

Identifying miRNA-mRNA regulation network of major depressive disorder in ovarian cancer patients

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Received March 29, 2018; Accepted July 26, 2018

DOI: 10.3892/ol.2018.9243

Abstract. Major depression disorder (MDD) has become increasingly common in patients with ovarian cancer, which complicates the treatment course. The microRNA (miRNA)-mRNA regulation network may help elucidate the potential mechanism of MDD in ovarian cancer. The differentially expressed microRNAs (DEmiRs) and mRNAs (DEmRNAs) were therefore identified from the GSE61741, GSE58105 and GSE9116 ovarian cancer datasets using GEO2R. The target genes of the DEmiRs were then obtained using the TargetScan, microRNAorg, microT-CDS, miRDB and miRTarBase prediction tools. The DAVID program was used to identify the KEGG pathways of target genes, and the core genes of major depressive disorder (MDD) were identified using the Kaplan-Meier Plotter for ovarian cancer. A total of 5 DEmiRs (miR-23b-3p, miR-33b-3p, miR-1265, miR-933 and miR-629-5p) were obtained from GSE61741 and GSE58105. The target genes of these DEmiRs were enriched in pathways that were considered high risk for developing MDD in ovarian cancer. A total of 11 risk genes were selected from these pathways as the core genes in the miRNA-mRNA network of MDD in ovarian cancer, and eventually identified the following 12 miRNA-mRNAs pairs: miR-629-5p-FGF1, miR-629-5p-AKT3, miR-629-5p-MAGI2, miR-933-BDNF, miR-933-MEF2A,

miR-23b-3p-TJP1, miR-23b-3p-JMJD1, miR-23b-3p-APAF1, miR-23b-3p-CAB39, miR-1265-CDKN1B, miR-33b-3p-CDKN1B, and miR-33b-3p-F2R. These results may provide novel insights into the mechanisms of developing MDD in ovarian cancer patients.

Introduction

With continuous progress in modern medicine, the overall survival of patients with malignant tumors has improved. However, accompanying depression has become increasingly common among cancer patients. A great deal of epidemiological studies have shown that the incidence of depression in cancer patients is 2-4 times higher than that in the normal population, and up to 20-50% of the patients are afflicted (1,2). Ovarian cancer has the highest mortality rate among all gynecological malignancies, which results in extreme anxiety and depression in the patients. Bodurka reported a depression rate of 21% among the patients with ovarian cancer (3), while Price *et al* (4), found clinical depression in 5.9% of 798 women with ovarian cancer in a prospective cohort study.

Due to the belief that depression is a normal and universal reaction to cancer, it is often underplayed in patients with cancer. However, depression not only results in emotional trauma, but more importantly also causes pathophysiological changes in the patients (5,6). Neuroendocrine-immune modulation (NIM) negative feedback network is one of the important pathophysiological basis of clinical depression in patients with cancer. Depression in pancreatic cancer patients has been linked to the secretion of amines resistant to emotional excitement (7).

Various genes are involved in clinical depression, and miRNA-mRNA interactions play an important role in regulating its pathophysiological basis. Micro RNAs bind to the 3'-untranslated region (3'-UTR) of target genes involved in cellular processes like proliferation, differentiation, apoptosis, and immune responses (8). The miRNA-mRNA regulatory network is of great significance in identifying the mechanism of major depression disorder (MDD) in ovarian cancer. In addition, the relevant miRNAs may be potential diagnostic markers for the early detection of ovarian cancer related

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Key words: major depressive disorder, ovarian cancer, miRNA-mRNA regulation network, gene ontology, KEGG pathway

depression, as well as prognostic indicators for treatment response. Although a large number of epidemiological studies have reported depression in cancer patients, few studies exist on the miRNA-mRNA networks related to depression in cancer patients, which can detect and diagnose MDD at early stages. Bioinformatics and expression profiling techniques can help identify such networks in various diseases.

In the present study, we analyzed the miRNA expression profiles of patients with ovarian cancer or MDD, and the mRNA expression profiles of depressed and non-depressed patients with ovarian tumors. Using bioinformatics, we identified the miRNAs and their target genes, and constructed an miRNA-mRNA-pathway regulatory network.

