Observational Study

Medicine®

OPEN

MMP7 as a potential biomarker of colon cancer and its prognostic value by bioinformatics analysis

Li Chen, MD[a], Xueying Ke, MD[b,*]

Abstract

Colon cancer is one of the most common cancers in the world. To identify the candidate genes in the carcinogenesis and progression of colon cancer, the microarray datasets GSE10950, GSE44861 and GSE74602 were downloaded from the Gene Expression Omnibus (GEO) database. The differentially expressed genes (DEGs) were identified, and functional enrichment analyses were performed. A total of 176 DEGs were identified, consisting of 55 genes upregulated and 121 genes downregulated in colon cancer tissues compared to non-cancerous tissues. The DEGs were mainly enriched in mineral absorption, nitrogen metabolism and complement and coagulation cascades. By using STRING database analysis, we constructed a coexpression network composed of 140 nodes and 280 edges for the DEGs with a combined score >0.4 and a significant interaction relation. Thirteen hub genes were identified, and poor OS of patients was only associated with high expression of Matrix Metallopeptidase 7 (*MMP7*), which may be involved in the carcinogenesis, invasion or recurrence of colon cancer. In conclusion, we propose that the DEGs and hub genes identified in the present study may be regarded as diagnostic biomarkers for colon cancer. Moreover, the overexpression of *MMP7* may correlate with poor prognosis.

Abbreviations: BiNGO = the Biological Networks Gene Oncology tool, BP = biological process, CC = cell composition, DAVID = The Database for Annotation, Visualization, and Integrated Discovery, DEGs = differentially expressed genes, GEO = Gene Expression Omnibus, GO = Gene Ontology, GPL = Gene Platform, GSE = Gene Expression Omnibus, KEGG = Kyoto Encyclopedia of genes and genomes, MCODE = The Molecular Complex Detection, MF = molecular function, PPI = protein-protein interaction, STRING = search tool for the retrival of interacting genes/proteins, TCGA = The Cancer Genome Atlas, UCSC = University of California, Santa Cruz.

Keywords: colon cancer, differentially expressed genes, function and pathway analysis, interaction network

1. Introduction

Colon cancer is a digestive tract cancer with high morbidity and mortality.[1] In recent years, although the survival time of patients has increased with the development of science and technology and the improvement of surgical skills, many patients still suffer from poor prognosis and distant metastasis, which seriously affects their quality of life. The prognosis of colon cancer is closely related to early diagnosis and treatment.[2] Due to the lack of effective early diagnostic methods, many patients are diagnosed at late stages, and most of them cannot undergo radical surgery; without surgery, the prognosis of patients is worse. In recent years, there have been many studies on the pathogenesis and treatment of colon cancer, but the effects of colon cancer treatment are still unsatisfactory, and we lack effective methods to decrease the mortality rate.[3] Therefore, it is necessary to find more efficient early diagnostic molecules and new therapeutic targets to establish an effective system for prevention, early diagnosis and treatment.

At present, research on genes and genomics is developing rapidly, and it is very helpful for understanding the underlying mechanism of certain diseases. For example, microarray technology and bioinformatics analysis have been widely used in research on cancer genetics.[4]

In this study, we downloaded and analyzed three mRNA microarray datasets from the Gene Expression Omnibus (GEO) to get differentially expressed genes (DEGs) between colon cancer tissues and normal control tissues. Subsequently, we conducted Gene Ontology (GO), Kyoto Encyclopedia of genes and genomes (KEGG) pathway enrichment analysis and protein-protein interaction (PPI) network analysis to help us understand the molecular mechanisms of carcinogenesis and progression. In conclusion, 176 DEGs and 13 hub genes were identified, which may be the potential biomarkers of colon cancer.

2. Materials and methods

2.1. Microarray data

GEO[5] (http://www.ncbi.nlm.nih.gov/geo) is a public functional genomics data warehouse for gene expression data, chips and microarrays. Three gene expression datasets (GSE10950,[6]

Editor: Mahesh Kathania.

The authors have no funding information to disclose.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the present study are publicly available.

[a] Department of Colorectal Surgery, [b] Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

[*] Correspondence: Xueying Ke, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China (e-mail: kexueying@zju.edu.cn).

How to cite this article: Chen L, Ke X. MMP7 as a potential biomarker of colon cancer and its prognostic value by bioinformatics analysis. Medicine 2021;100:9 (e24953).

Received: 4 August 2020 / Received in final form: 5 January 2021 / Accepted: 4 February 2021

http://dx.doi.org/10.1097/MD.0000000000024953

GSE44861 and GSE74602 [7]) were downloaded from GEO, which have been stored in GPL6104 (Illumina humanRef-8 v2.0 expression beadchip) and GPL3921 (Affymetrix HT Human Genome U133A Array). According to the annotation information in the platform, the probes were transformed into corresponding gene symbols. The GSE10950 dataset contains 24 colon cancer tissue samples and 24 non-cancerous tissue samples. GSE44861 contained 56 colon cancer tissue samples and 55 non-cancerous tissue samples. GSE74602 contained 30 colon cancer tissue samples and 30 non-cancerous tissue samples. This study was approved by the ethics committee of Sir Run Run Shaw Hospital Zhejiang University College of Medicine.

2.2. Identification of DEGs

Screening of DEGs in colon cancer and non-cancerous tissues by GEO2R method (http://www.ncbi.nlm.nih.gov/geo/geo2r). GEO2R is an interactive web tool that allows users to compare two or more datasets in the GEO series to identify DEGs under different experimental conditions. |log FC| >1 and adj. *P*-value <.01 were considered statistically significant.

2.3. Enrichment analysis of DEGs

The Database for Annotation, Visualization, and Integrated Discovery (DAVID)[8] is a full-featured functional annotation tool, which has been used for systematic and comprehensive analysis of large gene lists. The significance of the gene ontology (GO)[9] biological process terms and Kyoto Encyclopedia of Genes and Genomes (KEGG)[10] pathway enrichment analyses were determined by DAVID database, $P < .05$.

