基因分析，选用MCC算法，选取前10个Hub基因。

1.5 PPI功能模块分析

为进一步明确胃癌可能的信号通路，我们在进行PPI网络构建后，用Cytoscape软件中MCODE插件对PPI网络进行聚类分析后得到PPI功能模块，然后用DAVID数据库将功能模块中的基因进行KEGG pathway分析。

1.6 关键基因验证分析

为进一步验证Hub基因，我们利用GEPIA (Gene Expression Profiling Interactive Analysis, http://gepia.cancer-pku.cn)数据库[20]分析Hub基因在胃癌组织和正常组织中的表达水平，并绘制Hub基因的Kaplan-Meiter生存曲线。

1.7 COL1A1和microRNAs关系预测

为了解COL1A1参与胃癌的发生发展机制，我们通过在线数据库Target Scan 7.2 (http://www.targetscan.org/)预测与COL1A1相互作用的microRNAs。

1.8 microRNAs在胃癌组织的表达及其与生存预后的关系

基于OncomiR数据库(http://www.oncomir.org)分析miRNA在胃癌组织和正常组织中的表达，并对其进行预后分析。

2 结果

2.1 胃癌和正常组织的DEGs

通过对基因芯片GSE79973进行数据分析，结果显示有181个DEGs（胃癌组/正常对照组），其中上调基因和下调基因分别为57个和124个（图1）。

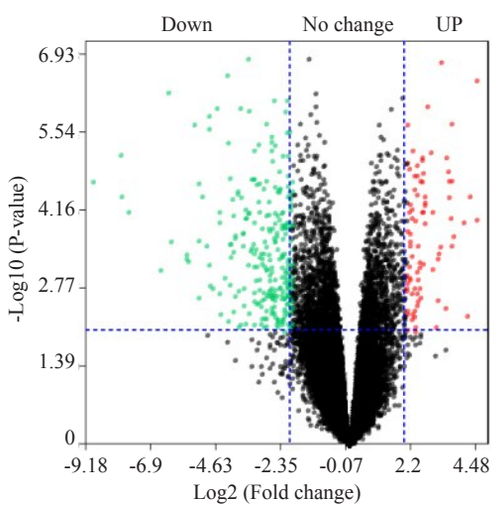

图1 差异表达基因火山图

Fig.1 Volcano plot of the differential expressed genes in gastric cancer.

2.2 GO和KEGG通路富集分析

GO可分为生物过程（biological process, BP）、细胞组成（cellular component, CC）和分子功能（molecular function, MF）。采用DAVID对181个DEGs进行GO和KEGG通路富集分析，结果如表1所示。DEGs主要涉及细胞黏附、细胞外基质组织、氧化还原过程、胶原蛋白分解代谢、异物的代谢等生物过程，细胞学组成分析显示这些基因大多参与细胞外泌体、细胞外基质、细胞外区等的组成。分子功能的变化主要集中在锌、铁离子结合、相同的蛋白结合、细胞外基质结构组成、肝素结合、氧化还原酶活性、血红素结合、氧气结合等。KEGG通路富集分析表明，差异基因主要涉及PI3K-Akt信号通路、ECM-受体相互作用、蛋白质消化吸收、化学致癌作用、视黄醇的新陈代谢、细胞色素P450代谢通路、矿物质的吸收、胃酸分泌等。

表1 胃癌相关差异表达基因的GO和KEGG通路富集分析

Tab.1 Enrichment analysis of GO and KEGG pathway of the differentially expressed genes in gastric cancer