Materials and methods

Acquisition of microarray data. Ovarian cancer and MDD associated gene expression datasets, original data and platform records were acquired from the Gene Expression Omnibus (GEO, <http://www.ncbi.nlm.nih.gov/geo/>) database from the National Center for Biotechnology Information (NCBI). The dataset GSE61741 (ovarian cancer) based on GPL9040 platform (febit *Homo Sapiens* miRBase 13.0) was submitted by Keller, and included 94 normal and 24 ovarian cancer samples. The MDD-associated dataset GSE58105 based on GPL1873 platform [Agilent-021827 Human miRNA Microarray (miRNA_107_Sep09)] was submitted by Lopez, and included 11 normal and 14 MDD samples. The GSE9116 dataset of depressed patients with ovarian tumors based on GPL96 platform [(HG-U133A) Affymetrix Human Genome U133A Array], was submitted by Cole, and included data from 5 depressed patients and non-depressed patients each, all with primary ovarian tumors.

Identification of differentially expressed microRNAs (DEmiRs) or DEmRNAs and miRNA target genes. GEO2R (<https://www.ncbi.nlm.nih.gov/geo/geo2r/>) is a useful online microarray data analysis tool that allows users to compare two or more groups of samples in a GEO series in order to identify DEmRNAs. The miRNA or mRNA with P-value <0.05 were regarded as DEmiRs or DEmRNAs respectively. The miRNA target genes were obtained from the following 5 prediction tools: TargetScan, microRNAorg, microT-CDS, miRDB and miRTarBase. Genes overlapping in three or more prediction tools were selected as putative target genes of miRNA.

Risk pathways and survival curves of target genes involved in risk pathways. Gene ontology (GO) is a widely used method for the large-scale functional annotation of genes, and is based on certain structured, defined and controlled terms (9). Kyoto Encyclopedia of Genes and Genomes (KEGG) database is a collection of online databases of gene functions, enzymatic pathways, and helps link genomic information with higher-order functional information (10). The Database for Annotation, Visualization and Integrated Discovery (<https://david.ncifcrf.gov/>, DAVID) provides a comprehensive set of functional annotation tools to identify KEGG pathways and biological process (11,12). To determine the cellular pathways of target genes, the DAVID program was used to identify KEGG pathways and biological process,

with P<0.05 as the threshold value. Kaplan-Meier Plotter for ovarian cancer (13), an online analysis tool, was used to assess the effect of the selected genes on ovarian cancer. P<0.05 was considered to indicate a statistically significant difference.

Construction of miRNA-mRNA-pathway regulation network. Cytoscape (<http://www.cytoscape.org/>), an open source software platform for complex network analysis and visualization, was used to construct the miRNA-target genes-pathways network.

Results

Co-differentially expressed miRNA and target genes in ovarian cancer and depression. After comparing 24 ovarian cancer and 94 normal samples from the GSE61741 dataset, we identified 300 DEmiRs with P<0.05. Similarly, 40 DEmiRs were identified from the GSE58105 dataset. Furthermore, overlapping DEmiRs from both datasets included 4 upregulated (miR-23b-3p, miR-33b-3p, miR-1265 and miR-933) and 1 downregulated (miR-629-5p) DEmiRs. We used five gene prediction programs on these DEmiRs, and selected the genes common to three or more prediction tools as the target genes. There were 130, 29, 41, 18 and 30 target genes of miR-23b-3p, miR-33b-3p, miR-1265, miR-933 and miR-33b-3p respectively, and 90, 14, 34, 12 and 22 of them respectively were also DEmRNAs in the GSE9116 dataset (Fig. 1).

Identification of the risk pathways, risk genes and miRNA-risk gene-pathways regulation network. GO annotations showed that these target genes were involved in biological process including neural tube closure, negative regulation of neuron apoptotic process, nerve growth factor signaling pathway, positive regulation of cell migration, and apoptosis (Fig. 2). The most significantly enriched pathways of target genes which also exist as DEmRNAs in the GSE9116 dataset are shown in Fig. 3. A P-value<0.05 indicated statistically significant enrichment. Pathways associated with ovarian cancer and MDD, considered risk pathways, included cAMP signaling, transcriptional dysregulation in cancer, dopaminergic synapse, hepatitis B, proteoglycans in cancer, MAPK signaling, cGMP-PKG signaling, sphingolipid signaling, tight junction, rap1 signaling, central carbon metabolism in cancer, PI3K-Akt signaling, and AMPK signaling. Genes enriched in these risk pathways, i.e. the risk genes, included 22 upregulated and 15 downregulated genes. The miRNA-mRNA regulatory network was constructed using 5 DEmiRs, 37 risk genes and 13 risk pathways (Fig. 4).