2.4. PPI network construction and module analysis

The PPI network of DEGs was predicted by using the online database search tool of STRING.[11] Then, the interaction of DEGs was selected to construct PPI network (combined score > 0.4), and cell landscape visualized using Cytoscape.[12] The Molecular Complex Detection (MCODE)[13] plugin in Cytoscape was used to identify the important modules of PPI network. The selection criteria were as follows: MCODE scores >5, degree cut-off = 2, node score cut-off = 0.2, max depth = 100 and k-score = 2. DAVID database was used to function and pathway enrichment analysis of DEGs in each module.

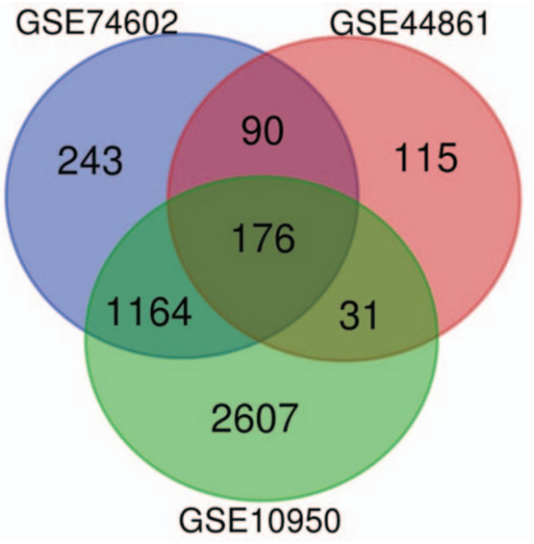

Figure 1. Venn diagram of DEGs. DEGs = differentially expressed genes.

2.5. Hub genes selection and analysis

Genes with degrees ≥10 were selected as hub genes. The online tool cBioPortal was used to analyze the network of genes and

Table 1

GO and KEGG pathway enrichment analysis of DEGs in colon cancer.

ID	Term	Count	*P*-value
GO function			
GO_BP:0071294	Cellular response to zinc ion	7	1.80E-08
GO_BP:0045926	Negative regulation of growth	7	1.80E-08
GO_BP:0015701	Bicarbonate transport	7	3.83E-06
GO_BP:0006508	Proteolysis	18	6.95E-06
GO_BP:0071276	Cellular response to cadmium ion	5	1.80E-05
GO_CC:0005615	Extracellular space	34	3.45E-07
GO_CC:0070062	Extracellular exosome	53	6.61E-07
GO_CC:0005576	Extracellular region	33	4.13E-05
GO_CC:0005578	Proteinaceous extracellular matrix	10	0.001026
GO_CC:0016324	Apical plasma membrane	10	0.001815
GO_MF:0004222	Metalloendopeptidase activity	9	1.20E-05
GO_MF:0008270	Zinc ion binding	26	1.05E-04
GO_MF:0005179	Hormone activity	7	2.70E-04
GO_MF:0004089	Carbonate dehydratase activity	4	2.82E-04
GO_MF:0005254	Chloride channel activity	5	0.0017
KEGG pathway			
hsa04978	Mineral absorption	8	1.15E-06
hsa00910	Nitrogen metabolism	4	0.001208
hsa04610	Complement and coagulation cascades	5	0.011494
hsa04960	Aldosterone-regulated sodium reabsorption	4	0.013266
hsa05205	Proteoglycans in cancer	8	0.013765

Top five terms were selected according to *P*-value.

BP = biological process, CC = cellular component, DEGs = differentially expressed genes, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function.

their co-expressed genes[14] (http://www.cbioportal.org). The biological process analysis of hub genes was carried out and visualized by using the Biological Networks Gene Oncology tool (BiNGO)[15] plugin for Cytoscape. The UCSC Cancer Genomics Browser[16] (http://genome-cancer.ucsc.edu) was used to construct the hierarchical clustering of hub genes. The Kaplan-Meier curve was used to performing the survival analyses of hub genes by TCGA database. Online meta-analysis analysis of tumor genes in the different gene databases was carried out by using the online database Oncomine (http://www.oncomine.com).

3. Results

3.1. Identification of DEGs

After preprocessing of microarray results, DEGs (3978 in GSE10950, 412 in GSE44861 and 1673 in GSE74602) were identified. The overlap of the three datasets contains 176 genes. As shown in Venn diagram (Fig. 1), 55 genes were up-regulated and 121 genes were down-regulated in colon cancer tissues compared to non-cancerous tissues.

3.2. Enrichment analysis of DEGs

We uploaded all 176 genes to the online software David to determine overrepresented GO categories and KEGG pathway. The results of GO analysis showed that the changes of the DEGs biological process (BP) were significantly enriched in the cellular response to zinc ion, negative regulation of growth and transport of bicarbonate. The changes of the cell composition (CC) were mainly enriched in the extracellular space, extracellular exosomes and extracellular regions. The changes of molecular function (MF) of DEGs were mainly enriched in metalloendopeptidase activity, zinc ion binding and hormone activity. KEGG pathway analysis showed that DEGs were mainly enriched in mineral absorption, nitrogen metabolism and complement and coagulation cascades (Table 1).