Category	ID	Term	Count	*P*
BP	GO:0007155	Cell adhesion	20	1.00E-08
BP	GO:0030198	Extracellular matrix organization	17	8.62E-12
BP	GO:0055114	Oxidation-reduction process	13	0.004225507
BP	GO:0030574	Collagen catabolic process	10	2.99E-09
BP	GO:0006805	Xenobiotic metabolic process	8	4.07E-06
BP	GO:0001501	Skeletal system development	8	1.57E-04
BP	GO:0030199	Collagen fibril organization	7	8.18E-07
BP	GO:0008202	Steroid metabolic process	7	1.49E-06
BP	GO:0007586	Digestion	7	1.44E-05
BP	GO:0034220	Ion transmembrane transport	7	0.008647397
BP	GO:0001525	Angiogenesis	7	0.011406595
BP	GO:0051216	Cartilage development	6	1.35E-04
CC	GO:0005576	Extracellular region	45	3.21E-13
CC	GO:0005615	Extracellular space	37	1.51E-10
CC	GO:0070062	Extracellular exosome	32	0.047465783
CC	GO:0005887	Integral component of plasma membrane	19	0.040478934
CC	GO:0005578	Proteinaceous extracellular matrix	15	4.36E-08
CC	GO:0031012	Extracellular matrix	14	9.79E-07
CC	GO:0005788	Endoplasmic reticulum lumen	13	5.98E-08
CC	GO:0005581	Collagen trimer	11	4.00E-09
CC	GO:0016324	Apical plasma membrane	11	1.43E-04
CC	GO:0009986	Cell surface	11	0.013726185
CC	GO:0005604	Basement membrane	6	4.73E-04
CC	GO:0031090	Organelle membrane	6	7.37E-04
MF	GO:0008270	Zinc ion binding	16	0.049404886
MF	GO:0042802	Identical protein binding	13	0.017914572
MF	GO:0005201	Extracellular matrix structural constituent	9	6.31E-08
MF	GO:0008201	Heparin binding	8	3.16E-04
MF	GO:0016491	Oxidoreductase activity	8	0.001188406
MF	GO:0020037	Heme binding	7	8.49E-04
MF	GO:0019825	Oxygen binding	6	3.69E-05
MF	GO:0016705	Oxidoreductase activity, acting on paired donors, with Incorporation or reduction of molecular oxygen	6	9.43E-05
MF	GO:0004497	Monooxygenase activity	6	1.03E-04
MF	GO:0005178	Integrin binding	6	0.001598275
MF	GO:0005506	Iron ion binding	6	0.007975728
MF	GO:0008392	Arachidonic acid epoxygenase activity	5	5.14E-06
KEGG pathway	hsa04151	PI3K-Akt signaling pathway	12	0.001311204
KEGG pathway	hsa04512	ECM-receptor interaction	10	3.88E-07
KEGG pathway	hsa04974	Protein digestion and absorption	10	4.29E-07
KEGG pathway	hsa04510	Focal adhesion	10	4.07E-04
KEGG pathway	hsa05204	Chemical carcinogenesis	9	2.34E-06
KEGG pathway	hsa00830	Retinol metabolism	7	6.72E-05
KEGG pathway	hsa00982	Drug metabolism-cytochrome P450	7	9.47E-05
KEGG pathway	hsa00980	Metabolism of xenobiotics by cytochrome P450	7	1.52E-04
KEGG pathway	hsa04978	Mineral absorption	6	1.12E-04
KEGG pathway	hsa04971	Gastric acid secretion	6	0.001205941
KEGG pathway	hsa05146	Amoebiasis	6	0.006138929
KEGG pathway	hsa00010	Glycolysis/Gluconeogenesis	4	0.03749949

2.3 差异表达基因的PPI网络分析

将181个显著差异基因输入STRING数据库中，然后将所得数据导入Cytoscape 中，利用插件cytoHubba找出前10个Hub基因，分别为COL1A1、COL1A2、COL4A1、COL2A1、SERPINH1、COL6A3、COL11A1、COL10A1、COL12A1、COL8A1（图2）。