Identification of core genes in ovarian cancer. Upon overexpression of the 22 upregulated risk genes, 10 risk genes could significantly increase the mortality of ovarian cancer patients, while only BDNF overexpression among the 15 downregulated risk genes could significantly increase survival rate. Taken together, 11 risk genes were identified as the core genes of MDD development in ovarian cancer, which are also DEmRNAs in GSE9116. The core genes include BDNF, MEF2A, FGF1, AKT3, MAGI2, TJP1, JMJD1C, APAF1, CAB39, CDKN1B and F2R (Fig. 5).

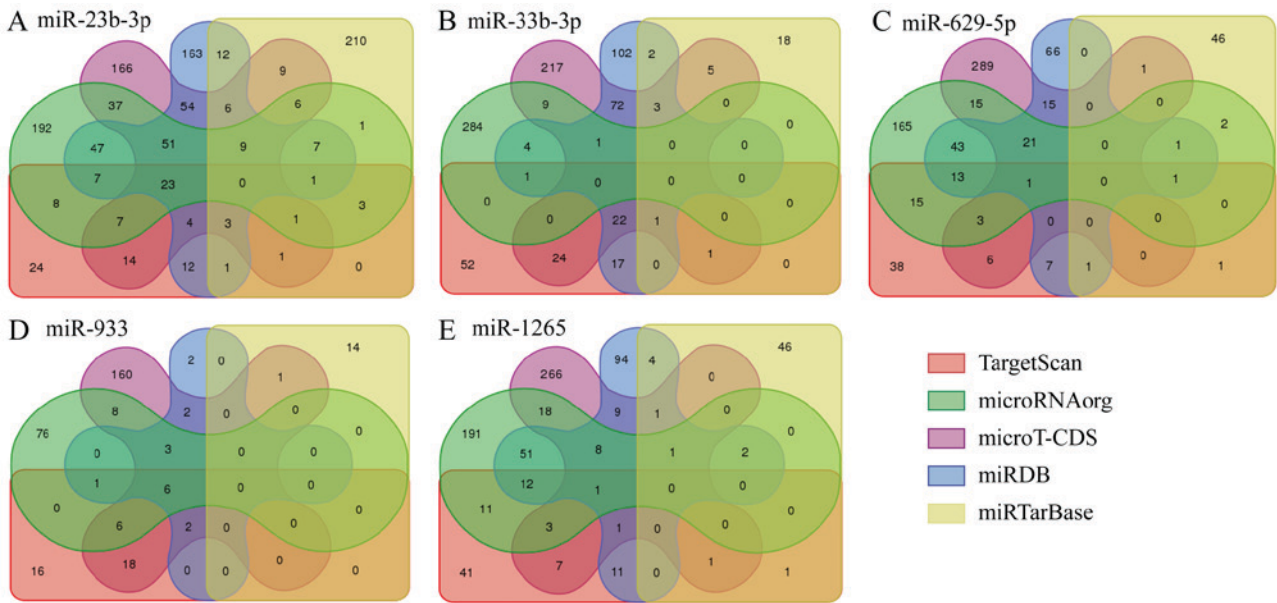


Figure 1. Intersection of miRNA target genes predicted by five kinds of software. (A) miR-23b-3p, (B) miR-33b-3p, (C) miR-629-5p, (D) miR-933 and (E) miR-1265.