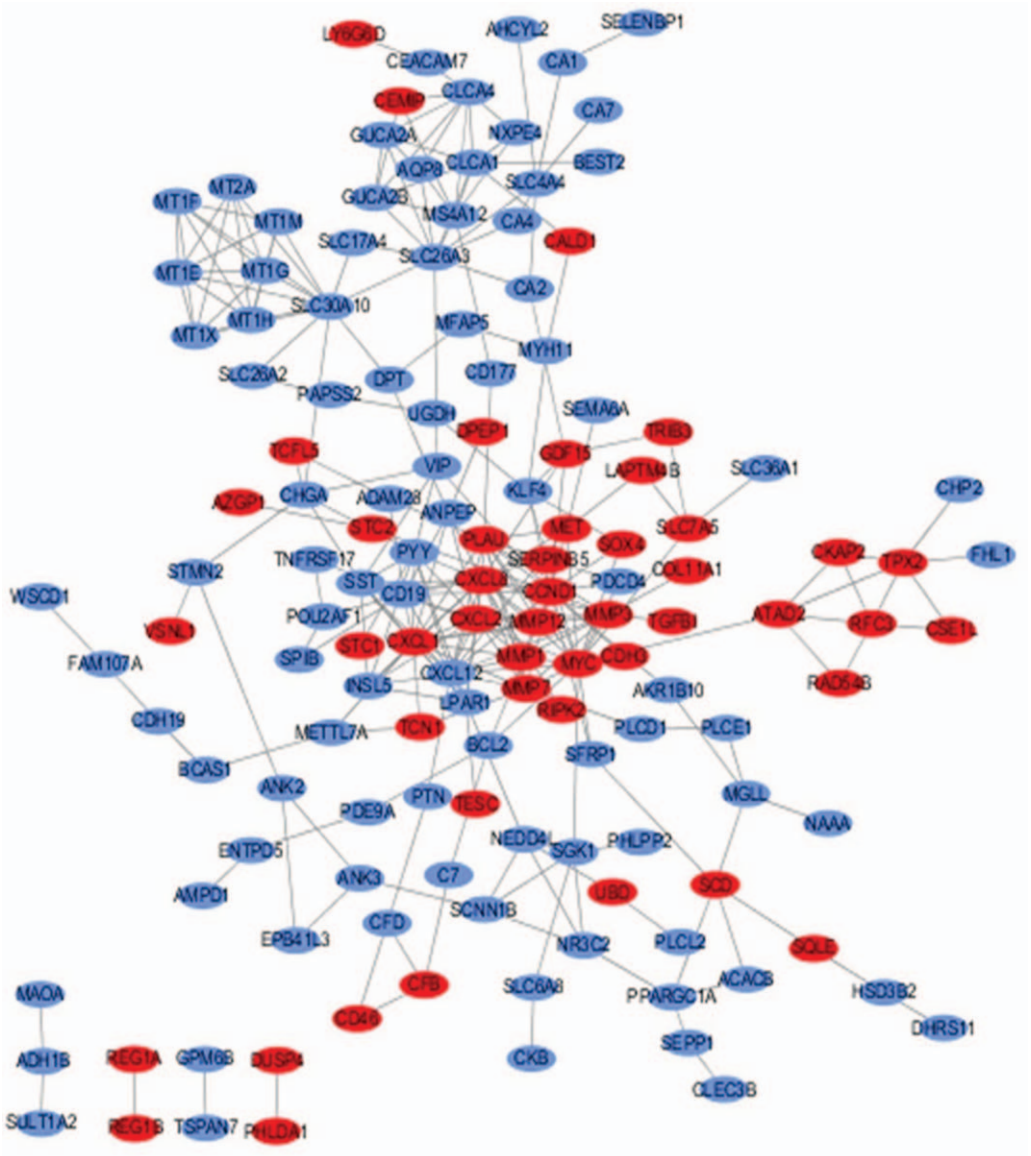

Figure 2. The PPI network of DEGs. Notes: Blue represents downregulated DEGs; red represents upregulated DEGs. DEGs = differentially expressed genes, PPI = protein–protein interaction.

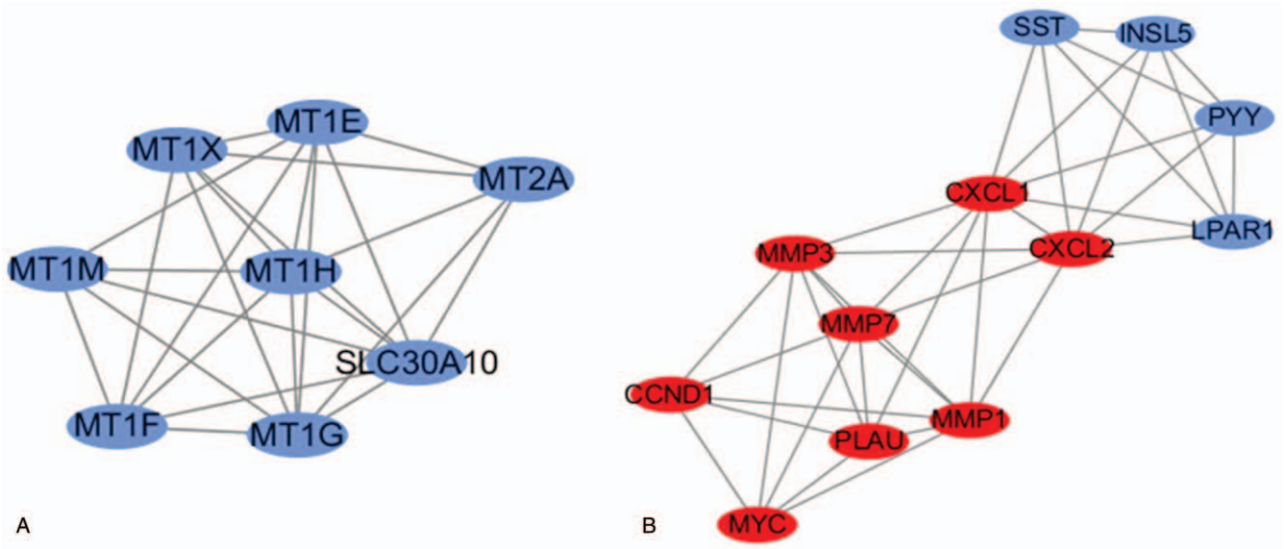

Figure 3. Functional modules in the PPI network. Notes: We clustered two functional modules, using MCODE: module 1(A) and module 2(B). Blue represents downregulated DEGs; red represents upregulated DEGs. DEGs = differentially expressed genes, MCODE = Molecular Complex Detection, PPI = protein–protein interaction.

