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Identification of potential targets for ovarian cancer treatment by systematic bioinformatics analysis

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Summary

Purpose of investigation: To provide a systematic overview to understand the mechanism of ovarian cancer. *Materials and Methods:* Data of GSE14407 downloaded from Gene Expression Omnibus (GEO) database and differentially expressed genes (DEGs) were identified. Gene ontology and pathway enrichment analysis were performed by Database for Annotation, Visualization and Integrated Discovery (DAVID). Furthermore, the authors constructed the protein-protein interaction (PPI) network and co-expression networks by Cytoscape. *Results:* A total 1,442 genes were identified to be differentially expressed. Regulatory effects of DEGs mainly focused on cell cycle, transcription regulation, and cellular protein metabolic process. Significant pathways were determined to be p53 signaling pathway, amino sugar, and nucleotide sugar metabolism. The most significant transcription factor was aryl hydrocarbon receptor nuclear translocator (ARNT). Abnormal spindle-like microcephaly-associated protein (ASPM), Aurora kinase (AURKA), Cyclin-A2 (CCNA2), G2/mitotic-specific cyclin-B1, (CCNB1), and Cyclin-dependent kinase 1 (CDK1) were significant nodes in PPI network. *Conclusion:* The significant genes and pathways show potential targets for the treatment of ovarian cancer.

Key words: Ovarian cancer; Protein-protein interaction; Co-expression network; Gene ontology analysis; Pathway enrichment analysis.

Introduction

Ovarian cancer is a gynecologic malignancy arising from the ovary and is characterized by uncontrolled tumor growth [1, 2]. It is one of the leading causes of cancer death among women [3]. The symptoms of patients with ovarian cancer are subtle at early stage, including bloating, pelvic pain, and frequent urination [4]. The five-year survival rate of ovarian cancer patients with advanced stage is only 30% after initial diagnosis [5]. It is reported that more than 90% of ovarian cancers originate from surface epithelium of the ovary [6]. In 2012, there were around 22,280 new cases of ovarian cancer [5]. Ovarian cancer is a health concern highlighted all over the world.

Many studies have been conducted to explore the mechanism underlying ovarian cancer progression. One of the important mechanism of ovarian cancer has been determined to be the dysregulation of transcription factors in ovarian cancer [7, 8]. A series of transcription factors (TFs) formed complex regulatory network to regulate gene expressions in cancers [9]. TFs played critical roles in regulating transcription activation by suppressing or triggering target genes with binding sites in regulatory regions [10]. It is reported that TFs in the progression of ovarian cancer are mainly involved in the regulation of cell cycle and cell differentiation [4]. Furthermore, the development of ovarian cancer is revealed to be the accumulation of genetic changes [11]. The oncogenes or tumor suppressor genes have been found to be expressed abnormality in ovarian cancer such as human epidermal growth factor receptor 2 (HER-2/neu), c-myc (Myc), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (K-ras), and p53 (tumor protein 53) [12]. However, the molecular mechanism underlying the progression of ovarian cancer is largely unknown.

Here, the authors applied bioinformatics technology to identify the differentially expressed genes between human ovarian cancer epithelia tissues and normal ovarian surface epithelial tissues. They constructed the Protein-Protein interaction network and co-expressed network of the differential expression genes. Through investigation of critical genes in function levels, they further explored systematically the mechanism underlying ovarian cancer.

Materials and Methods

Affymetrix microarray data and differential expression analysis

The gene expression profile (GSE14407) was downloaded from Gene Expression Omnibus (GEO) which is a public functional genomics data repository. The expression data was collected by Bowen N.J., *et al* [13]. A total of 24 samples were available for analysis, including 12 samples of human ovarian cancer epithelia tissues and 12 samples of normal ovarian surface epithelial tissues. The raw CEL data and the annotation files for probes were downloaded based on the platform of GPL570 (Affymetrix Human Genome U133 Plus 2.0 Array) for further analysis.

