Gene expression profiling analysis of ovarian cancer

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Abstract. As a gynecological oncology, ovarian cancer has high incidence and mortality. To study the mechanisms of ovarian cancer, the present study analyzed the GSE37582 microarray. GSE37582 was downloaded from Gene Expression Omnibus and included data from 74 ovarian cancer cases and 47 healthy controls. The differentially-expressed genes (DEGs) were screened using linear models for microarray data package in R and were further screened for functional annotation. Next, Gene Ontology and pathway enrichment analysis of the DEGs was conducted. The interaction associations of the proteins encoded by the DEGs were searched using the Search Tool for the Retrieval of Interacting Genes, and the protein-protein interaction (PPI) network was visualized by Cytoscape. Moreover, module analysis of the PPI network was performed using the BioNet analysis tool in R. A total of 284 DEGs were screened, consisting of 145 upregulated genes and 139 downregulated genes. In particular, downregulated FBJ murine osteosarcoma viral oncogene homolog (FOS) was an oncogene, while downregulated cyclin-dependent kinase inhibitor 1A (CDKN1A) was a tumor suppressor gene and upregulated cluster of differentiation 44 (CD44) was classed as an 'other' gene. The enriched functions included collagen catabolic process, stress-activated mitogen-activated protein kinases cascade and insulin receptor signaling pathway. Meanwhile, FOS (degree, 15), CD44 (degree, 9), B-cell CLL/lymphoma 2 (BCL2; degree, 7), CDKN1A (degree, 7) and matrix metallopeptidase 3 (MMP3; degree, 6) had higher connectivity degrees in the PPI network for the DEGs. These genes may be involved in ovarian cancer by interacting with other genes in the module of the PPI network (e.g., BCL2-FOS, BCL2-CDKN1A, FOS-CDKN1A, FOS-CD44, MMP3-MMP7 and MMP7-CD44). Overall, BCL2, FOS, CDKN1A, CD44, MMP3 and MMP7 may be correlated with ovarian cancer.

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Introduction

Ovarian cancer is a common malignant tumor of the female reproductive organs, with an incidence ranked third of all malignant tumors, and the majority of these tumors are epitheliomas (1). With not only non-typical early symptoms but also complex ovarian embryonic development, tissue dissection and endocrine functions, only 19% of all ovarian cancers can be diagnosed at an early stage, and the mortality rate for this disease is highest in the field of gynecological oncology (2).

In recent years, a number of studies have been performed to investigate the molecular mechanisms of ovarian cancer. For example, as a member of the protein kinase B family, v-akt murine thymoma viral oncogene homolog 2 (AKT2) can be frequently activated and induce the apoptosis of human primary ovarian cancer by inhibiting the phosphoinositide 3-kinase (PI3K)/Akt pathway (3). With elevated expression levels in patients with epithelial ovarian cancer, ovarian cancer carbohydrate antigen 125 can be used for monitoring patients with ovarian cancer (4). As a chemokine receptor, chemokine (C-X-C motif) receptor 4 can be expressed on a subset of ovarian cancer cells and may have important roles in the development of site-specific metastasis (5,6). Chemokine (C-X-C motif) ligand 12 may affect ovarian cancer through several methods, such as stimulating cell migration and invasion, inducing establishment of a cytokine network and DNA synthesis in conditions that are suboptimal for tumor cell growth (7). PI3Ks are lipid kinases associated with neoplasia (8), and phosphoinositide-3-kinase, catalytic subunit α (which encodes the p110alpha catalytic subunit of PI3-kinase) is an oncogene that plays a critical role in ovarian cancer (9).

In 2012, Zhao *et al* (10) used a whole-genome microarray approach to analyze genes that differed between ovarian cancer cases and healthy controls, and obtained a total of 10,435 mRNA genes that could be used for downstream analysis. Using the data obtained by Zhao *et al* (10), the present study aimed to obtain the differentially-expressed genes (DEGs) and investigate their possible functions by Gene Ontology (GO) and pathway enrichment analyses. In addition, the interaction associations between these DEGs were searched using the protein-protein interaction (PPI) network and modules of the PPI network.

Materials and methods

Microarray data. The expression profile of GSE37582, deposited by Zhao *et al* (10), was downloaded from Gene Expression

Omnibus (http://www.ncbi.nlm.nih.gov/geo/) and was based on the platform of the GPL6947 Illumina HumanHT-12 V3.0 expression beadchip. GSE37582 included data from 74 ovarian cancer cases and 47 healthy controls.

