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Original Article

An exploration of the correlation between ovarian cancer and miRNA based on bioinformatics

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Abstract: Objective: The study aims to explore the correlation between the changes in miRNA in the occurrence and development of ovarian cancer with ovarian cancer using bioinformatics technology. Methods: Based on Platform GPL570 of the GEO database, the gene chip associated with ovarian cancer was searched through the comparison between normal women and cancerous women. The total genes were screened according to the set conditions ($P<0.05$, $|Log FC|>2$), and the disease genes were compared with the data in the GeneCards database. A Venn diagram was plotted. A PPI network construction and a DAVID enrichment analysis were performed with the screened core genes. A gene-miRNA correlation analysis was performed with the core genes using WebGestalt, and the resulting miRNA was imported into a Kaplan Meier-Plotter for a survival analysis. Results: The data from the GSE23391, GSE29450, and GSE38666 gene chips were screened according to the set conditions ($P<0.05$, $|Log FC|>2$). The obtained 803 significant genes were compared with the 6,657 pathogenic genes in the GeneCards database, and a total of 346 core genes were obtained. The PPI network map and DAVID enrichment analysis showed that the core genes were closely related to each other and mostly related to cancer pathways. In addition, the core genes were imported into WebGestalt for the gene-miRNA correlation analysis, and the miRNAs of a total of 19 core genes were selected for up-regulation and down-regulation analyses. Then the obtained miRNAs were imported into the Kaplan Meier-plotter for the online survival analysis, and it was found that almost all the obtained core miRNA genes were closely related to the occurrence and development of ovarian cancer. Conclusion: The obtained miRNAs of the core genes were closely related to ovarian cancer and other cancers. MiR-138, miR-98, miR-124, miR-9, miR-367, and miR-429 can be used as prediction genes for ovarian cancer.

Keywords: Ovarian cancer, genes, bioinformatics, microRNA, survival analysis

Introduction

MicroRNAs (miRNAs) are short regulatory RNAs (about 22 nucleotides) which regulate gene expression and are abnormally expressed in many diseases, including cancers. In total, 1,900 kinds of miRNAs have been found [1], accounting for about 1%-2% of the total human genome [2]. Their main function is to regulate important cellular physiological processes such as cell growth, differentiation, metabolism and apoptosis by participating in the regulation of human proteins and combining with target genes to inhibit the expression of target genes [3]. Ovarian cancer has a low rate of early detection, a high recurrence rate, and a high mortality rate. The mortality rate of ovarian cancer ranks first among all gynecological tumors. However, current studies have shown that the pathogenesis of ovarian cancer is still unclear and may be related to endocrine or genetic factors [4]. Many researchers have found that the dysregulation of miRNA expression is a significant feature of ovarian cancer during its development [5].

Research methods

Gene screening

In the GEO database (https://www.ncbi.nlm.nih.gov/), three gene chips (GSE23391, GSE29450, and GSE38666) from Platform GPL570 were selected. GSE23391 was used to

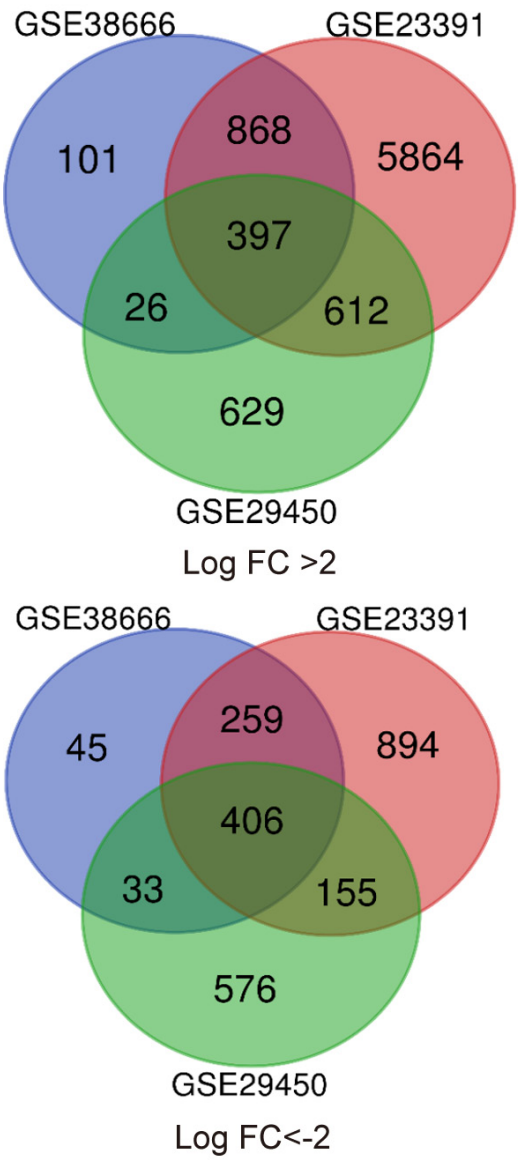

Figure 1. Our Venn analysis of the up-regulated and down-regulated genes on the three gene chips confirmed 397 significantly up-regulated genes and 406 significantly down-regulated genes.

compare the gene expressions in five cases of normal ovarian epithelial cells and three cases of ovarian epithelial cells. GSE29450 was used to compare the gene expressions in 10 cases of clear ovarian cancer cells and 10 cases of normal ovarian epithelial cells. GSE38666 was used to compare the gene expressions of eight normal ovarian epithelial patients and 18 ovarian cancer patients. The obtained total genes were screened based on the set conditions (P<0.05, |Log FC|>2). The up-regulation genes and down-regulation genes were grouped.