The CEL source files were processed into expression estimates by Robust Multi-array Average (RMA) algorithm in R [14] and the probe numbers were converted into gene symbols

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Table 1. — *GO analysis for DEGs in BP, CC and MF (Top10).*

Group	Category	Term	Count	*p* value
Upregulated gene	GOTERM_BP_FAT	GO:0006508~proteolysis	88	0.002645
	GOTERM_BP_FAT	GO:0008104~protein localization	78	0.001048
	GOTERM_BP_FAT	GO:0010941~regulation of cell death	67	0.012448
	GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	66	0.016469
	GOTERM_BP_FAT	GO:0015031~protein transport	65	0.006445
	GOTERM_BP_FAT	GO:0045184~establishment of protein localization	65	0.007858
	GOTERM_BP_FAT	GO:0010605~negative regulation of macromolecule metabolic process	64	0.004237
	GOTERM_BP_FAT	GO:0042127~regulation of cell proliferation	64	0.018194
	GOTERM_BP_FAT	GO:0009057~macromolecule catabolic process	63	0.021948
	GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	63	0.036824
	GOTERM_CC_FAT	GO:0005829~cytosol	123	1.88E-06
	GOTERM_CC_FAT	GO:0000267~cell fraction	88	0.004232
	GOTERM_CC_FAT	GO:0031090~organelle membrane	86	0.011726
	GOTERM_CC_FAT	GO:0005739~mitochondrion	84	0.017747
	GOTERM_CC_FAT	GO:0005783~endoplasmic reticulum	79	0.005094
	GOTERM_CC_FAT	GO:0012505~endomembrane system	69	0.001726
	GOTERM_CC_FAT	GO:0005626~insoluble fraction	65	0.035922
	GOTERM_CC_FAT	GO:0005624~membrane fraction	62	0.04772
	GOTERM_CC_FAT	GO:0031982~vesicle	59	0.004134
	GOTERM_CC_FAT	GO:0031410~cytoplasmic vesicle	54	0.014695
	GOTERM_MF_FAT	GO:0005509~calcium ion binding	74	0.006233
	GOTERM_MF_FAT	GO:0042802~identical protein binding	58	0.001377
	GOTERM_MF_FAT	GO:0008134~transcription factor binding	41	0.046794
	GOTERM_MF_FAT	GO:0008289~lipid binding	40	0.011424
	GOTERM_MF_FAT	GO:0003712~transcription cofactor activity	36	0.003236
	GOTERM_MF_FAT	GO:0004857~enzyme inhibitor activity	31	7.07E-04
	GOTERM_MF_FAT	GO:0005506~iron ion binding	28	0.027835
	GOTERM_MF_FAT	GO:0003735~structural constituent of ribosome	22	9.88E-04
	GOTERM_MF_FAT	GO:0003924~GTPase activity	22	0.014236
	GOTERM_MF_FAT	GO:0005543~phospholipid binding	19	0.018164
Downregulated gene	GOTERM_BP_FAT	GO:0007049~cell cycle	58	2.11E-27
	GOTERM_BP_FAT	GO:0022402~cell cycle process	48	1.07E-24
	GOTERM_BP_FAT	GO:0022403~cell cycle phase	46	1.57E-28
	GOTERM_BP_FAT	GO:0000278~mitotic cell cycle	43	2.34E-27
	GOTERM_BP_FAT	GO:0000279~M phase	42	2.57E-28
	GOTERM_BP_FAT	GO:0000280~nuclear division	37	4.09E-29
	GOTERM_BP_FAT	GO:0007067~mitosis	37	4.09E-29
	GOTERM_BP_FAT	GO:0000087~M phase of mitotic cell cycle	37	7.92E-29
	GOTERM_BP_FAT	GO:0048285~organelle fission	37	1.78E-28
	GOTERM_BP_FAT	GO:0051301~cell division	36	1.89E-23
	GOTERM_CC_FAT	GO:0043232~intracellular non-membrane-bounded organelle	67	3.23E-08
	GOTERM_CC_FAT	GO:0043228~non-membrane-bounded organelle	67	3.23E-08
	GOTERM_CC_FAT	GO:0005856~cytoskeleton	38	3.00E-05
	GOTERM_CC_FAT	GO:0044430~cytoskeletal part	36	3.68E-08
	GOTERM_CC_FAT	GO:0043233~organelle lumen	35	0.027639
	GOTERM_CC_FAT	GO:0031974~membrane-enclosed lumen	35	0.035493
	GOTERM_CC_FAT	GO:0031981~nuclear lumen	34	0.001665
	GOTERM_CC_FAT	GO:0070013~intracellular organelle lumen	34	0.032755
	GOTERM_CC_FAT	GO:0005694~chromosome	32	8.10E-14
	GOTERM_CC_FAT	GO:0015630~microtubule cytoskeleton	32	8.61E-12
	GOTERM_MF_FAT	GO:0003677~DNA binding	40	0.018296
	GOTERM_MF_FAT	GO:0017076~purine nucleotide binding	33	0.034046
	GOTERM_MF_FAT	GO:0032555~purine ribonucleotide binding	32	0.031985
	GOTERM_MF_FAT	GO:0032553~ribonucleotide binding	32	0.031985
	GOTERM_MF_FAT	GO:0001882~nucleoside binding	30	0.017844
	GOTERM_MF_FAT	GO:0001883~purine nucleoside binding	30	0.016382
	GOTERM_MF_FAT	GO:0030554~adenyl nucleotide binding	30	0.013526
	GOTERM_MF_FAT	GO:0032559~adenyl ribonucleotide binding	29	0.012329
	GOTERM_MF_FAT	GO:0005524~ATP binding	29	0.010385
	GOTERM_MF_FAT	GO:0046983~protein dimerization activity	13	0.031639