DEG screening and functional annotation. Once GSE37582 had been downloaded, microarray data was preprocessed by robust multi-array average (11) background correction. Next, quantile normalization was conducted. The average value of multiple probes mapped with one gene was obtained as the ultimate gene expression value. The linear models for microarray data package in R (12) was used to analyze the DEGs between ovarian cancer cases and healthy controls. A false discovery rate (FDR) of <0.05 and $|\log_2$fold-change$|>1$ were used as the cut-off criteria.

To predict genes with functions of transcription factors, the DEGs were screened in combination with the transcription factors database. In combination with the tumor suppressor gene (TSG) (13) and tumor-associated gene (14) databases, the TSGs and oncogenes were then further screened from the DEGs.

Functional and pathway enrichment analysis. Through use of controlled and structured vocabularies, GO (www.geneontology.org/) can act as a community-based bioinformatics resource and classify gene product functions (15). As an integrated database resource, the Kyoto Encyclopedia of Genes and Genomes (KEGG; www.genome.jp/kegg/) consists of systems information, genomic information and chemical information (16). GO and KEGG pathway enrichment analyses were performed for the DEGs. P<0.05 was used as the cut-off criterion.

PPI network and module construction. The Search Tool for the Retrieval of Interacting Genes online software (17) was used to search interaction associations of the proteins encoded by the DEGs, and the required confidence (combined score) of >0.4 was used as the cut-off criterion. Cytoscape (18) was used to visualize the PPI network. Next, connectivity degree analysis was conducted and key nodes (i.e., hub proteins) (19) were searched. The proteins in the network were defined as the nodes. Next, the BioNet (20) analysis tool in R was used to screen modules of the PPI network. The FDR was set to 3.

Results

DEG analysis and functional annotation. A total of 284 DEGs were screened, consisting of 145 upregulated genes and 139 downregulated genes. Only 1 transcription factor was significantly upregulated, while 8 transcription factors were significantly downregulated. For the upregulated genes, there was 1 oncogene, 4 TSGs and 3 'other' genes [the influence of 'other' genes on tumors was unclear, and could therefore not be distinguished as oncogenes or tumor suppressor genes, including cluster of differentiation 44 (CD44)]. For the downregulated genes, there were 4 oncogenes [such as FBJ murine osteosarcoma viral oncogene homolog (FOS)], 11 TSGs [such as cyclin-dependent kinase inhibitor 1A (CDKN1A)] and 5 'other' genes (Table I).

Functional and pathway enrichment analysis. The enriched GO functions for the DEGs are listed in Table II. For the upregulated genes, the enriched GO functions included the collagen catabolic process ($P=1.86\times10^{-2}$), extracellular matrix disassembly ($P=4.50\times10^{-3}$) and negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage by p53 class mediator ($P=3.07\times10^{-3}$). For the downregulated genes, the enriched GO functions included the negative regulation of cell growth ($P=1.39\times10^{-4}$), stress-activated mitogen-activated protein kinases (MAPK) cascade ($P=1.73\times10^{-3}$) and insulin receptor signaling pathway ($P=1.19\times10^{-2}$).

The enriched KEGG pathways for the DEGs are listed in Table III. For the upregulated genes, the enriched KEGG pathways included the pentose phosphate pathway ($P=2.43\times10^{-2}$), hematopoietic cell lineage ($P=4.46\times10^{-2}$) and rheumatoid arthritis ($P=4.84\times10^{-2}$). Meanwhile, for the downregulated genes, the enriched KEGG pathways included the MAPK signaling pathway ($P=3.77\times10^{-6}$), pathways in cancer ($P=7.47\times10^{-3}$) and toxoplasmosis ($P=7.24\times10^{-5}$).

PPI network and module construction. The PPI network consisted of 110 nodes and 136 interactions. There were 45 upregulated genes and 65 downregulated genes in the PPI network of the DEGs (Fig. 1). The number of upregulated genes was less than that of the downregulated genes. The DEGs, which encoded proteins with connectivity degrees of ≥5, included FOS (degree, 15), CD44 (degree, 9), B-cell CLL/lymphoma 2 (BCL-2; degree, 7), CDKN1A (degree, 7), DnaJ heat shock protein family (Hsp40) member B1 (degree, 7), AKT2 (degree, 7) and matrix metalloproteinase 3 (MMP3; degree, 6).