Comparison of the significant genes and disease-related genes

The screened significant genes were compared with the ovarian cancer-related genes in Genecards (https://www.genecards.org/) to determine the core ovarian cancer-related genes.

Enrichment analysis of the core genes

In order to explore the role of the target proteins, the core genes were imported into the website (https://string-db.org/) to plot the PPI network map. Meanwhile, the core genes were imported into the DAVID database for a GO gene enrichment analysis and a KEGG enrichment pathway analysis.

Gene survival analysis

The gene-miRNA correlation analysis was performed with the obtained core genes. The resulting miRNAs were then imported into the Kaplan Meier-Plotter for the online survival analysis.

Results

Gene screening

The gene chips downloaded from the GEO database were screened according to the set conditions (P<0.05, |Log FC|>2). There were 11,864 significant genes in GSE23391, including 7,741 significantly up-regulated genes and 1,714 significantly down-regulated genes. There was a total of 3,382 significant genes in GSE29450, including 1,664 significantly up-regulated genes and 1,170 significantly down-regulated genes. There were 2,433 significant genes in GSE38666, including 1,392 significantly up-regulated genes and 743 significantly down-regulated genes. The Venn analysis of the up-regulated and down-regulated genes on the three gene chips confirmed that there were 397 significantly up-regulated genes and 406 significantly down-regulated genes (**Figure 1**).

Comparison of the significant genes and disease genes in GeneCards

We logged in (GeneCards) https://www.genecards.org/, and searched for Ovarian cancer. We received 6657 disease genes, and we got 803 significant genes in comparison, then we received 346 core genes, which raised gene in

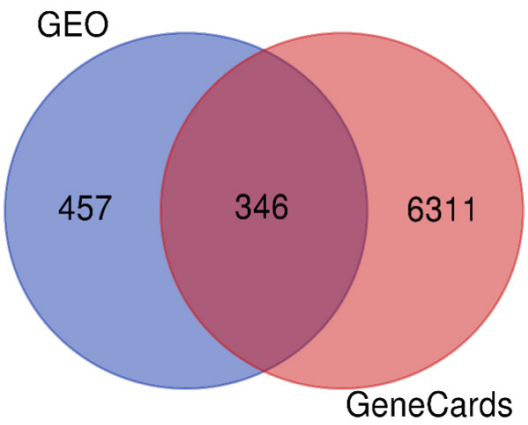

Figure 2. Two databases received 346 core genes, which raised gene in 173 core, core cut 173 genes.

173 core, core cut 173 genes (**Figure 2**; **Tables 1** and **2**).

Core gene analysis

Establishment of the PPI network map of the core genes: The obtained 346 genes were imported into the website (https://string-db.org/) to plot the PPI network map. After removing the unlinked genes from the PPI network, a total of 340 genes with 1,713 edges were obtained. The related parameters obtained were as follows: average node degree (10.1), average local clustering coefficient (0.438), and the expected quantity of edges (680) (P<1.0e-16). Among them, KIF14, MELK, CDT1, CDC6, NEK2, and TPX2 were most closely correlated with other genes. These genes may have a highly synergistic effect in the development of ovarian cancer (**Figure 3**).

GO enrichment analysis of the core genes: In terms of biological processes (BP), the GO enrichment analysis results of the 346 core genes indicated that 298 genes were correlated with the biological regulation processes, such as various cellular tissue processes, anatomical structure development, system development and the positive regulation of biological processes. In terms of molecular functions (MF), 269 genes were correlated with protein binding, ion binding, signal receptor binding, sequence-specific double-stranded DNA binding, and DNA binding of the transcriptional regulatory region. In terms of cell components (CC), 185 genes were correlated with the cell membrane, the extracellular region, the nucleus, the extracellular matrix, and the plasma membrane (**Figure 4**).

KEGG pathway analysis of the core genes: A KEGG signaling pathway enrichment analysis was performed with the 346 core genes. The KEGG signaling pathway was the most closely related to the cancer pathway, followed by the cell cycle, complement and coagulation cascades, proteoglycans in cancer, basal cell carcinoma, oocyte meiosis, the PI3K-Akt signaling pathway, and other signaling pathways (**Figure 5**).

Gene-miRNA network construction: The obtained up-regulated and down-regulated core genes were imported into the WebGestalt database for the gene-miRNA correlation analysis. According to the set conditions (P<0.05), 173 up-regulated core genes yielded 9 related miRNAs, including miR-138, miR-98, miR-485, miR489, miR-524, miR-124, miR-520d, miR-199a, and miR-27b. The 173 down-regulated core genes yielded 10 related miRNAs, including miR-9, miR-21, miR-381, miR-154, miR-367, miR-520f, miR-429, miR-526b, miR-491, and miR-200b. Among these related miRNAs, miR-429, miR-9, miR-200d, miR-381, miR-124, miR-98, miR-27b, miR-524, miR-520f, and miR-367 were most closely correlated with the up-regulated genes. Among them, miR-200b, miR-429 and miR-9 were correlated with the corresponding 12 down-regulated core genes. Eight or more core genes were correlated with miR-124, miR-27b, miR-524, miR-367, miR-381, miR-520f, and miR-98. The resulting correlated miRNAs and genes were imported into Cytoscape-3.7.1 to plot an miRNA-gene intersection diagram (**Figure 6**).