3.3. PPI network construction and module analysis

Through the analysis of STRING database, we constructed a coexpression network for DEGs composed of 140 nodes and 280 edges, the combined score of the network is > 0.4, which has a significant interaction relationship (Fig. 2). The combined score > 0.4 indicates that the interaction between nodes is significant. Using MCODE Cytoscape software, we further identified the distinct modules of the 140 DEGs and their interaction genes. In these modules, two subnetworks with scores >5 were selected (Fig. 3A & B). The score between the two subnetworks >5 indicates that the relationship between them is significant. DAVID was used to analyze the function of the genes involved in module 1. The results showed that the genes in module 1 were mainly enriched in the negative regulation of growth, perinuclear region of cytoplasm and absorption of mineral (Table 2).

3.4. Hub gene selection and analysis

A total of 13 genes (*CXCL8*, *CCND1*, *MYC*, *CXCL1*, *CXCL12*, *PLAU*, *CXCL2*, *CD19*, *SLC30A10*, *MMP3*, *MMP7*, *SLC26A3* and *PYY*) were identified as hub genes with degrees ≥10. A network of hub genes and their co-expressed genes was analyzed using the cBioPortal online platform (Fig. 4A). The biological process analysis of the hub genes is shown in Figure 4B. Hierarchical clustering showed that the hub genes could basically differentiate the colon cancer samples from the non-cancerous samples (Fig. 5). Meta-analysis showed that *MMP7* was significantly over-expressed in colon cancer samples from the different datasets (Fig. 6). Subsequently, we downloaded clinical data and mRNA expression of 308 colon cancer patients of TCGA database from the Firebrowse website (http://firebrowse.org/api-docs/) for Cox survival regression analysis. In univariate

Table 2

GO and KEGG pathway enrichment analysis of DEGs in module 1.

ID	Term	Count	*P*-value
GO function			
GO_BP:0045926	Negative regulation of growth	7	6.10E-18
GO_BP:0071294	Cellular response to zinc ion	7	6.10E-18
GO_BP:0071276	Cellular response to cadmium ion	5	2.51E-11
GO_BP:0036018	Cellular response to erythropoietin	2	8.34E-04
GO_BP:0010038	Response to metal ion	2	0.004162
GO_CC:0048471	Perinuclear region of cytoplasm	7	1.04E-08
GO_CC:0005737	Cytoplasm	7	0.002918
GO_CC:0005634	Nucleus	7	0.003585
GO_MF:0008270	Zinc ion binding	7	7.18E-07
GO_MF:0046872	Metal ion binding	7	2.11E-05
KEGG pathway			
hsa04978	Mineral absorption	7	4.81E-14

BP = biological process, CC = cellular component, DEGs = differentially expressed genes, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, MF = molecular function.