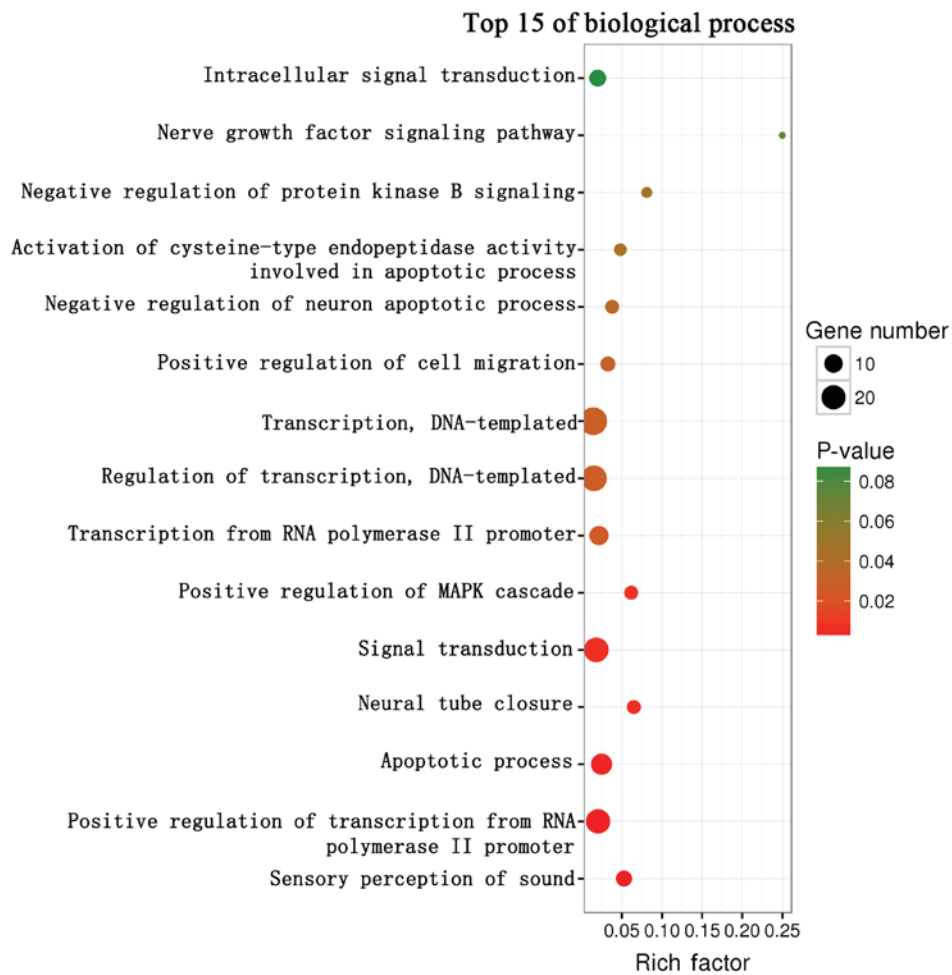


Figure 2. Top 15 biological process of the risk genes.

Analysis of miRNA-core gene-pathway regulation network. We confirmed 12 pairs of miRNA-mRNA interaction including

miR-629-5p-*FGF1*, miR-629-5p-*AKT3*, miR-629-5p-*MAGI2*, miR-933-*BDNF*, miR-933-*MEF2A*, miR-23b-3p-*TJPI1*,

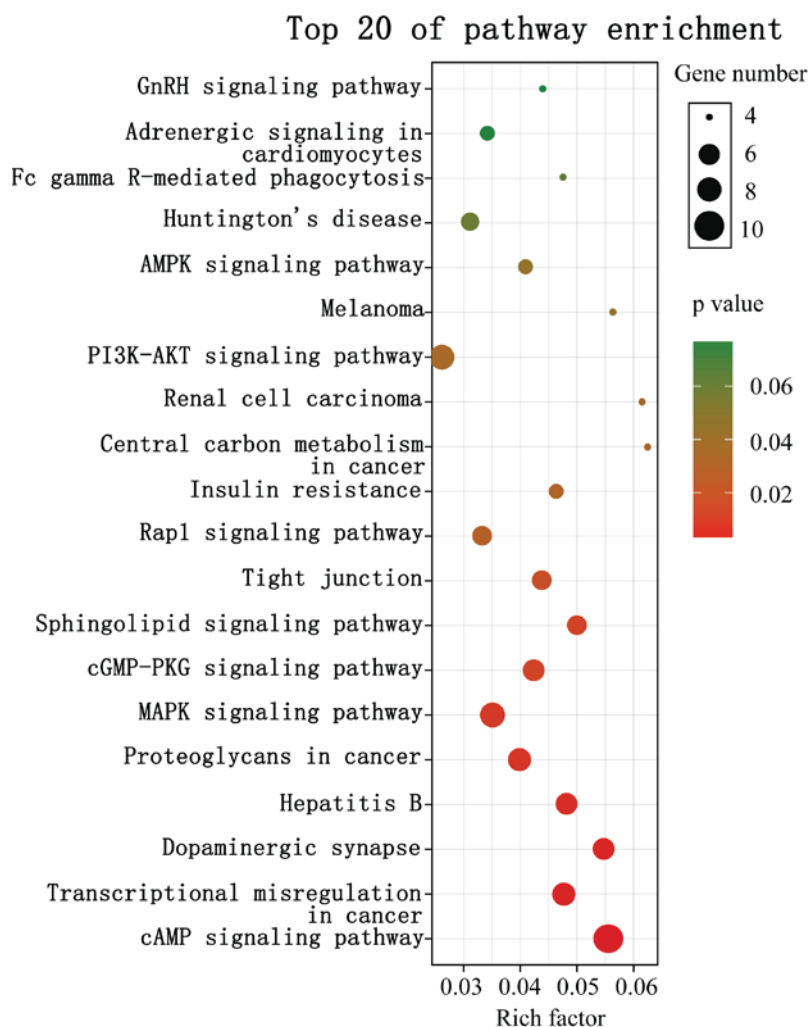


Figure 3. Top 20 pathway enrichment of the risk genes.

miR-23b-3p-*JMJD1*, miR-23b-3p-*APAF1*, miR-23b-3p-*CAB39*, miR-1265-*CDKN1B*, miR-33b-3p-*CDKN1B*, and miR-33b-3p-*F2R* (Fig. 6).