MiRNA survival analysis of the core genes: The obtained core miRNAs were imported into a Kaplan Meier-Plotter for an online survival analysis of ovarian cancer. It was found that, in the survival analysis of the obtained miRNAs, all the *P*-values were almost always less than 0.05. Then, according to the value of the risk rate (HR), the obtained miRNAs was extremely closely correlated with ovarian cancer. The high expression levels and the risks indicated that these core miRNAs suggested a high risk for the pathogenesis of ovarian cancer (**Figure 7**). The expression levels of these core miRNAs can be used to predict the risk of ovarian cancer (**Figure 8**). Among these miRNAs, miR-138,

Table 1. Up-regulated core genes

Up-regulated core genes						
XDH	BIRC5	FOXQ1	CARD11	CDCA2	ADGRG1	IGF2BP2
CXCR4	FGF8	ACVRL1	MUC1	MAGEA11	LPAR3	GATA3
GPSM2	MFAP5	HTR2C	ELF3	GJC1	TUBB2B	TACC3
CXCL13	CDC6	KIF18B	KCNH2	NEK2	CLDN3	PRIMA1
SLC8A1	PKHD1	FOLR1	TNNI3	CDC25A	CCNB2	CEP55
HES1	AURKA	MAL	PIGR	ESM1	CDT1	KLB
CCNE1	AURKB	KIFC1	CDC25C	ESPL1	GDF11	TFAP2A
FOXM1	RRAD	STON2	DLX6	SLC6A2	MECOM	COL4A1
CDK1	FANCA	LZTS1	F11	ATXN7L1	VCAN	MKI67
TFR2	AOC1	SOX17	TCEA2	AHSG	SLC52A2	GPLD1
KIF14	SST	SFN	ZIC1	WFDC1	KNL1	TPX2
PTGER1	ACE2	S100A1	NOX4	LIMK1	WNT7A	IGF2BP3
KCNK10	DNA2	MUC4	VWF	BMP8B	MSX1	ZNF93
CYP19A1	PDE4D	BUB1	CXXC5	CEP70	HK2	KIF20A
SOX9	KLK12	POLQ	RXFP1	EHF	FGF18	ITGB3
HOXB8	POR	PRR11	SCGB2A1	BIK	SPC25	F12
IL23A	ACKR2	L1CAM	DUXAP10	ZYG11A	CEACAM7	HMGA1
MELK	NUF2	STIL	HMGA2	DEFB1	BUB1B	SLC4A11
MUC20	CHMP4C	TFDP1	ANGPT2	ADGRV1	DTL	CLDN18
SHANK3	EPCAM	KDM4C	LHX1	RECQL4	RAD54L	STC2
E2F7	RGS1	SDC1	TK1	NOTCH3	PAX8	PRAME
SCGB1D2	ECT2	PSAT1	RARA	NOTCH1	SLC29A2	UHRF1
MMP1	DIAPH3	RRM2	CD24	HAPLN1	FAM107A	CP
CBX2	COL4A2	TOP2A	TPM4	ITPR3	MUC5AC	
CKS2	FLT1	NR5A2	CDCA3	CSPG4	GPM6B	

Table 2. Down-regulated core genes

Down-regulated core genes						
CLMP	S100A10	HPSE	PCDH17	PROS1	NPY1R	PLA2G4A
AQP9	SNX1	C4BPA	ALDH1A3	GPM6A	CALB2	VIM
ANXA3	FABP4	DCN	NAV3	MAGI2-AS3	SLC31A2	EDNRB
VGLL3	DDR2	N4BP2L1	LAMP2	CRNDE	KLF9	ABI3BP
ZNF385B	TFPI2	SLIT2	CLDN1	OGN	COL8A1	USP53
BCHE	GATM	BNC2	NFKB1	ADCYAP1	MEGF6	ITPR2
DPYD	SCG5	AOX1	KCNJ8	TACC1	LSAMP	C7
TPBG	SFRP1	AKT3	SLC16A1	NKX3-1	PTGER4	MTUS1
BST1	PTGIS	PROCR	SATB1	ARMCX1	PARP8	TXNIP
SORBS2	NDN	PSD3	KAT2B	HTRA1	EFEMP1	COL3A1
KLF4	SPOCK1	PTGER3	NR0B1	PGR	BNC1	PRKAR2B
SFRP2	HSD17B2	TGFB2	CFH	SOX6	NR3C2	DSC3
CYP3A5	FRAS1	ITLN1	DPP10-AS1	GAS1	MTUS2	MAOB
TCF21	FRY	PNPLA4	PRSS35	PEG3	CHGB	ID4
KLF2	GHR	BCO2	MNDA	FGF13	HNRNPD	ANOS1
SNCAIP	GATA6	TIMP3	RSPO1	PLPP1	ARX	CCDC80
CASP1	C3	PTGDR	LRRN4	RARRES1	TCEAL7	CAV1
B2M	MEIS2	CNTN4	HPGD	MBP	AKAP12	ALDH1A1
NT5E	IFI16	ARFGEF3	SGCG	ADAMTS9-AS2	TUSC3	WNT2B
IL18	ZFPM2	LINC01116	MGARP	CAV2	DMRT2	BEX1
MGP	PDGFD	EFNB3	CLDN15	CALCRL	HOXC6	LGALS8
PODXL	WNT5A	THBD	DLG2	FGFR1OP2	ASCL1	COL14A1
SNCA	RUNX1T1	FZD7	GPR37	IL16	CAST	PDE8B
OPTN	HHIP	FGF9	SMARCA2	LHX9	RNF128	
CFI	ADH1B	TNFSF13B	TLL1	SEMA3C	NFIB	