A module was obtained from the PPI network of the DEGs (Fig. 2). The module had 62 nodes and 93 interactions. In this module, the number of upregulated genes was less than the number of downregulated genes. Moreover, BCL2 could interact with FOS and CDKN1A, FOS could interact with CDKN1A and CD44, and MMP7 could interact with MMP3 and CD44. The enriched GO functions for the DEGs in the module included extracellular matrix organization ($P=2.86\times10^{-6}$), response to drug ($P=3.36\times10^{-4}$) and regulation of cell motility ($P=1.37\times10^{-3}$) (Table IV). The enriched KEGG pathways for the DEGs in the module are listed in Table V, including pathways in cancer ($P=9.01\times10^{-5}$), prostate cancer ($P=3.98\times10^{-5}$), colorectal cancer ($P=7.89\times10^{-5}$) and acute myeloid leukemia ($P=7.44\times10^{-4}$).

Discussion

In the present study, a total of 284 DEGs were screened, consisting of 145 upregulated genes and 139 downregulated genes. In particular, downregulated FOS was an oncogene, while downregulated CDKN1A was a tumor suppressor gene and upregulated CD44 was classed as an 'other' gene. The enriched functions included the collagen catabolic process, stress-activated MAPK cascade and insulin receptor signaling pathway. Meanwhile, FOS (degree, 15), CD44 (degree, 9), BCL2 (degree, 7), CDKN1A (degree, 7) and MMP3 (degree, 6) had higher connectivity degrees in the PPI network for the DEGs. Also, a module was obtained from the PPI network of the DEGs.

Bcl-2 belongs to an family of pro- and antiapoptotic proteins (21), able to enhance cell survival by inhibiting

Table I. Functional annotations of the differentially-expressed genes.

Regulation	TF numbers	TF symbols	TAG numbers	TAG symbols
Up	1	KLF12	8	TCL1B, CTNND1, MUC1, PTPRF, STARD13, CD44, FES, MIAT
Down	8	ASCL1, ETV4, HSF1, LMO3, PML, RUNX3, TCF7, USF2	20	AKT2, FOS, GNA12, PVT1, CD82, CDKN1A, FBXO32, GADD45G, MAL, PML, PPP1R3C, RUNX3, SCGB3A1, SOCS1, VHL, ASCL1, BCAS1, OGG1, PMS2, RHOB

TF, transcription factor; TAG, tumor-associated gene.