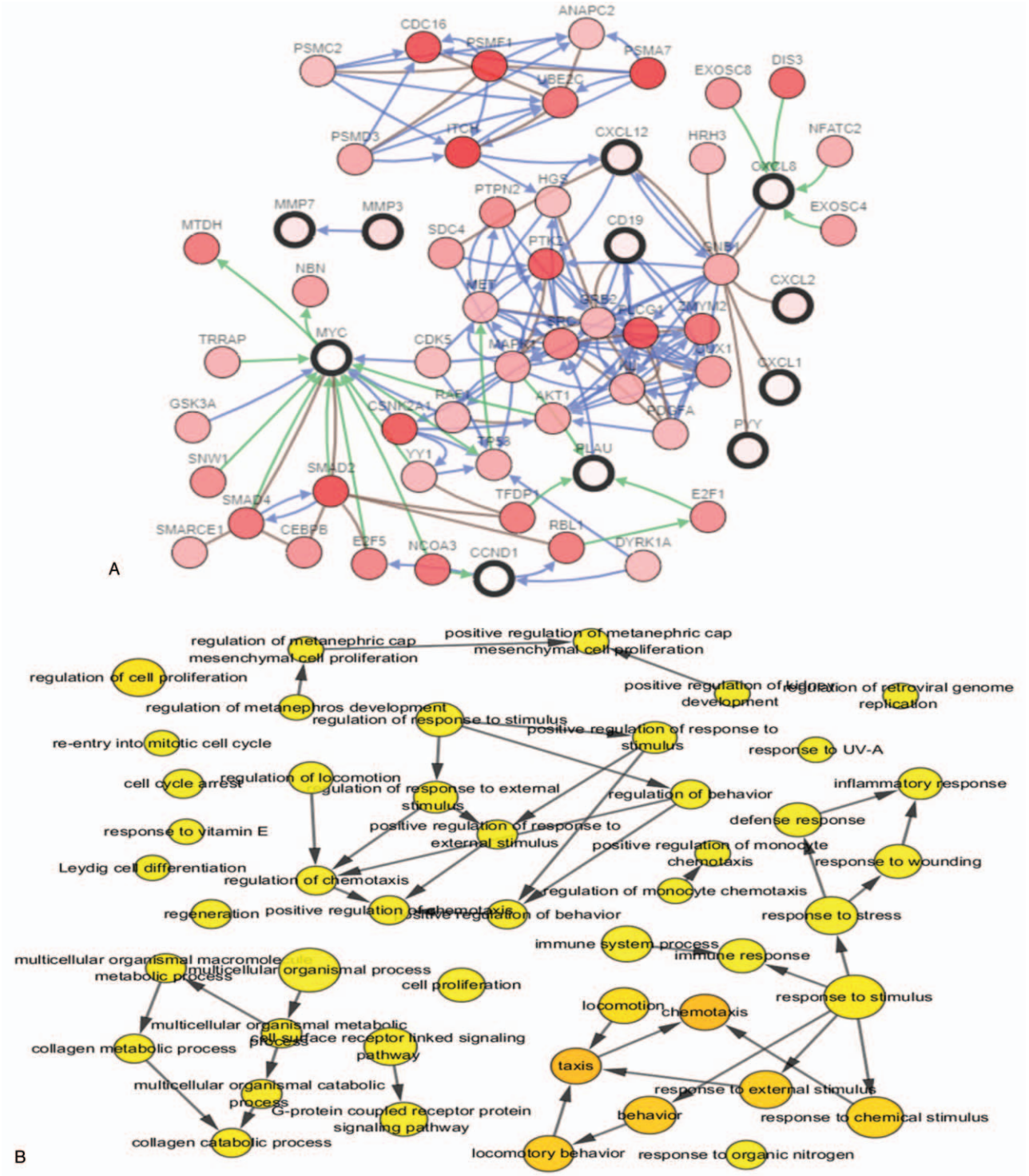

Figure 4. Interaction network and biological process analysis of the hub genes. Notes: (A) Hub genes and their co-expression genes were analyzed using cBioPortal. Nodes with bold black outline represent hub genes. Nodes with thin black outline represent the co-expression genes. (B) The biological process analysis of hub genes was constructed using BiNGO. $P < .01$ was considered statistically significant.

analysis, we found that high pathologic stage and high mRNA expressions of *MMP7* were related to shorter OS of colon cancer patients (Table 3). Multivariate analysis showed that high mRNA expressions of *MMP7* and high pathologic stage were independently associated with significantly shorter OS of colon cancer patients (Table 4). These results showed that transcriptional expressions of *MMP7* were independent prognostic factors for OS of colon cancer patients. Besides, our results showed that poor OS of patients was only associated with high expression of *MMP7* in the TCGA COAD cohort (Fig. 7).

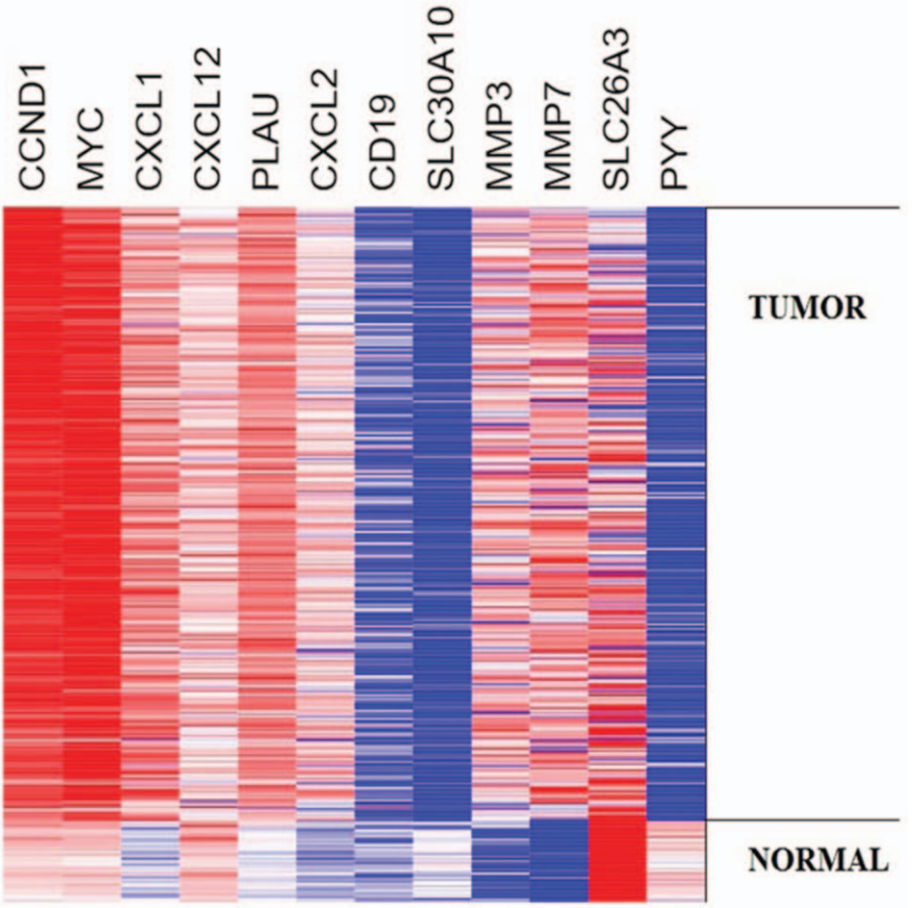

Figure 5. Hierarchical clustering of hub genes was constructed using UCSC. Notes: Upregulation of genes is marked in red; downregulation of genes is marked in blue.

4. Discussion

Colorectal cancer is a common malignant tumor of the digestive tract, with high morbidity and mortality. The prognosis of colorectal cancer is associated with early diagnosis and treatment.[17] It has been reported that the 5-year survival rate of early-stage patients after radical surgery can be as high as 90%, while the 5-year survival rate of patients with metastatic colorectal cancer is lower.[18] Thus, potential biomarkers for diagnosis and highly effective treatment are urgently needed.

In 1986, Herrera et al. found that the *APC* gene was closely related to familial adenomatous polyposis (FAP) and sporadic colorectal cancer.[19] In 1990, Fearon et al. proposed a classical molecular model for gradual changes in oncogenes and tumor suppressor genes during the histogenesis of colorectal cancer from normal mucosal epithelium to adenoma to adenocarcinoma.[20] The accumulation of these genetic and epigenetic changes leads to the dysfunction of important signaling pathways, which is a key factor in the development of colorectal cancer. In particular, mutations of *APC*, *KRAS*, *SMAD4*, *DCC*, *TP53* and DNA mismatch repair genes are the most common and characteristic molecular events.[21–23] Due to the popularity of single cell sequencing and the study of gene and genomics, more and more new tumor markers have been applied, especially in colorectal cancer. Yang et al. found seven differentially expressed mRNAs which were associated with prognosis in colon cancer patients by transcriptomic analysis, involving (SGCG, CLDN23, SLC4A4, CCDC78, SLC17A7, OTOP3, and SMPDL3A).[24] Nfonsam et al. found that secreted frizzled-related protein 4 (SFRP4) was over-expressed in early-onset colon cancer that could be targeted for diagnosis and therapy.[25] Although many molecular markers are still in the basic research stage, at present, microsatellite instability (MSI) status, RAS gene, RAF gene and so on have played a key role in the treatment and prognosis of colorectal cancer. With the development of genomics, microarray technology has enabled us to explore genetic alterations in colorectal cancer.[26] In addition, based on bioinformatics analysis, we can discover molecules and pathways that play an important role in the process of tumorigenesis, some of which have been proven to be potential tumor markers or therapeutic targets.