Discussion

MDD is a relatively common, yet frequently overlooked, co-morbidity of cancer. It is essential to study this condition, since comorbidities often complicate the treatment of cancer and may lead to poor clinical outcome. Although MDD occurs in a considerable proportion of patients with malignant tumors, its specific mechanism and pathophysiological basis are still unclear. Previous studies have linked the pathogenesis of malignant cancer associated MDD with psychological stress. Changes in the gene regulatory network underlies the interaction of MDD and cancer (5). However, few studies have reported any role of the miRNA-mRNA regulatory network in MDD accompanying cancer. Using bioinformatics analysis of the miRNA and mRNA expression profiles, we constructed an miRNA-mRNA interaction network with a putative role in the occurrence of MDD in ovarian cancer patients.

We analyzed the miRNA expression profiles of ovarian cancer patients with depression, and selected the differentially expressed miRNAs (DEmiRs) with $P < 0.05$. Target gene

prediction suggested multiple target gene regulation by a single miRNA, and regulation of a single target gene by several miRNAs simultaneously. Therefore, miRNA mediated regulatory networks are very complex. The target genes predicted by the DEmiRs in our study were involved in multiple biological processes. We hypothesized therefore that the aberrant expression of miRNAs may play an important role in the development of MDD in ovarian cancer patients by regulating various target genes and signaling pathways. The target genes that were enriched in the risk pathways were considered as the risk genes. One of the risk pathways, cAMP signaling, controls a diverse range of cellular processes, and studies have shown the frequent dysregulation of this pathway in patients with MDD (14). The MAPK signaling pathways regulate the expression of various genes through phosphorylation cascades. A constitutively active MAPK signaling pathway with mutations in the individual component(s) have been identified in several malignancies, including ovarian cancer (15). ERK1/2 signaling pathway, one of five MAPK signaling pathways, plays a key role in the regulation of cell growth and differentiation. Furthermore, Dwivedi *et al* (16) found significantly lower activity of ERK 1/2 in the prefrontal cortex and hippocampus of suicidal patients with MDD compared to healthy individuals. The dopaminergic synapse pathway is involved in the regulation the dopamine