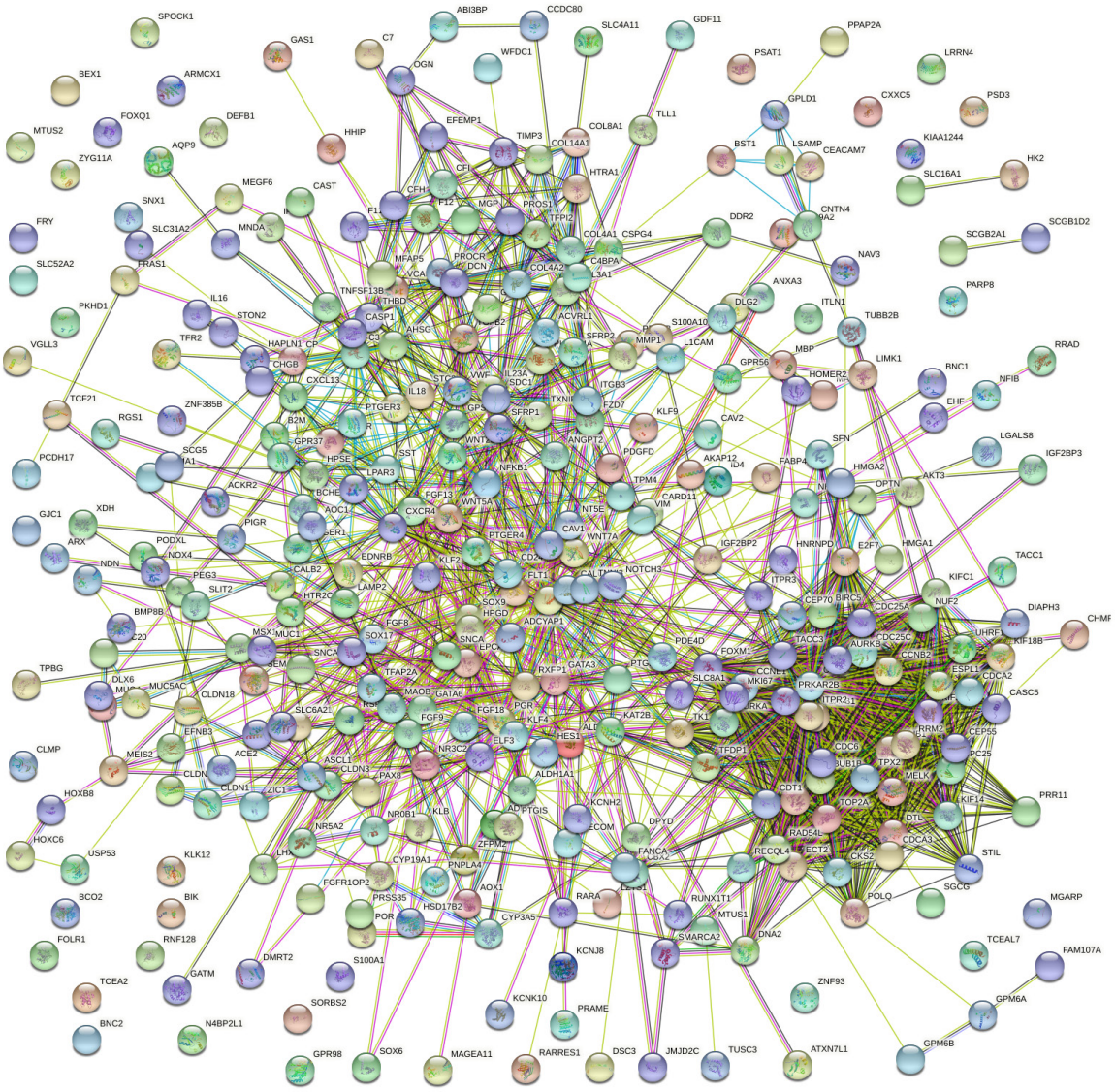

Figure 3. The PPI network map has a total of 340 genes with 1,713 edges obtained. The related parameters were obtained as follows: average node degree (10.1), average local clustering coefficient (0.438), and the expected quantity of edges (680) (P<1.0e-16). Among them, KIF14, MELK, CDT1, CDC6, NEK2, and TPX2 were most closely correlated with other genes.

miR-98, miR-524, miR-124, miR-489, miR-9, miR-429, miR-367, and miR-520f had the closest correlations with ovarian cancer.

Discussion

Abnormal miRNA expression is a common phenomenon in tumors and is mainly manifested in the dysregulation of four mechanisms: epigenetic modification, gene variation, biogenesis change, and transcriptional inhibition. Abnormal miRNA expression affects the occurrence of tumors and is correlated with various tumor development stages. The expression levels of miRNAs in tumors are closely related to the risk of tumors. Ovarian cancer is one of the most common malignant tumors of the female reproductive system, and its incidence is only lower than that of cervical cancer and endometrial cancer [4]. However, ovarian cancer has the highest mortality rate [5]. According to published data, about 22,240 new cases of and 14,070 deaths from ovarian cancer occur in the United States every year [6]. There are about 52,100 new cases and 22,500 deaths in China every year [7]. The incidence of and deaths