In this study, 3 mRNA microarray datasets were analyzed to identify DEGs between colon cancer tissues and non-cancerous tissues. A total of 176 DEGs were screened, which consisted of 55 upregulated genes and 121 downregulated genes. Moreover, we selected two significant modules with several key DEGs in the colon carcinoma regulatory network.

We selected 13 DEGs with degrees ≥10 as hub genes. Among these hub genes, *CXCL8* and *CCND1* showed the highest node degrees. The data showed that *CXCL8* is enriched in bladder cancer, NOD-like receptor signaling, transcriptional

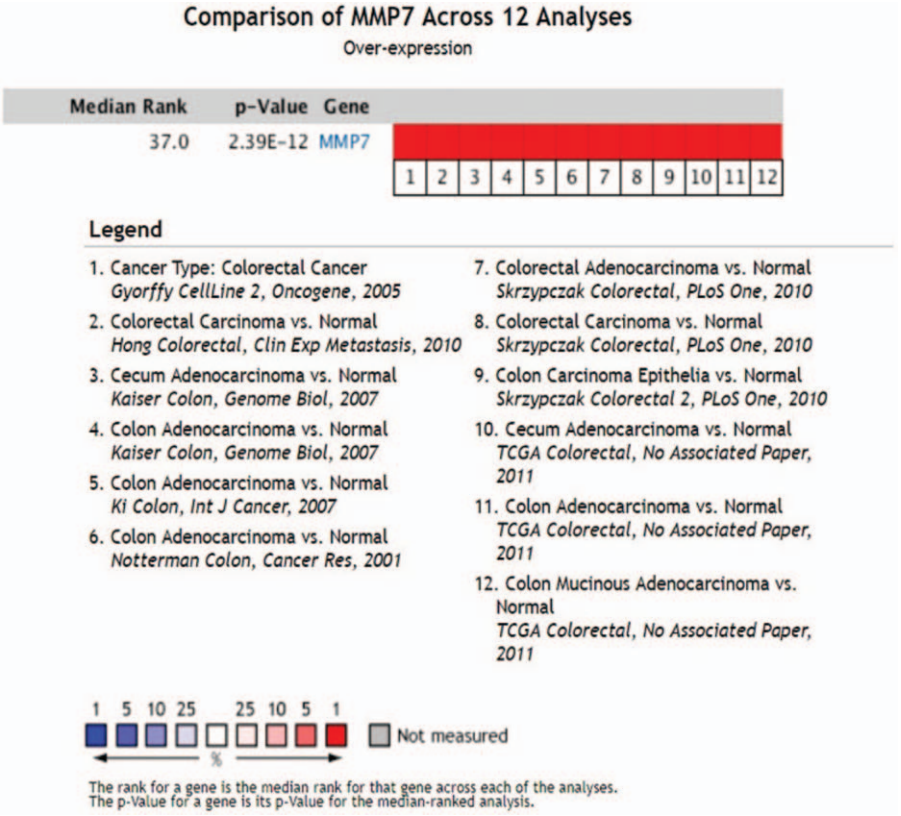

Figure 6. Oncomine analysis of cancer vs. normal tissue of *MMP7*.

misregulation in cancer and NF-kappa B signaling, which has a significant association with the progression of cancer. *CXCL8* is a protein coding gene. The protein encoded by this gene is a member of the CXC chemokine family and is a major mediator of the inflammatory response.[27] Previously, it was reported that the overexpression of *CXCL8* induced cell proliferation, migration and invasion of colon cancer LoVo cells. The author found that *CXCL8* may act by inducing EMT via the PI3K/AKT/NF-κB signaling axis.[28] In addition, Signs SA et al. found that in stromal fibroblasts, miR-20a modulates *CXCL8* function, therefore influencing tumor latency.[29] The protein encoded by this gene is also a potent angiogenic factor, which may play an important role in tumor metastasis. The data showed that *CCND1* (cyclin D1) is enriched in proteoglycans in cancer, bladder cancer and PI3K-Akt signaling.[30–31] The protein encoded by this gene, which belongs to the highly conserved cyclin family, is a regulatory protein involved in mitosis. Cell proliferation, differentiation, senescence and apoptosis of both normal cells and cancer cells are cell cycle-dependent. Previously, cyclin D was shown to be misregulated in many cancer types. Although there may be no statistically significant difference in survival analysis in these two genes due to small sample sizes and incomplete data, we also speculate that the overexpression of *CXCL8* and *CCND1* may contribute to colon cancer progression and metastasis.

Finally, the survival analysis of these hub genes revealed that the overexpressed gene that significantly correlated with the poor OS of patients in the TCGA COAD cohort was *MMP7*. This gene encodes a member of the peptidase M10 family of matrix metalloproteinases (MMPs).[32] Proteins in this family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development,

Table 3

Univariate analysis of overall survival in 308 TCGA-COAD specimens.

Variables	Hazard ratio	95%CI	*P*-value
Pathologic stage			
I	1		<.001
II	2.357	0.672–8.275	
III	6.771	2.048–22.383	
IV	14.665	4.493–47.862	
MMP7 expression			
low	1		.007
high	2.002	1.205–3.326	

Table 4

Multivariate analysis of overall survival in 308 TCGA-COAD specimens.