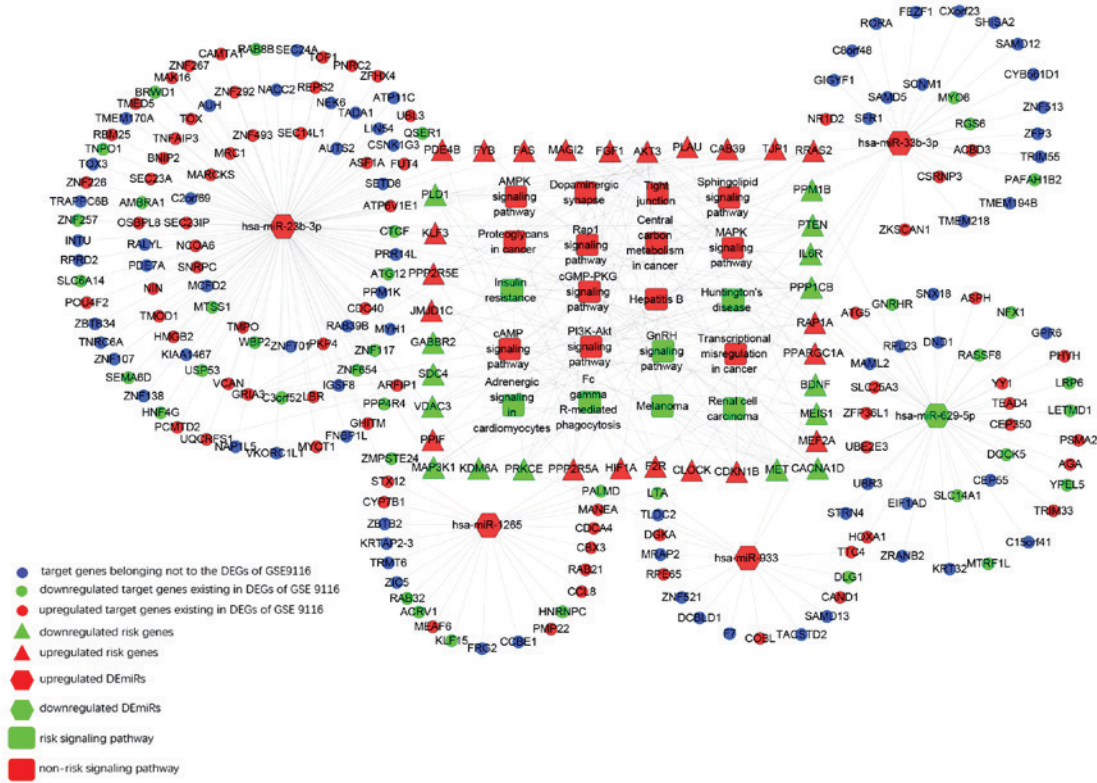


Figure 4. miRNA-risk genes-pathways regulation network. The blue circle represents target genes belonging not to the DEGs of GSE9116; The green circle represents downregulated target genes existing in DEGs of GSE9116; The red circle represents upregulated target genes existing in DEGs of GSE9116; The green triangle represents downregulated risk genes; The red triangle represents upregulated risk genes; The red hexagonal represents upregulated DEmiRs; The green hexagonal represents downregulated DEmiRs. The green square represents risk signaling pathway; The red square represents non-risk signaling pathway.

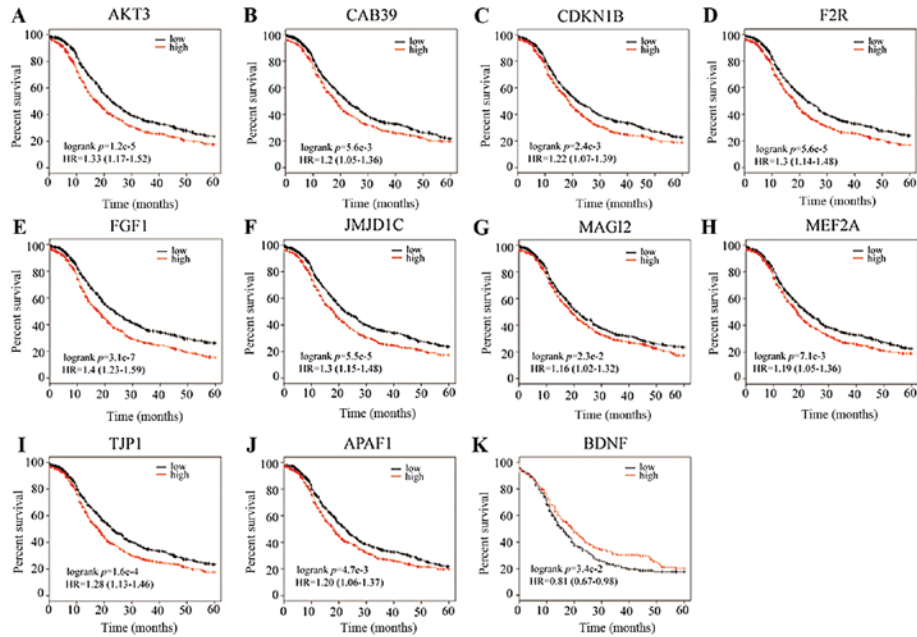


Figure 5. Kaplan-Meier curves of overall survival for 11 core genes. (A) AKT3, (B) CAB39, (C) CDKN1B, (D) F2R, (E) FGF1, (F) JMJD1C, (G) MAGI2, (H) MEF2A, (I) TJP1, (J) APAF1 and (K) BDNF.

transporter (DAT), and the deficiency of dopamine (DA) has been correlated with MDD (17). The density of DAT in the striatum of MDD patients is significantly higher than that in normal individuals. The excessive levels of DAT at the synaptic terminals increase the recovery of DA, and thus reduce the level

of DA in the synaptic gap resulting in symptoms of MDD. The other risk signaling pathways also play important roles in tumor progression and depression. Previous studies have shown that reduced cGMP levels caused by inhibition of guanylate cyclase and phosphodiesterase activity in the cGMP-PKG signaling