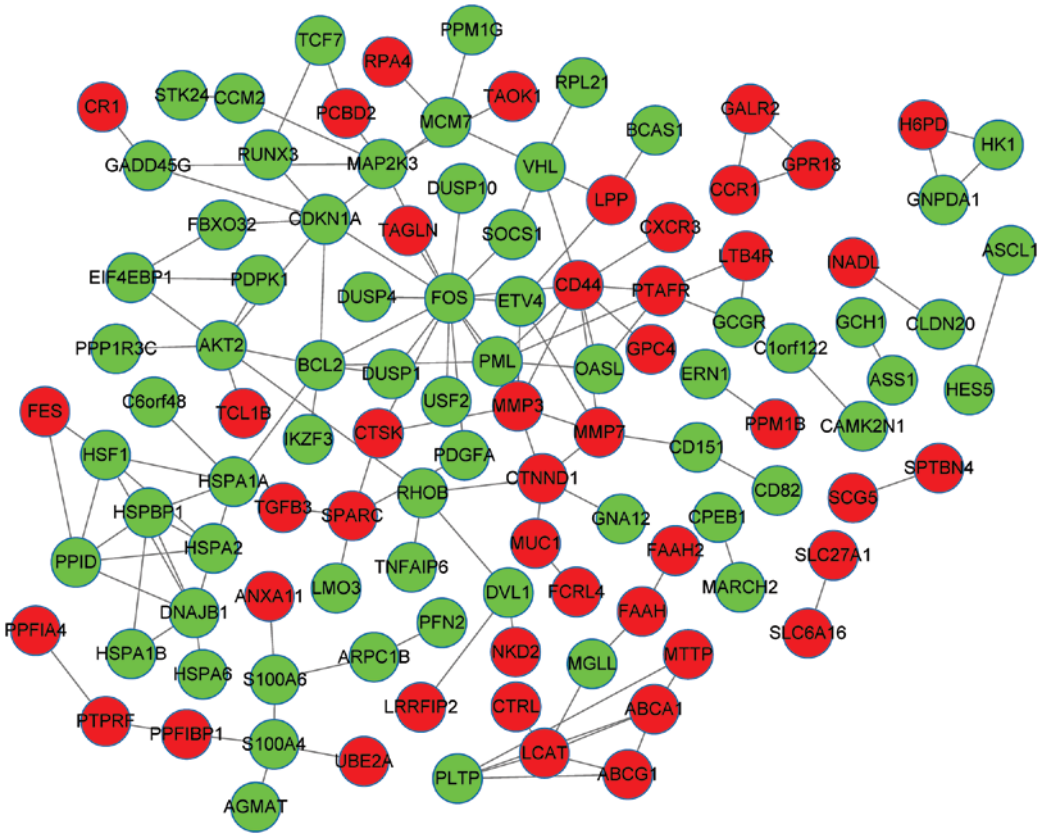

Figure 1. Protein-protein interaction network of the differentially-expressed genes. Red and green circles represent the up- and downregulated genes, respectively.

apoptosis (22). BCL2 is frequently expressed in primary ovarian carcinoma and may be an important determinant of drug-induced apoptosis in ovarian cancer (23,24). By deregulating programmed cell death and changing sensitivity to chemotherapy, alteration of the Bax/Bcl-2 balance may affect the clinical course of ovarian cancer (25). As a member of the Bcl-2 family, ABT-737 can significantly improve the activity of carboplatin and thus may be of great use in the treatment of patients with ovarian cancer (26). These data may indicate that the expression level of BCL2 is associated with ovarian cancer. The c-fos protein may act as a tumor suppressor and may be involved in apoptosis (27). Expression of Fos can affect the progression of ovarian carcinoma and may function as a prognostic factor (28). Thus, we speculated that FOS may play a role in ovarian cancer. In the module, the present study found that BCL2 exhibited interaction associations with FOS, indicating that BCL2 may also play a role in ovarian cancer by mediating FOS.

As one of the most important CDK inhibitors, p27Kip1 can function in the G_1 cell cycle arrest induced by anti-human epidermal growth factor receptor type 2 antibody and inhibit tumor growth through post-translational regulation (29). As the product of the CDKN2A gene at chromosome 9p2, the CDK inhibitor p16 is associated with the progression and unfavorable prognosis of ovarian cancer (30,31). p21, also known as CDKN1A, regulates several processes, including cell growth (32), differentiation (33) and apoptosis (34). Over-expressed CDK inhibitor p21 can reduce the phosphorylation

Table II. Enriched GO functions for the differentially-expressed genes.

Gene regulation	GO term	Description	Gene number	Gene symbol	P-value
Upregulated genes	GO:0042158	Lipoprotein biosynthetic process	5	ABCA1, LCAT, MTTP, PIGF, PPM1B	$1.30x10^{-4}$
	GO:0007204	Elevation of cytosolic calcium ion concentration	5	CCR1, CXCR3, GALR2, LIME1, TPCN2	$1.34x10^{-2}$
	GO:0022617	Extracellular matrix disassembly	4	CTSK, KLKB1, MMP3, MMP7	$4.50x10^{-3}$
	GO:0051592	Response to calcium ion	4	ANXA11, KCNMB1, MTTP, SPARC	$5.28x10^{-3}$
	GO:0030574	Collagen catabolic process	3	CTSK, MMP3, MMP7	$1.86x10^{-2}$
	GO:0010875	Positive regulation of cholesterol efflux	2	ABCA1, ABCG1	$3.07x10^{-3}$
	GO:1902166	Negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage by p53 class mediator	2	CD44, MUC1	$3.07x10^{-3}$
	GO:003443	Cholesterol esterification	2	ABCG1, LCAT	$3.67x10^{-3}$
	GO:0034616	Response to laminar fluid shear stress	2	ABCA1, TGFB3	$3.67x10^{-3}$
	GO:0034375	High-density lipoprotein particle remodeling	2	ABCG1, LCAT	$5.01x10^{-3}$
Downregulated genes	GO:0006469	Negative regulation of protein kinase activity	8	CDKN1A, DUSP1, DUSP10, DUSP4, DVL1, GADD45G, PDPK1, SOCS1	$4.97x10^{-5}$
	GO:0030308	Negative regulation of cell growth	7	BCL2, CDKN1A, HSPA1B, PML, PPP1R9B, SCGB3A1, SERTAD3	$1.39x10^{-4}$
	GO:0051403	Stress-activated MAPK cascade	7	AKT2, CCM2, CDC42EP5, DUSP10, DUSP4, FOS, MAP2K3	$1.73x10^{-3}$
	GO:0046777	Protein autophosphorylation	6	CAMKK2, ERN1, PDGFA, PDPK1, PIM3, STK24	$3.65x10^{-3}$
	GO:0006986	Response to unfolded protein	5	DNAJB1, ERN1, HSPA1B, HSPA2, HSPA6	$4.61x10^{-3}$
	GO:0008286	Insulin receptor signaling pathway	5	AKT2, EIF4EBP1, PDPK1, SOCS1, TCIRG1	$1.19x10^{-2}$
	GO:0048146	Positive regulation of fibroblast proliferation	3	CDKN1A, PDGFA, S100A6	$4.29x10^{-3}$
	GO:0045069	Regulation of viral genome replication	3	BCL2, OASL, PPID	$9.26x10^{-3}$
	GO:0030833	Regulation of actin filament polymerization	3	ARPC1B, CDC42EP5, PFN2	$3.98x10^{-2}$
	GO:0008295	Spermidine biosynthetic process	2	AGMAT, AMD1	$3.78x10^{-4}$