Variables	Hazard ratio	95%CI	*P*-value
Pathologic stage			
I	1		<.001
II	2.458	0.700–8.636	
III	6.842	2.069–22.625	
IV	14.358	4.398–46.867	
MMP7 expression			
low	1		.034
high	1.741	1.044–2.903	

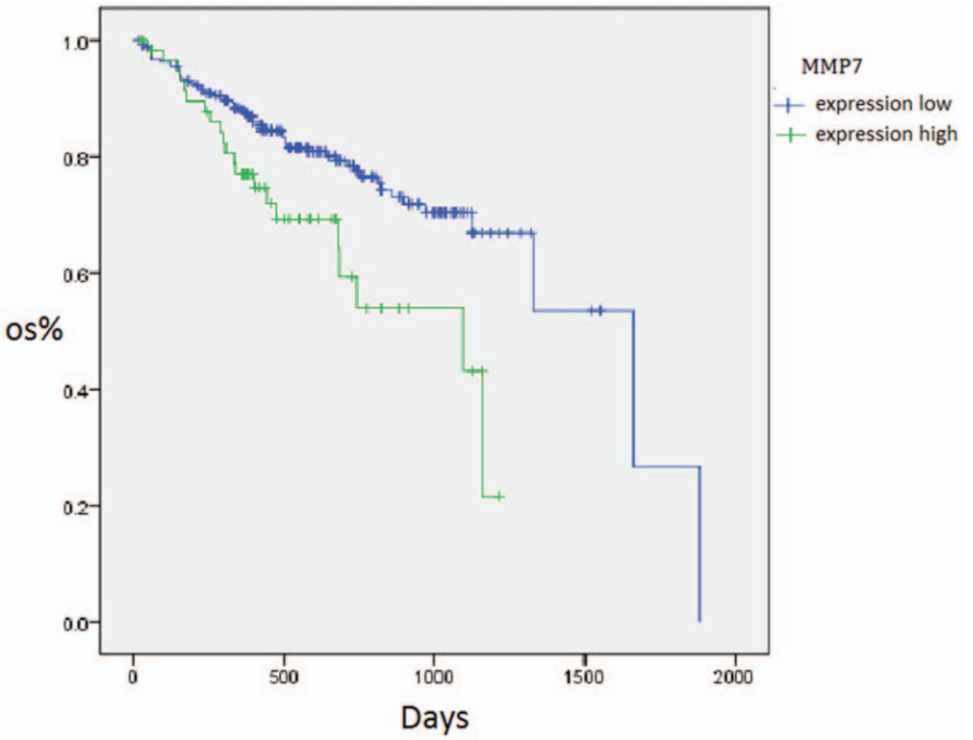

Figure 7. Survival analysis of *MMP7* was performed using TCGA database.

reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis.[33] Klupp et al. found that the expression of *MMP7* in the serum of patients with colon cancer was different from that of healthy individuals.[34] In addition, the overexpression of *MMP7* in the serum of patients with colon cancer was associated with poor prognosis.[35] Similarly, UALCAN analysis showed that the expression of *MMP7* increased with the later stage of colon cancer. Moreover, Fan et al. found that *MMP7* was of great significance in the treatment of colon cancer with chemotherapy.[36] Kobayashi et al. revealed that MMP played an important role in the epithelial-mesenchymal transition and invasion of colon cancer.[37] MMP-7 plays an important role in the occurrence and development of colorectal cancer, including the transformation from early colorectal adenoma to invasive carcinoma and distant metastasis.[38] MMP-7 expression is a predictor of poor prognosis in colorectal cancer. According to our study and previous studies,[39] it may be a potential target for tumor therapy. The present study is still in the initial stage, and further large-scale clinical studies are needed to evaluate the therapeutic effect of MMP-7 inhibitors in the future. Of course, this result might be affected by the gene expression of non-neoplastic cells in the tissue, but considering the influence is small. Taken together, we speculate that the overexpression of *MMP7* may contribute to colon cancer progression and invasion and correlate with poor prognosis.

In conclusion, the present study was designed to identify DEGs that may be involved in the carcinogenesis or progression of colon cancer. A total of 176 DEGs and 13 hub genes were identified and may be regarded as diagnostic biomarkers for colon cancer. Moreover, the overexpression of *MMP7* may correlate with poor prognosis.[40] However, further experimental studies are still required to prove our findings and determine the potential clinical value of these as biomarkers.

Acknowledgments

This work was supported by the Zhejiang University College of Medicine.

Our special thanks are due to Prof. He Chao for his helpful discussion with preparing the manuscript.

Author contributions

Conceptualization: Li Chen.
Data curation: Li Chen.
Formal analysis: Li Chen.
Methodology: Li Chen.
Resources: Xueying Ke.
Software: Xueying Ke.
Writing – original draft: Li Chen, Xueying Ke.
Writing – review & editing: Li Chen, Xueying Ke.

References

[1] Mouchli MA, Ouk L, Scheitel MR, et al. Colonoscopy surveillance for high risk polyps does not always prevent colorectal cancer. World J Gastroenterol 2018;24:905–16.
[2] Shankaran V, Jolly S, Blough D, et al. Risk Factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: a population-based exploratory analysis. J Clin Oncol 2012;30:1608–14.
[3] Ivanov P, Vasilev K, Kotashev G, et al. Laparoscopic vs open resection for rectal carcinoma–a prospective analysis. Khirurgiia 2013;23–9.
[4] Rays M, Chen Y, Su YA. Use of a cDNA microarray to analyse gene expression patterns in human cancer. Nat Genet 1996;14:457–60.