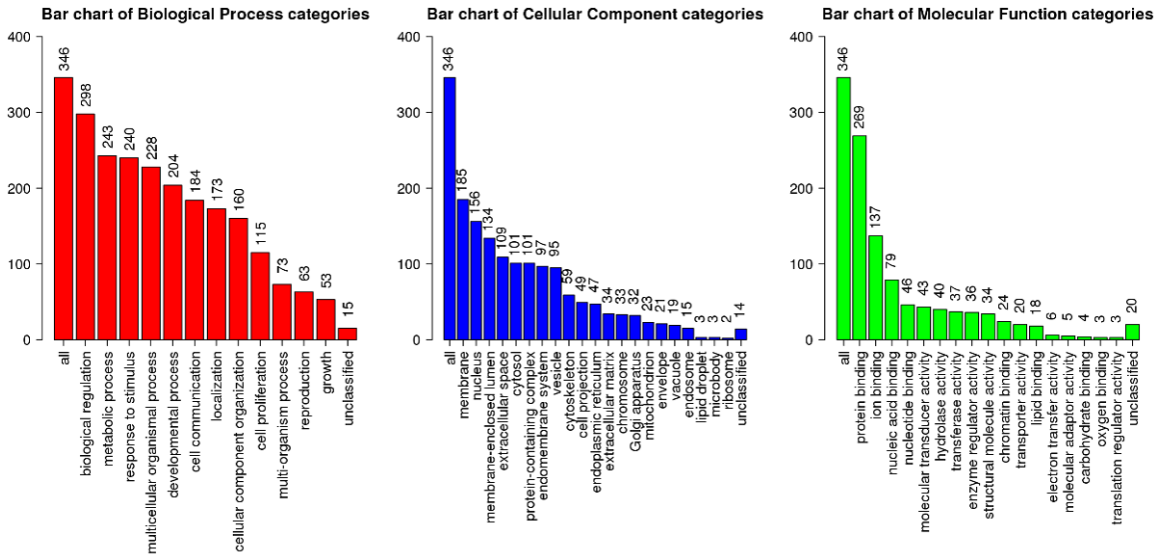

Figure 4. In terms of biological processes (BP), the GO enrichment analysis results of the 346 core genes indicated that 298 genes were correlated with the biological regulation processes, such as various cellular tissue processes, anatomical structure development, system development, and the positive regulation of biological processes. In terms of molecular functions (MF), 269 genes were correlated with protein binding, ion binding, signal receptor binding, sequence-specific double-stranded DNA binding, and the DNA binding of the transcriptional regulatory region. In terms of cell components (CC), 185 genes were correlated with the cell membrane, the extracellular region, the nucleus, the extracellular matrix, and the plasma membrane.

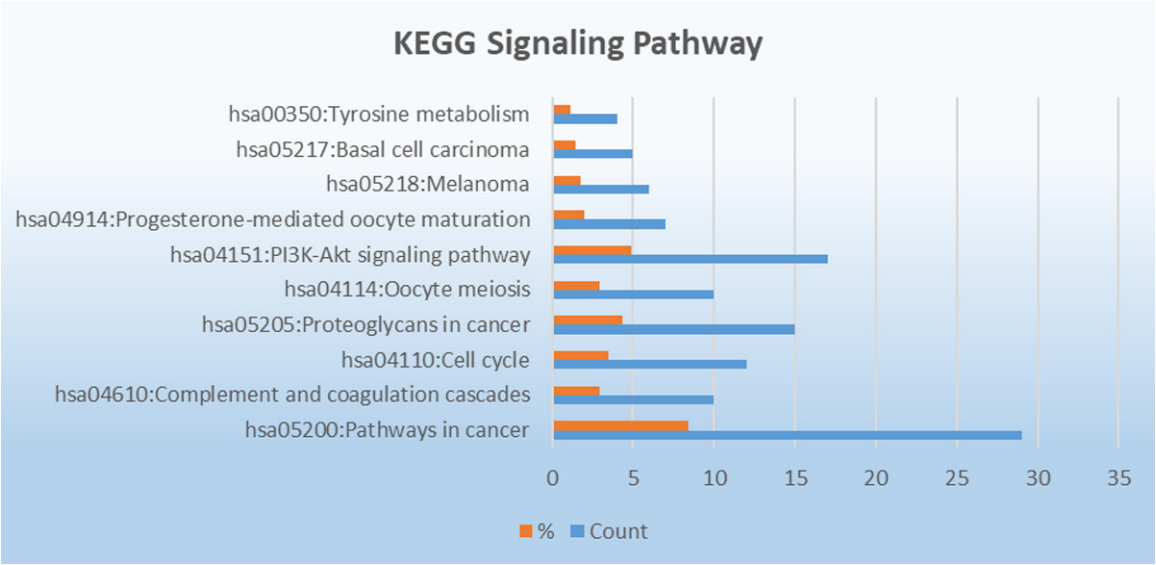

Figure 5. A KEGG signaling pathway enrichment analysis was performed with the 346 core genes. The KEGG signaling pathway was most closely related to the cancer pathway, followed by the cell cycle, the complement and coagulation cascades, proteoglycans in cancer, basal cell carcinoma, oocyte meiosis, the PI3K-Akt signaling pathway, and other signaling pathways.

from ovarian cancer are increasing yearly. Ovarian cancer is characterized by atypical early symptoms, an advanced stage at diagnosis, and a high mortality rate. Therefore, the early diagnosis of ovarian cancer is the key to improving patients' quality of life and survival times, and it is also an important problem to be solved in gynecological cancer research. With