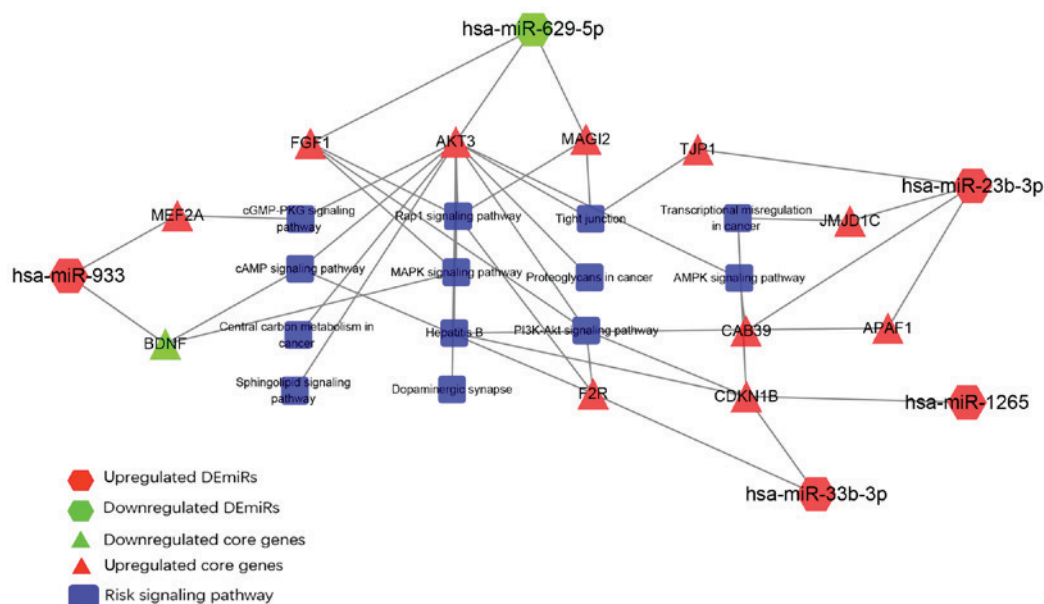


Figure 6. miRNA-core gene-risk signaling pathway regulation network. The red hexagonal represents upregulated DE miRNAs; The green hexagonal represents downregulated DE miRNAs; The green triangle represents downregulated core genes; The red triangle represents upregulated core genes; The blue square represents risk signaling pathway. DE miRNAs, differentially expressed microRNAs.

pathway can help alleviate symptoms of depression (18). In addition, inactivation of the cGMP-PKG signal may promote tumor cell proliferation and angiogenesis. Many studies have shown low expression levels of PKG in various tumors including gastric cancer (19), lung cancer (20) and breast cancer (21). Over-activation of the PI3K/AKT signaling pathway suppresses apoptosis and has been linked with ovarian cancer development, invasion and metastasis (22). In addition, the PI3K/AKT pathway exerts a protective action on the central nervous system.

Based on survival analysis of the risk genes, we selected the following core genes involved in the survival of ovarian cancer patients: AKT3, CAB39, CDKN1B, F2R, FGF1, JMJD1C, MAGI2, MEF2A, TJP1, AFAF1 and BDNF. As presented in Table I, All the core genes of the regulatory network were involved in the top 15 significant biological process. The damage to neural plasticity and neural cell regeneration may be the pathophysiological basis for MDD in ovarian cancer. Neurotrophic factors play a very important role in the development and maintenance of peripheral and central nervous system. BDNF, or brain-derived neurotrophic factor, is involved in nerve regeneration (23). BDNF levels are significantly decreased in the hippocampus and prefrontal cortex of depression patients (17). Bachis (24) correlated increased expression of BDNF with hippocampal neurogenesis, and decreased expression with anxiety disorder. FGF1 (Fibroblast growth factor 1) is a core member of the FGFs family which play important roles in cell proliferation, angiogenesis, morphogenesis and regeneration, and is closely related to tumor development (25). FGF1 also has a nutritive function in the regeneration of central nervous system and impaired neuronal repair (26). AKT3, a member of the AKT subfamily of serine/threonine protein kinases, is involved in several biological processes including cell proliferation, differentiation, apoptosis, and tumorigenesis (27,28). It plays an important role in ovarian tumorigenesis via regulation of VEGF secretion and angiogenesis (29). Moreover,

one study (30) showed that AKT3 is the most abundant AKT paralog in the brain during neurogenesis, and protects nerve cells and promotes neurogenesis. Membrane-associated guanylate kinase inverted 2 (MAGI2) is a scaffold protein with multiple domains, and functions in raising and anchoring cell signaling proteins. It is highly expressed in brain tissues, and is involved in the formation and maintenance of synapses in the central nervous system of vertebrates, and in the occurrence and development of nervous system diseases. In addition, it has been reported as a potential tumor suppressor (31-33). The GO analysis indicated another function of MAGI2 as a negative regulator of AKT signaling (Fig. 2). Due to its involvement in the nerve growth factor signaling pathway, MAGI2 may play a role in the occurrence and development of MDD. The interaction between the core genes and DE miRNAs need to be further experimentally validated.