GO, Gene Ontology; MAPK, mitogen-activated protein kinases.

Table III. Enriched KEGG pathways for the differentially-expressed genes.

Gene regulation	Term	Description	Gene number	Gene symbol	P-value
Upregulated genes	30	Pentose phosphate pathway	2	H6PD, RBKS	2.43×10^{-2}
	4640	Hematopoietic cell lineage	3	CD1C, CD44, CR1	4.46×10^{-2}
	5323	Rheumatoid arthritis	3	CTSK, MMP3, TGFB3	4.84×10^{-2}
Downregulated genes	4010	MAPK signaling pathway	13	AKT2, DUSP1, DUSP10, DUSP4, FOS, GADD45G, GNA12, HSPA1A, HSPA1B, HSPA2, HSPA6, MAP2K3, PDGFA	3.77×10^{-6}
	5200	Pathways in cancer	9	AKT2, BCL2, CDKN1A, DVL1, FOS, PDGFA, PML, TCF7, VHL	7.47×10^{-3}
	5145	Toxoplasmosis	8	AKT2, BCL2, HSPA1A, HSPA1B, HSPA2, HSPA6, MAP2K3, SOCS1	7.24×10^{-5}
	4141	Protein processing in endoplasmic reticulum	8	BCL2, DNAJB1, ERN1, HSPA1A, HSPA1B, HSPA2, HSPA6, HSPBP1	3.41×10^{-4}
	5215	Prostate cancer	6	AKT2, BCL2, CDKN1A, PDGFA, PDPK1, TCF7	3.48×10^{-4}
	4910	Insulin signaling pathway	6	AKT2, EIF4EBP1, HK1, PDPK1, PPP1R3C, SOCS1	3.42×10^{-3}
	4144	Endocytosis	6	CHMP6, HSPA1A, HSPA1B, HSPA2, HSPA6, PML	2.01×10^{-2}
	3040	Spliceosome	5	HSPA1A, HSPA1B, HSPA2, HSPA6, PRPF6	1.13×10^{-2}
	5221	Acute myeloid leukemia	4	AKT2, EIF4EBP1, PML, TCF7	3.11×10^{-3}
	5210	Colorectal cancer	4	AKT2, BCL2, FOS, TCF7	4.22×10^{-3}

KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinases.

Table IV. Top 10 enriched GO functions for the differentially-expressed genes in the module.