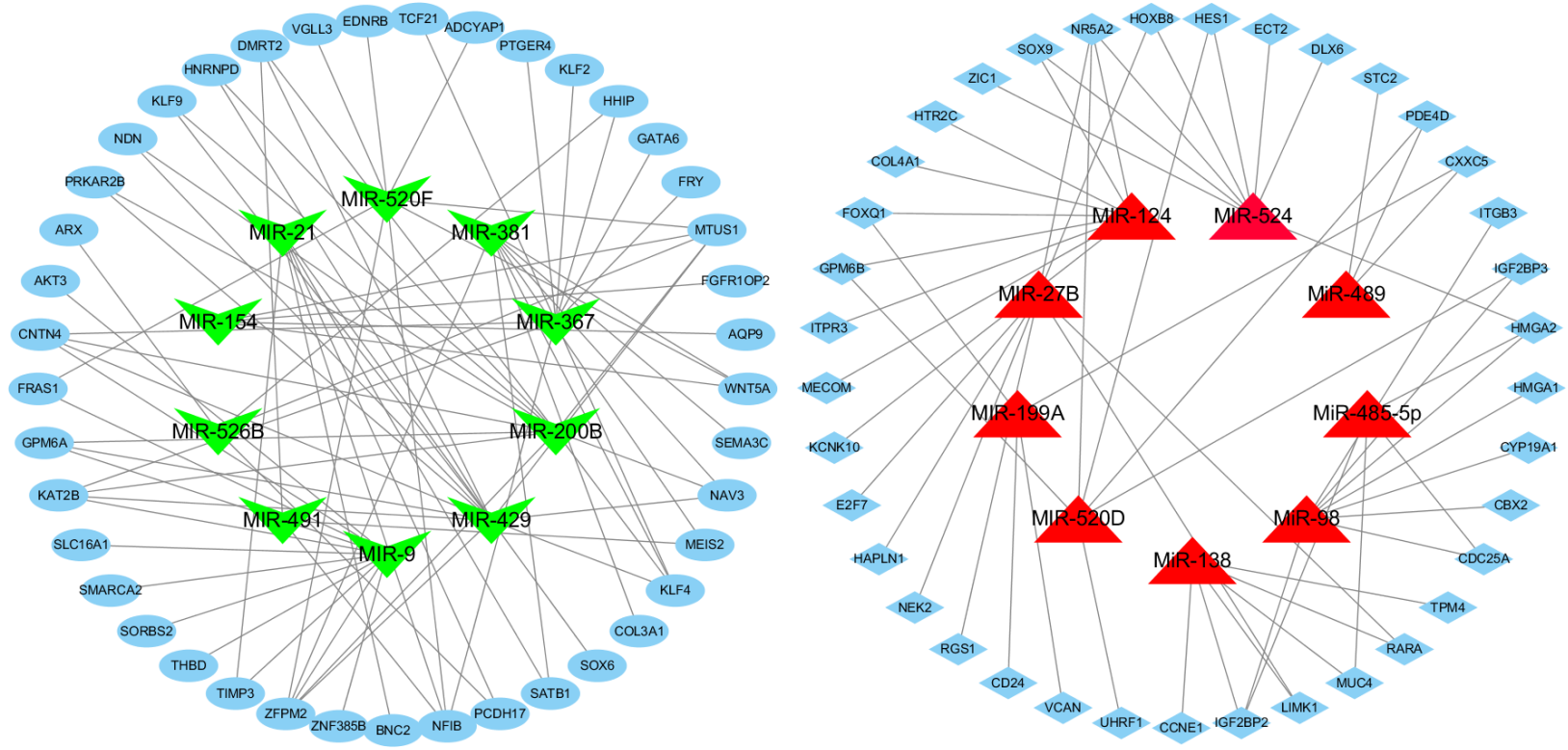

Figure 6. Blue indicates the core gene; red indicates the up-regulated core gene-related miRNAs; green indicates the down-regulated core gene-related miRNAs.