2.4 PPI功能模块分析

我们用Cytoscape软件中MCODE插件对PPI网络

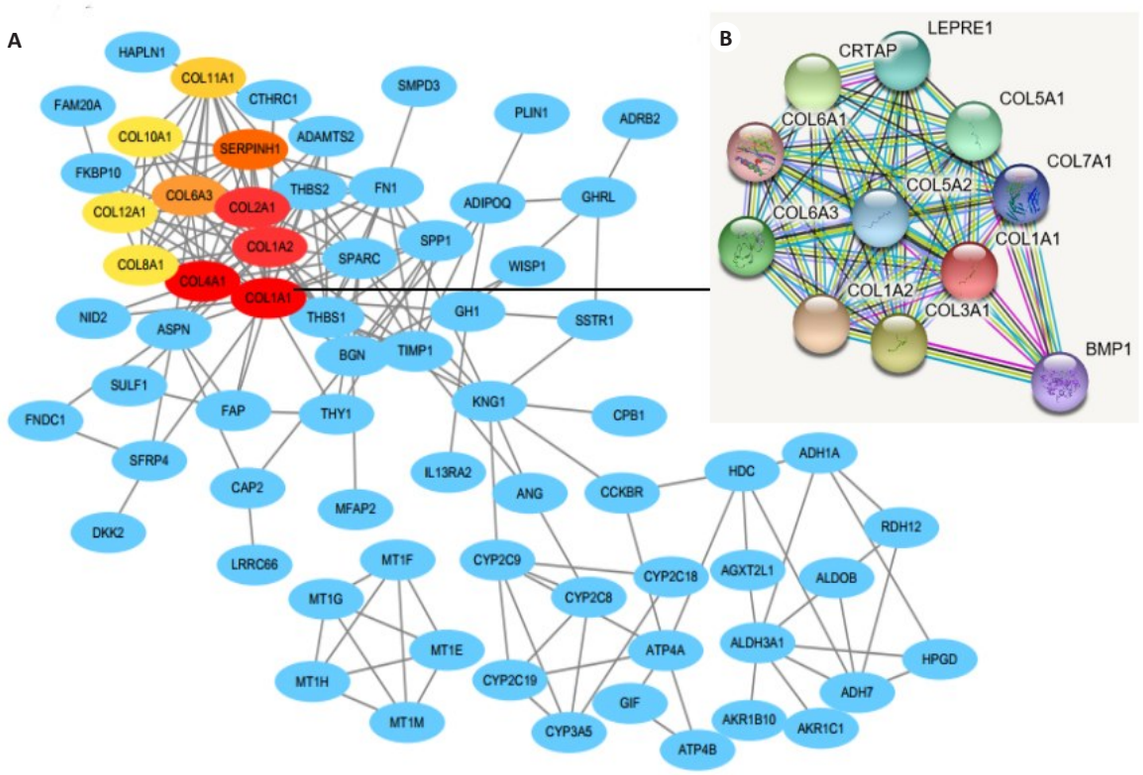

图2 差异基因编码蛋白质的 PPI 分析图和关键基因筛选

Fig.2 PPI analysis of the proteins encoded by the differential genes and screening of the key genes. **A**: PPI network for the DEGs; **B**: Amplification of the network for PPI associated with COL1A1.

进行聚类分析后得到不同的PPI功能模块，Score得分最高的模块如图3所示。然后我们通过DAVID在线分析工具对模块中包含的基因进行KEGG pathway分析，主要涉及蛋白质消化吸收、PI3K-Akt信号通路、ECM-受体相互作用、血小板激活信号通路(表2)。

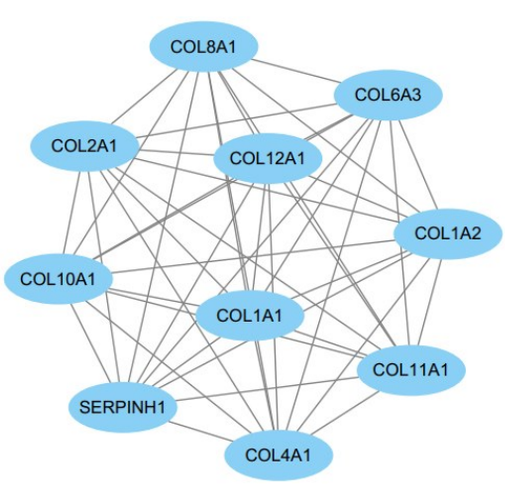

图3 功能模块图

Fig.3 Functional module diagram.