In conclusion, we analyzed the miRNA expression profiles of ovarian cancer patients with MDD, and eventually constructed a miRNA-mRNA regulatory network through bioinformatics analysis. The miRNA-mRNA regulatory network provides new insights into the pathophysiological mechanisms of MDD in ovarian cancer.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from Chinese National Natural Science Foundation Grant (grant nos. 81671541, 81273202 and 31400773), Clinical Medicine Science & Technology Project of Jiangsu Province of China (grant no. BL2013024), Jiangsu Provincial key research and development program (grant no. BE2016721).

Table I. Top 15 significant biological process of risk genes.

| GOTERM_BP_DIRECT | Genes | P-value | Fold enrichment |
|--|---|---------|-----------------|
| Sensory perception of sound | HOXA1, TJP1, USP53, CDKN1B, MYO6, POU4F2, CACNA1D | 0.002 | 5.524 |
| Positive regulation of transcription from RNA polymerase II promoter | CAMTA1, ZNF292, MEF2A, HMGB2, MYO6, YY1, MET, CTCF, RORA, CSRNP3, NCOA6, LRP6, POU4F2, FGF1, CLOCK | 0.002 | 2.140 |
| Apoptotic process | KLF15, MEIS1, PPARGC1A, WBP2, HIF1A, MEF2A, PRKCE, TOX3, PTEN, ZFP36L1, GHITM, CSRNP3, ATG5, BNIP2, MAP3K1, APAF1, FAS, TNFAIP3, LTA | 0.003 | 2.591 |
| Neural tube closure | COBL, KDM6A, LRP6, APAF1, SDC4 | 0.006 | 6.815 |
| Signal transduction | MRC1, FYB, MAGI2, PPP2R5A, MET, CCL8, RASSF8, PRKCE, SDC4, HIF1A, STAC, PDE4B, RAP1A, PPP2R5E, FAS, CSNK1G3, FGF1, CLOCK, PLAU, LTA, AKT3 | 0.007 | 1.898 |
| Positive regulation of MAPK cascade | BNIP2, FAS, IL6R, PRKCE, F2R | 0.007 | 6.478 |
| Transcription from RNA polymerase II promoter | CAMTA1, MEF2A, ZNF292, HIF1A, CSRNP3, POU4F2, CTCF, KLF15, MEIS1, CLOCK, NFX1 | 0.024 | 2.250 |
| Regulation of transcription, DNA-templated | MEAF6, HMGB2, MEF2A, ZKSCAN1, RORA, ZNF654, MEIS1, PPARGC1A, ZFP36L1, HOXA1, ZFH4, ZNF226, HIF1A, NR1D2, PNRC2, JMJD1C, TMPO, ZNF117, CLOCK, ZNF257, ZNF493, ZNF267, KLF3 | 0.027 | 1.605 |
| Transcription, DNA-templated | MEAF6, HMGB2, MEF2A, CBX3, ZKSCAN1, RORA, ZNF654, HOXA1, ZNF226, NR1D2, TEAD4, ASF1A, ZNF493, ZNF267, ZMYM2, YY1, HNF4G, TOX3, BRWD1, ZFH4, HIF1A, TRIM33, PNRC2, JMJD1C, ZNF117, CLOCK, ZNF257, KLF3 | 0.028 | 1.503 |
| Positive regulation of cell migration | SEMA6D, RRAS2, F7, FGF1, PLAU, F2R | 0.031 | 3.422 |
| Negative regulation of neuron apoptotic process | BDNF, AMBRA1, PPARGC1A, TOX3, F2R | 0.037 | 3.975 |
| Activation of cysteine-type endopeptidase activity involved in apoptotic process | CDKN1B, APAF1, FAS, F2R | 0.044 | 5.058 |
| Negative regulation of protein kinase B signaling | MAGI2, PTEN, DLG1 | 0.048 | 8.509 |
| Nerve growth factor signaling pathway | MAGI2, RAP1A | 0.073 | 26.238 |
| Intracellular signal transduction | DGKA, FYB, STAC, RGS6, SOCS6, CAB39, PRKCE, AKT3 | 0.089 | 2.083 |

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

CW conceived the idea for the study and wrote the manuscript. YZ, YL, XY, MY, YM and ZP collected the data and analyzed the data. SQ, SX, JY, PY, BW and QS conceived the idea for the study and revised the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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