GO term	Description	Gene number	Gene symbol	P-value
GO:0030198	Extracellular matrix organization	9	CTSK, MMP3, CD44, CD151, SPARC, PDGFA, MMP7, VHL, TGFB3	2.86×10^{-6}
GO:0006954	Inflammatory response	9	LTB4R, CD44, MAP2K3, FOS, CR1, DUSP10, PTAFR, CXCR3, TNFAIP6	1.41×10^{-4}
GO:0022612	Gland morphogenesis	7	BCL2, CD44, CTNND1, ETV4, PML, PDGFA, TGFB3	2.37×10^{-7}
GO:0006469	Negative regulation of protein kinase activity	7	DVL1, CDKN1A, GADD45G, SOCS1, DUSP10, DUSP1, PDPK1	2.82×10^{-6}
GO:0042493	Response to drug	7	BCL2, CDKN1A, MCM7, FOS, PDGFA, MMP7, GNA12	3.36×10^{-4}
GO:2000145	Regulation of cell motility	7	BCL2, MMP3, FES, AKT2, PDGFA, CXCR3, PDPK1	1.37×10^{-3}
GO:0043583	Ear development	6	BCL2, DVL1, CCM2, SPARC, PDGFA, TGFB3	9.35×10^{-5}
GO:0051403	Stress-activated MAPK cascade	6	MAP2K3, AKT2, FOS, CCM2, DUSP10, TAOK1	1.69×10^{-4}
GO:0043068	Positive regulation of programmed cell death	6	CDKN1A, PML, RHOB, DUSP1, PPID, TGFB3	1.71×10^{-3}
GO:0060333	Interferon-γ-mediated signaling pathway	5	CD44, OASL, SOCS1, PML, PTAFR	9.81×10^{-6}

GO, Gene Ontology; MAPK, mitogen-activated protein kinases.

Table V. Enriched KEGG pathways for the differentially-expressed genes in the module.

Term	Description	Gene number	Gene symbol	P-value
4010	MAPK signaling pathway	14	GADD45G, MAP2K3, HSPA2, AKT2, HSPA1A, FOS, HSPA1B, PDGFA, DUSP10, DUSP1, GNA12, TAOK1, HSPA6, TGFB3	$2.91x10^{-9}$
5200	Pathways in cancer	10	BCL2, DVL1, CDKN1A, AKT2, FOS, PML, PDGFA, VHL, TCF7, TGFB3	$9.01x10^{-5}$
5145	Toxoplasmosis	9	BCL2, MAP2K3, HSPA2, AKT2, HSPA1A, SOCS1, HSPA1B, HSPA6, TGFB3	$3.30x10^{-7}$
4141	Protein processing in endoplasmic reticulum	7	BCL2, DNAJB1, HSPA2, HSPA1A, HSPA1B, HSPBP1, HSPA6	$1.68x10^{-4}$
5215	Prostate cancer	6	BCL2, CDKN1A, AKT2, PDGFA, TCF7, PDPK1	$3.98x10^{-5}$
4144	Endocytosis	6	HSPA2, HSPA1A, HSPA1B, PML, HSPA6, TGFB3	$3.17x10^{-3}$
5210	Colorectal cancer	5	BCL2, AKT2, FOS, TCF7, TGFB3	$7.89x10^{-5}$
4910	Insulin signaling pathway	5	AKT2, SOCS1, EIF4EBP1, PPP1R3C, PDPK1	$3.14x10^{-3}$
5221	Acute myeloid leukemia	4	AKT2, PML, EIF4EBP1, TCF7	$7.44x10^{-4}$
4612	Antigen processing and presentation	4	HSPA2, HSPA1A, HSPA1B, HSPA6	$2.18x10^{-3}$

KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinases.