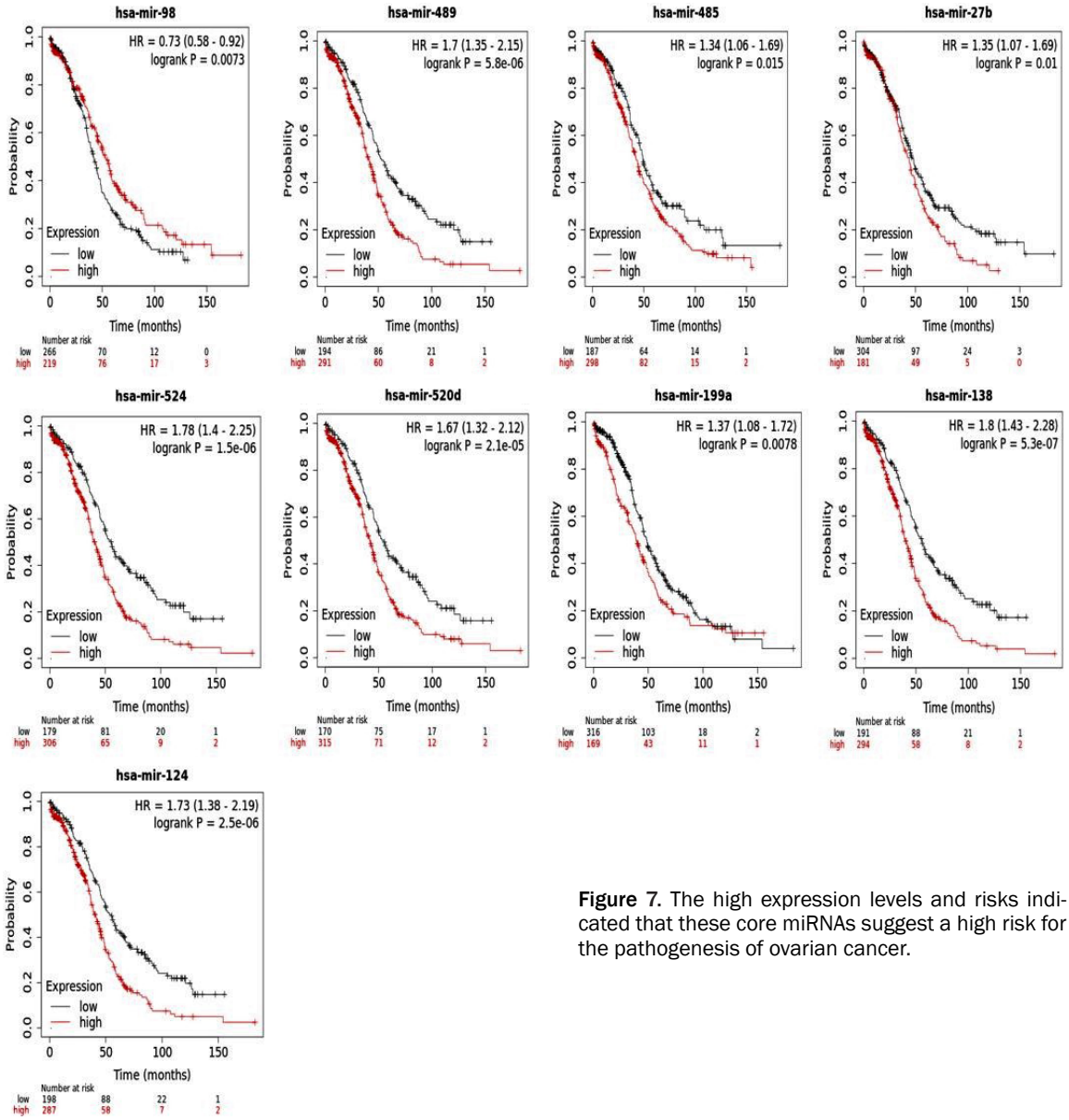

Figure 7. The high expression levels and risks indicated that these core miRNAs suggest a high risk for the pathogenesis of ovarian cancer.

the further study of miRNA, more miRNAs have been found to be correlated with the occurrence and development of ovarian cancer.

Qu et al. [8] compared the clinical specimens of 38 cases of ovarian cancer patients and 19 cases of tissues adjacent to carcinoma and found that the miR-138 expressions in the ovarian cancer tissues were significantly lower than the expressions in the tissues adjacent to the carcinoma ($P<0.01$) and that the overexpression of miR-138 could significantly inhibit the proliferation of SKOV3 cells. Wang et al. [9] found that miR-98 can inhibit the proliferation of ovarian cancer cells, and its inhibitory effect is gradually enhanced. Shu et al. [10] found that miR-124 overexpression can significantly inhibit cell proliferation, migration, and invasion and induce apoptosis, and that the inhibition might be related to the inhibition of the phosphatidylinositol-3 kinase (PI3K)/AKT signaling pathway in ovarian cancer cells. Liu et al. [11] also found that miR-124 can inhibit the growth of transplanted human epithelial ovarian cancer tumor in nude mice in vitro. Liu et al. [12] found that miR-199a inhibited the invasion and metastasis of ovarian cancer cells in vitro by down-regulating the DDR and WNT/β-catenin pathways. Liu et al. [13] found that ovarian cancer cells with a high expression of miR-27b had

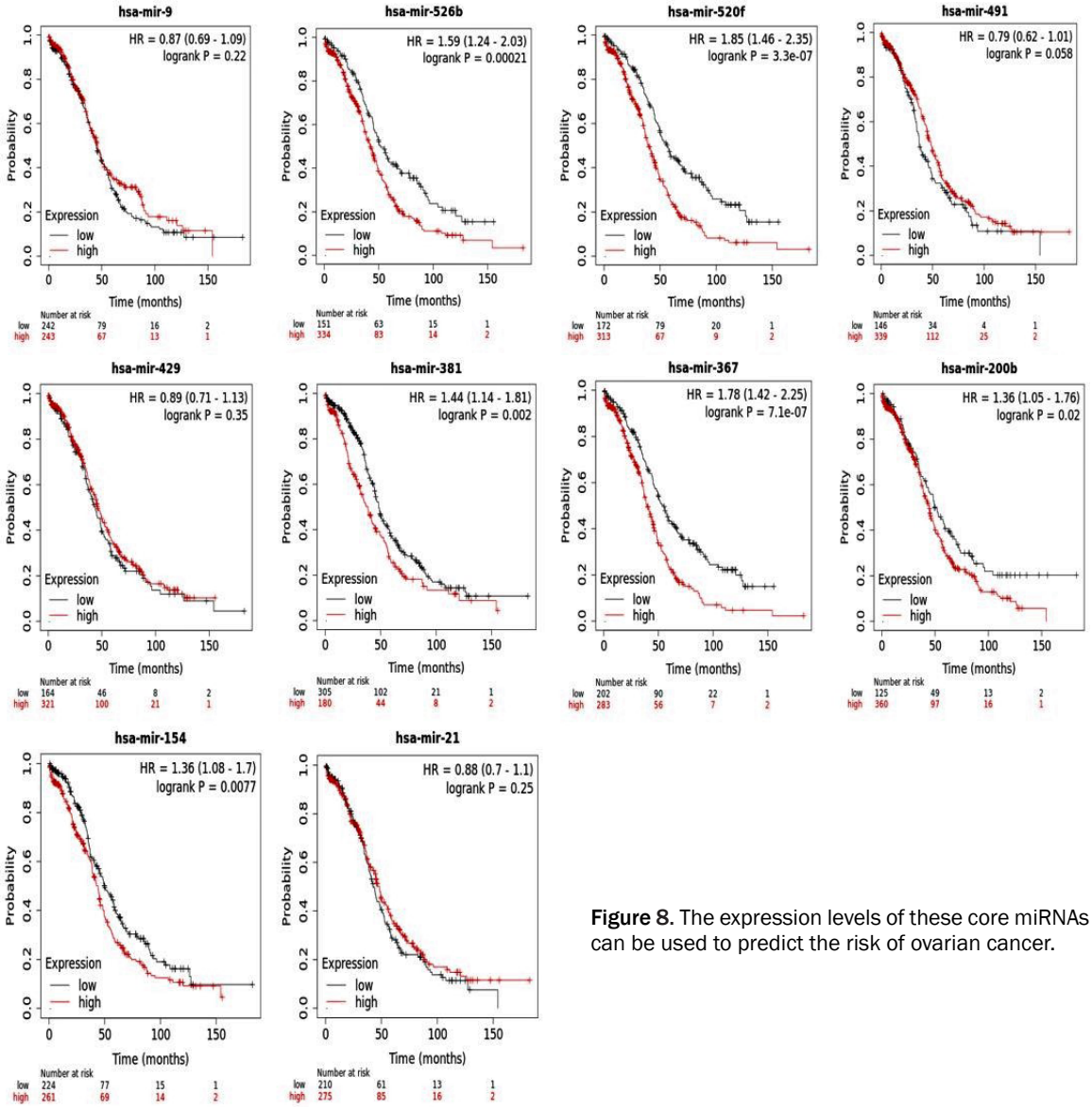

Figure 8. The expression levels of these core miRNAs can be used to predict the risk of ovarian cancer.

no angiogenesis capacity, suggesting that miR-27b plays an anti-tumor angiogenesis role and inhibits the occurrence and development of ovarian cancer.