2.5 关键基因验证

用GEPIA数据库进一步验证分析了10个Hub基因在胃癌组织(408例)和正常组织(211例)的表达水平中的表达情况，发现除了COL2A1在胃癌组织中低表达外，其他9个Hub基因均在胃癌组织中高表达，差异有统计学意义(P<0.05，图4)。最后我们用GEPIA数据库绘制了Hub基因高表达胃癌组织和低表达胃癌组织的Kaplan-Meiter生存曲线，结果显示COL1A1、COL4A1、COL12A1高表达的胃癌组织的生存率低于低表达组织，差异具有统计学意义(P<0.05)，与患者不良预后密切相关(图5)。COL1A1的高表达与不良预后的相关性更加显著。

2.6 COL1A1与miRNA相互作用预测结果

用Target Scan数据库预测到miR-129-5p直接与COL1A1 mRNA的3'UTR结合，是COL1A1转录后调节因子(图5)。

2.7 miR-129-5p在胃癌中的表达水平与生存预后分析

经OncomiR数据库检索发现，miR-129-5p在胃癌组织中的表达显著低于正常组织(P=3.32e-05，图7A)。为分析miR-129-5p与胃癌生存预后之间的关系，我们使用此数据库进一步分析了miR-129-5p在胃癌组织中的表达水平与生存期的关系，结果发现，低表达组生存期时间短于正常组织，但差异不具有统计学意义(P=0.1182，图7B)。

表2 功能模块内基因的KEGG Pathway分析

Tab.2 KEGG pathway analysis of the genes in the functional modules

Category	ID	Term	Count	*P*
KEGG pathway	hsa04974	Protein digestion and absorption	7	3.69E-12
KEGG pathway	hsa04512	ECM-receptor interaction	5	3.51E-07
KEGG pathway	hsa05146	Amoebiasis	5	7.80E-07
KEGG pathway	hsa04510	Focal adhesion	5	1.12E-05
KEGG pathway	hsa04151	PI3K-Akt signaling pathway	5	8.61E-05
KEGG pathway	hsa04611	Platelet activation	4	1.27E-04

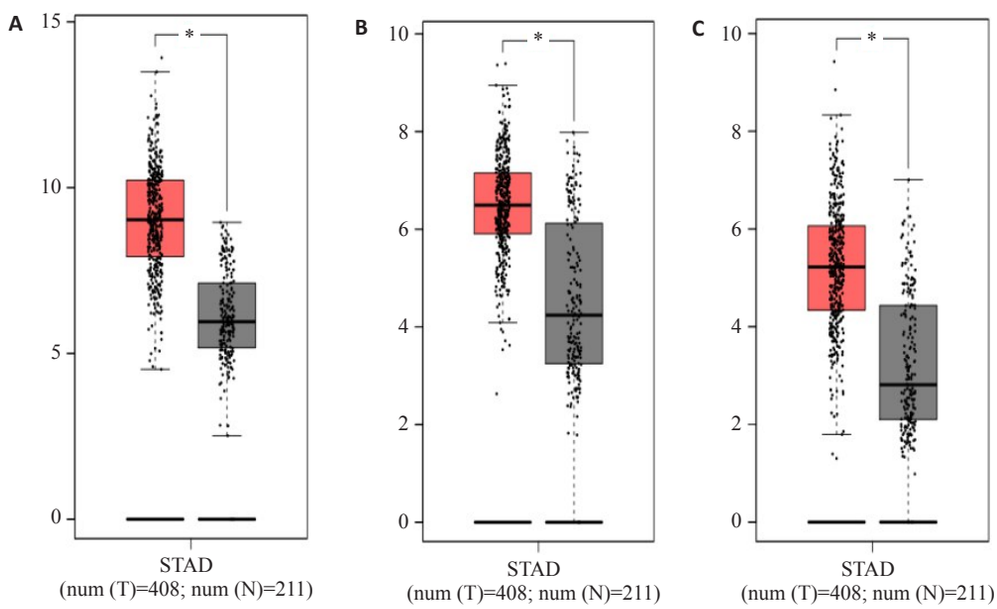

图4 胃癌关键基因在肿瘤组织及正常组织中的表达水平

Fig.4 Expression levels of the key genes in gastric cancer and normal tissues. **A**: COL1A1 expression level; **B**: COL4A1expression level; **C**: COL12A1expression level. **P*<0.05 *vs* normal tissue. The X axis represents tissue type, T the tumor, and N the normal tissue. The Y axis represents log2(TPM+1). TPM: Number of transcripts per million reads.