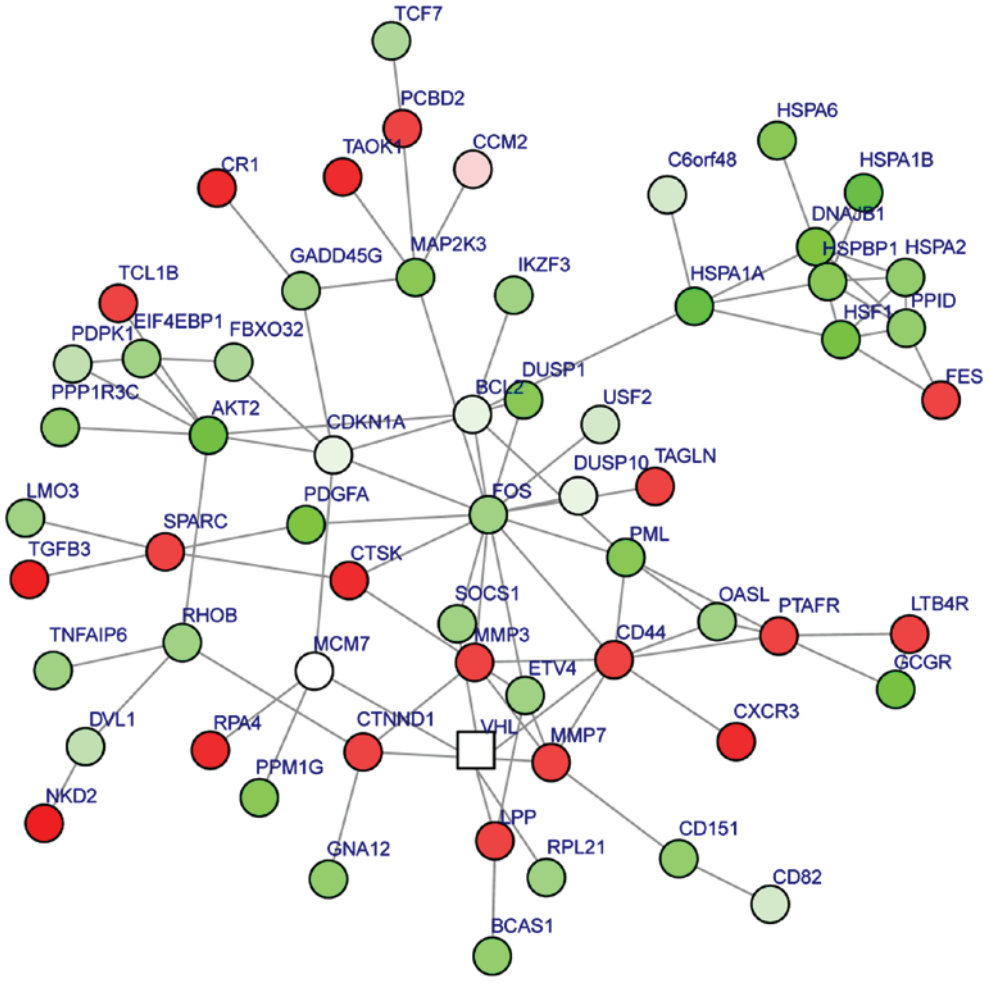

Figure 2. Module obtained from the protein-protein interaction network of the differentially-expressed genes. The shape of the nodes depicts the score: Square indicates a negative score; circle indicates a positive score. A square node with a negative score has a lower importance compared with other nodes. Red circles indicate the upregulated genes and green circles indicate the downregulated genes. The shade of a node has positive association with its $|\log_2$fold-change|.

of retinoblastoma protein in trichostatin A-treated ovarian cancer cells, and therefore p21 may be involved in the cell cycle blockade and the differentiation of the cells (35). These data may indicate that the expression level of CDKN1A exhibits an association with ovarian cancer. In the module in the present study, it was found that CDKN1A could interact with FOS and BCL2, indicating that CDKN1A may also affect ovarian cancer by mediating the two genes.

CD44 is regarded as the main cell surface receptor for hyaluronan (36), an extracellular polysaccharide associated with the progression of ovarian cancer (37). Significant overexpression of CD44 in ovarian cancer cells can induce strong adhesion to the peritoneal mesothelium (38,39), and CD44 has a close association with the implantation of ovarian cancer metastasis (40). The $CD44^+/CD117^+$ status can be a molecular marker of ovarian cancer-initiating cells (41). As a stem cell marker, CD44 combined with higher aldehyde dehydrogenase 1 family member A1 activity may be used to define ovarian cancer stem cells (42). These data indicate that CD44 may play a role in ovarian cancer. In the module, the present study found that CD44 had interaction associations with FOS, indicating that CD44 may also play a role in ovarian cancer by mediating FOS.

MMPs are a family of zinc-dependent neutral endopeptidases that are overexpressed in the tumor microenvironment and are able to degrade essentially all extracellular matrix components (43,44). Members of the MMP family are involved in tumor cell metastasis and invasion, including the progression of ovarian cancer (45). As the smallest member of the MMP family, MMP7 can be overexpressed in malignant ovarian epithelium and may assist tumor cell invasion by inducing progelatinase activation (46). Meanwhile, MMP7 may act as a marker for detection and as a target for treatment in ovarian cancer (47). These data suggest that MMP7 may have a close association with ovarian cancer. In the module, the present study found there were several interaction associations (e.g., MMP3-MMP7 and MMP7-CD44), indicating that MMP7 may also play a role in ovarian cancer by mediating MMP3 and CD44.

In conclusion, a comprehensive bioinformatics analysis of DEGs that may affect ovarian cancer was conducted in the present study. A total of 284 DEGs were screened, and it was found that BCL2, FOS, CDKN1A, CD44, MMP3 and MMP7 may have a correlation with ovarian cancer. However, further research is required to unravel their roles in ovarian cancer.

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