Bo et al. [14] indicated that the overexpression of mir-9 can promote the migration and invasion of ovarian cancer cells and that the miR-9 inhibitors can effectively inhibit these processes. The oncogenic mechanism may involve the promotion of ovarian cancer metastasis by targeting E-cadherin. The mechanism suggested a new way to control the metastasis of ovarian cancer. You Juan et al. [15] clinically compared 80 cases of patients with ovarian cancer (the malignant group) with 50 cases of patients with ovarian benign lesions (the benign group) and 50 cases of healthy women (the healthy group) and found that the serum miR-21 and CA125 levels in the three groups decreased in the following order: malignant group, benign group, and healthy group ($P<0.05$). The serum mir-21 and CA125 expression levels in the ovarian cancer patients were significantly increased. Therefore, the combined quantification of the mir-21 and CA125 expression levels could improve the clinical diagnosis and disease evaluation of ovarian cancer. In their study on transplanted tumors in nude mice, Bertucci et al. [16] also found that the inhibition of miR-21 resulted in a substantial inhibition of tumor growth. Bairong et al. [17] found that miR-381

expression is down-regulated in EOC tissues and cell lines and that the overexpression of miR-381 significantly inhibits the proliferation, migration, and invasion of EOC cells. The proliferation, migration, and invasion of EOC cells are at least partially inhibited by inhibiting the expression of YY1. Lin et al. [18] found that miR-363 is down-regulated in the tissues of ovarian cancer patients and in four ovarian cancer cell lines (SKOV3, A2780, OVCAR, and HO-8910). Low miR-367 levels were correlated with late OC, lymph node metastasis, and poor prognoses. High miR-367 expressions decreased SKOV3 cell growth, colony formation, migration, and invasiveness. Moreover, mir-367 may play a role in inhibiting cancer in OC by inhibiting NOB1. Through knockout studies, Hong et al. [19] found that the expression of the miR-429 target gene, KIAA010, was up-regulated in metastatic EOC tissues and enhanced the migration activity and drug resistance of EOC cells, indicating that both miR-429 and KIAA0101 might be potential therapeutic targets of EOC. Through an ovarian cancer survival analysis, Zavesky et al. [20] found that miR-429 can be used as a potential diagnostic and prognostic biomarker of ovarian cancer. Wang et al. [21] found that miR-200b is highly expressed in the serum and ovarian tissues of epithelial ovarian cancer patients, indicating that miR-200b might induce the migration and invasion of epithelial ovarian cancer cells by regulating the expression of the MMP-9 protein and its mRNA level.

MiRNA expression disorders are a common phenomenon in tumors. MiRNA expression disorders exist in almost all cancers, and different tumors may involve different miRNA expression disorders. Eleven of the 20 core miRNAs identified in the study have been shown to promote or inhibit ovarian cancer. The remaining miRNAs are more or less correlated with cancer. MiRNA-485 can inhibit cancer in non-small cell lung cancer [22], colorectal cancer [23], and prostate cancer [24]. MiRNA-489 is abnormally expressed in breast cancer [25], colon cancer, and non-small-cell lung cancer [26]. Hu et al. [27] found that miR-524 can regulate the proliferation and apoptosis of non-small cell lung cancer by targeting FABP5. Liu et al. [28] found that the regulation of miR-520d can improve the treatment of triple-negative breast cancer, and Deng et al. [29] found that the expression of miR-520d in gastric cancer tissues is significantly increased. Bolandghamat et al. [30] found that miR-154 can participate in the pathogenesis of breast cancer and improve its prognosis. MiR-154 is also linked to gastric, prostate, and non-small-cell lung cancer. Cui et al. [31] found that the inhibition of miR-520f can increase the expressions of ROCK1, CDKN1B, and AKT3 and promote the proliferation, invasion, and migration of NSCLC cells. Li-hua Chen [32] found that both miR-526b and KDNM4a-siRNA can inhibit the proliferation and invasion of GC cells and promote apoptosis. The overexpression of KDM4A has the opposite effect, and significantly blocks the regulation of miR-526b on cell growth and invasion. Zhang et al. [33] found that miR-491 is down-regulated in gastric cancer and inhibits the progression of gastric cancer cells induced by SNHG8. Further studies showed that SNHG8 promotes the proliferation and invasion of gastric cancer cells by targeting the miR491/PDGFRA axis. These findings may provide new insights into potential treatment strategies for gastric cancer in the future.

Most of the obtained core genes have been shown to be related to ovarian cancer, but the others are also closely related to various cancers. Thus, miR-524, miR-520d, miR-485, miR-154, miR-520f, miR-491, miR-489, and miR-520d, which have not been shown to be associated with ovarian cancer, might be one of the directions for future studies on ovarian cancer. MiR-138, miR-98, miR-124, miR-9, miR-367, and miR-429 can be used as prediction indicators of ovarian cancer genes.

Disclosure of conflict of interest

None.

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