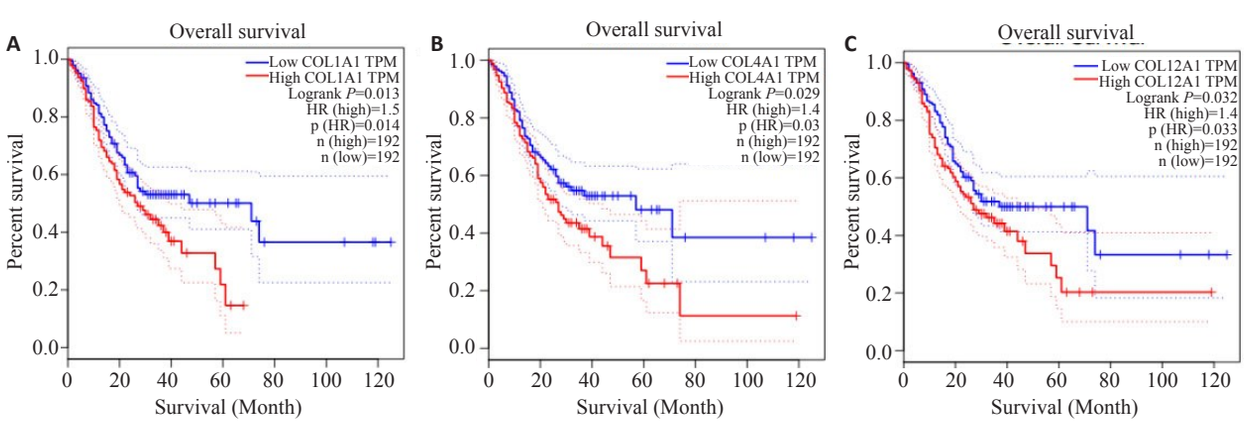

图5 关键基因对胃癌患者生存分析的验证结果

Fig.5 Validation of the key genes in survival analysis of the patients with gastric cancer. **A**: COL1A1 validation result; **B**: COL4A1 validation result; **C**: COL12A1validation result. The red line represents the high expression group, and the blue line represents the low expression group. HR: Risk ratio.

Position 96-102 of COL1A1 3' UTR	5'	...AACCCCCUCAAAAGCCAAAAAAU...
hsa-miR-129-5p	3'	CGUUCGGGUCUGGC--GUUUUUC
Position 225-231 of COL1A1 3' UTR	5'	...UGCAUUCAACCUUACCAAAAAAA...
hsa-miR-129-5p	3'	CGUUCGGGUCUGGCGUUUUUC

图6 COL1A1 mRNA 3'UTR中miR-129-5p结合位点的预测结果
Fig.6 Prediction of miR-129-5p binding sites in COL1A1 mRNA 3'UTR.

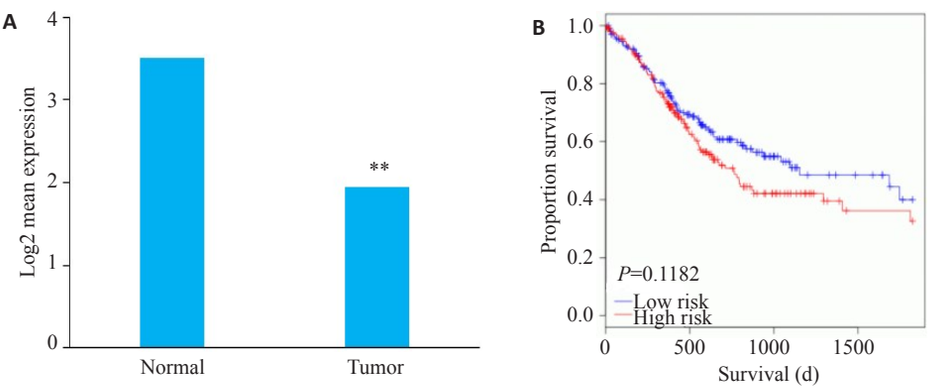

图7 miR-129-5p在胃癌中的表达与其生存预后分析
Fig.7 Expression of miR-129-5p in gastric cancer and analysis of the survival outcomes of the patients. **A**: Expression of miR-129-5p in gastric cancer (**P<0.05 *vs* normal); **B**: Relationship between miR-129-5p expression level and the survival outcomes.