[5] Edgar R, Domrachev M, Lash AE. Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. Nucleic Acids Res 2002;207–10.
[6] Ola W, Robin A, Alvaro RI, et al. Cancer associated epigenetic transitions identified by genome-wide histone methylation binding profiles in human colorectal cancer samples and paired normal mucosa. BMC Cancer 2011;11:450.
[7] Gao P, He M, Zhang C, et al. Integrated analysis of gene expression signatures associated with colon cancer from three datasets. Gene 2018;654:95–102.
[8] Huang DW, Sherman BT, Tan Q, et al. The DAVID Gene Functional Classification Tool: a novel biological module-centric algorithm to functionally analyze large gene lists. Genome Biol 2007;8:R183.
[9] Ashburner M, Ball CA, Blake JA, et al. Gene ontology: tool for the unification of biology. Gene 2000;25:25–9.
[10] Tanabe M, Kanehisa M. Using the KEGG Database Resource. Curr Protoc Bioinformatics 2012;1.12.
[11] Franceschini A, Szklarczyk D, Frankild S, et al. STRING V9.1: protein-protein interaction networks, with increased coverage and integration. Nucleic Acids Res 2013;808–15.
[12] Smoot ME, Ono K, Ruscheinski J, et al. Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics 2011;431–2.
[13] Bandettini WP, Kellman P, Mancini C, et al. MultiContrast Delayed Enhancement (MCODE) improves detection of subendocardial myocardial infarction by late gadolinium enhancement cardiovascular magnetic resonance: a clinical validation study. J Cardiovasc Magn Reson 2012; 14:83.
[14] Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:l1.
[15] Maere S. BiNGO: a Cytoscape plugin to assess overrepresentation of Gene Ontology categories in biological networks. Bioinformatics 2005;3448–9.
[16] Kent WJ, Sugnet CW, Furey TS, et al. The human genome browser at UCSC. Genome Res 2002;12:996–1006.
[17] Huo X, Zhang L, Li T. Analysis of the association of the expression of KiSS-1 in colorectal cancer tissues with the pathology and prognosis. Oncol Lett V 15 2018;3056–60.
[18] Griffith A, Sanoff H. Current trends in systemic therapies in elderly patients with metastatic colorectal cancer. Curr Colorectal Cancer Rep 2019;15:105–11.
[19] Cottrell S, Bicknell D, Kaklamanis L, et al. Molecular analysis of APC mutations in familial adenomatous polyposis and sporadic colon carcinomas. Lancet 1992;340:626–30.
[20] Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
[21] Grady WM. Molecular biology of colon cancer. Curr Clin Oncol 2007;1–31.
[22] Huycke MM, Gaskins HR. Commensal bacteria, redox stress, and colorectal cancer: mechanisms and models. Exp Biol Med 2004;229:586–97.
[23] Heyer J, Yang K, Lipkin M, et al. Mouse models for colorectal cancer 1999;18:5325–33.
[24] Yang H, Liu H, Lin HC, et al. Association of a novel seven-gene expression signature with the disease prognosis in colon cancer patients. Aging 2019;11:8710–27.
[25] Nfonsam LE, Jandova J, Jecius HC, et al. SFRP4 expression correlates with epithelial mesenchymal transition linked genes and poor overall survival in colon cancer patients. World J Gastrointest Oncol 2019.
[26] Mchugh SM, O'Donnell J, Gillen P. Genomic and oncoproteomic advances in detection and treatment of colorectal cancer. World J Surg Oncol 2009;7:36.
[27] Gilowska I. CXCL8–the key inflammatory mediator in chronic obstructive pulmonary disease? Postepy Higieny I Medycyny Doswiadczalnej 2014;68:842–50.
[28] Shen T, Yang Z, Cheng X, et al. CXCL8 induces epithelial-mesenchymal transition in colon cancer cells via the PI3K/Akt/NF-κB signaling pathway. Oncol Rep 2017;37:2095–100.
[29] Signs SA, Fisher RC, Tran U, et al. Stromal miR-20a controls paracrine CXCL8 secretion in colitis and colon cancer. Oncotarget 2018;9:13048–59.
[30] Seiler R, Thalmann GN, Rotzer D, et al. CCND1/CyclinD1 status in metastasizing bladder cancer: a prognosticator and predictor of chemotherapeutic response. Mod Pathol 2014;27:87–95.
[31] Russell A, Thompson MA, Hendley J, et al. Cyclin D1 and D3 associate with the SCF complex and are coordinately elevated in breast cancer. Oncogene 1999;18:1983–91.
[32] Mori M, Barnard GF, Mimori K, et al. Overexpression of matrix metalloproteinase-7 mRNA in human colon carcinomas. Cancer 2015;75(S6):1516–9.
[33] Galasso O, Familiari F, De Gori M, et al. Recent findings on the role of gelatinases (Matrix Metalloproteinase-2 and -9) in osteoarthritis. Adv Orthop 2012;2012:1–7.
[34] Kahlert C, Fiala M, Musso G, et al. Prognostic impact of a compartment-specific angiogenic marker profile in patients with pancreatic cancer. Oncotarget 2014;5:12978–89.
[35] Wu Q, Yang Y, Wu S, et al. Evaluation of the correlation of KAI1/CD82, CD44, MMP7 and β-catenin in the prediction of prognosis and metastasis in colorectal carcinoma. Diagn Pathol 2015;10:1–9.
[36] Peng Z, Chen J, Drachenberg CB, et al. Farnesoid X receptor represses matrix metalloproteinase 7 expression, revealing this regulatory axis as a promising therapeutic target in colon cancer. J Biol Chem 2019;294: 8529–42.
[37] Yamada D, Kobayashi S, Wada H, et al. Role of crosstalk between interleukin-6 and transforming growth factor-beta 1 in epithelial-mesenchymal transition and chemoresistance in biliary tract cancer. Eur J Cancer 2013;49:1725–40.
[38] Y Newell KJ, Witty JP, Rodgers WH, et al. Expression and localization of matrix-degrading metalloproteinases during colorectal tumorigenesis. Mol Carcinog 1994;10:199–206.
[39] Y Zucker S, Vacirca J. Role of matrix metalloproteinases (MMPs) in colorectal cancer. Cancer Metastasis Rev 2004;23:101–17.
[40] McShane LM, Altman DG, Sauerbrei W, et al. Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. REporting recommendations for tumour MARKer prognostic studies (REMARK). Br J Cancer 2005;93:387–91.