3 讨论

胃癌早期诊断具有一定难度,大多数胃癌患者确诊时已是晚期[21],已失去最佳治疗时机,死亡率一直居高不下。因此,探究新的早期肿瘤生物标志物对胃癌的防治具有一定价值。本研究采用生物信息学方法对GEO数据库中的胃腺癌组织和正常胃黏膜组织的基因芯片数据进行分析。首先比较胃癌组织和正常胃黏膜组织中的基因表达情况,共筛选出181个DEGs(胃癌组/正常对照组),其中上调基因和下调基因分别为57个和124个。为进一步了解DEGs,我们进行了GO和KEGG通路富集分析,DEGs的生物过程主要涉及细胞黏附、氧化还原过程、胶原蛋白分解代谢等,细胞学组成分析显示这些基因大多参与细胞外泌体、细胞外基质、细胞外区等的组成。分子功能的变化主要集中在锌、铁离子结合、相同的蛋白结合、细胞外基质结构组成、肝素结合、氧化还原酶活性、血红素结合、氧气结合等。正常情况下,机体的氧化还原过程处于动态平衡状态,而细胞氧化还原环境持续遭到破坏,则可能导致肿瘤的发生[22]。功能模块分析显示:KEGG通路主要涉及蛋白质消化吸收、PI3K-Akt信号通路、ECM-受体相互作用、血小板激活信号通路。这与一项胃癌关键基因的生物信息学分析的研究结果相似[23]。PI3K-Akt通路在许多肿瘤中都具有较高的易感性[24]。PI3K-Akt通路通过促进细胞增殖,在肿瘤细胞侵袭、转移中起着重要的作用[25]。

PPI网络筛选出10个Hub基因,由GEPIA验证得知COL1A1(Collagen, type I, alpha 1)的高表达与不良预后显著相关,有研究已证实此结果[26]。最近有研究[27]提出了COL1A1可作为胃癌早期筛查的标志。Ⅰ型胶原是纤维胶原家族的主要成分,主要参与细胞外基质结构的组成,被认为是一种肿瘤相关基因[28],可能参与了肿瘤的侵袭和进展[29],有研究表明[30],COL1A1的上调有助于卵巢癌细胞对顺铂耐药。为进一步了解COL1A1参与胃癌发生发展的分子机制,我们预测了调控COL1A1的转录后调节因子miRNAs,miRNA是内源性小型非编码RNA分子,其长度为18-24个核苷酸,可通过诱导mRNA降解或通过与mRNA的3'-UTR的互补结合而抑制mRNA[31]。预测结果显示miR-129-5p可直接与COL1A1 mRNA的3'UTR结合。miR-129-5p是一种有效的肿瘤抑制因子[32-33],为验证胃癌中miR-129-5p与COL1A1的关系,我们通过OncomiR数据库检索了miR-129-5p在胃癌中的表达与生存预后,结果显示miR-129-5p在胃癌组织中的表达显著低于正常组织(P=3.32e-05),生存期也短于正常组织。由此得出miR-129-5p调控的COL1A1是胃癌潜在的治疗靶点。这与最近的一项miR-129-5p通过抑制COL1A1来抑制胃癌细胞的侵袭和增殖[34]的研究结果一致。

综上所述，我们通过生物信息学分析确定了差异表达的基因，由富集分析和蛋白互作可知，COL1A1在胃癌中是一种高表达分子。此外，在胃癌中预测到miR-129-5p可下调COL1A1的表达。COL1A1应该是miR-129-5p调控胃癌治疗的靶点。为了得到更准确的相关性结果，还需要进行一系列的实验来验证预测结果。

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