Table 2. — *Significant pathways by KEGG pathway enrichment analysis.*

Group	Category	Term	Count	*p* value
Upregulated gene	KEGG_PATHWAY	hsa03010: Ribosome	15	0.00159
	KEGG_PATHWAY	hsa04610: Complement and coagulation cascades	14	5.04E-04
	KEGG_PATHWAY	hsa04142: Lysosome	14	0.045549
	KEGG_PATHWAY	hsa00520: Amino sugar and nucleotide sugar metabolism	10	0.00202
	KEGG_PATHWAY	hsa00010: Glycolysis / gluconeogenesis	9	0.043399
Upregulated gene	KEGG_PATHWAY	hsa00071: Fatty acid metabolism	8	0.014944
	KEGG_PATHWAY	hsa00280: Valine, leucine and isoleucine degradation	8	0.024487
	KEGG_PATHWAY	hsa03050: Proteasome	8	0.033933
	KEGG_PATHWAY	hsa00340: Histidine metabolism	7	0.010619
	KEGG_PATHWAY	hsa00620: Pyruvate metabolism	7	0.046584
	KEGG_PATHWAY	hsa04110: Cell cycle	12	6.09E-08
	KEGG_PATHWAY	hsa05200: Pathways in cancer	9	0.023424
	KEGG_PATHWAY	hsa04114: Oocyte meiosis	7	0.001094
	KEGG_PATHWAY	hsa04115: p53 signaling pathway	6	7.64E-04

by Bioconductor algorithm in R combined with annotation files. The differentially expressed genes were identified by limma package in R [15]. The authors defined |logFC|>1.0 and p-value < 0.01 as the cut-off value.

Gene Ontology (GO) and pathway enrichment analysis

GGO database provides structured and controlled information for community use in annotations of genes [16]. It is commonly used to analyze the over-represented terms for a set of genes [17]. Kyoto Encyclopedia of Genes and Genomes (KEGG) is a database for systematic analysis of genes functions and involved pathways [18]. The Database for Annotation, Visualization and Integrated Discovery (DAVID) is a program for assessing the significance of clustering for GO and KEGG terms [19].

The authors performed GO analysis and KEGG pathway analysis for DEGs identified in this paper by DAVID online tool and set p-value < 0.05 as threshold value.

The construction of protein-protein interaction (PPI) network

Search Tool for the Retrieval of Interacting Genes (STRING) database consists of integrated information of known and predicted protein–protein associations [20]. The interactions of DEGs were mapped into protein associations based on STRING database. The protein interactions were displayed with confidence score. The authors established the PPI network of significant protein pairs with confidence score > 0.4 using Cytoscape [21] and the higher expressed network clusters were further analyzed with the application of plugin Molecular Complex Detection (MCODE) of Cytoscape [22].

Co-expression network construction of differentially expressed genes

The University of California, Santa Cruz (UCSC) Genome Browser is publicly available for a large collection of related annotations, which records the integrated information of transcription factor binding sites [23]. To evaluate the co-expression power in DEGs, the authors calculated the genes correlations by Pearson's correlation coefficients (PCCs). The gene pairs which had transcription factors regulation were filtered based on UCSC database [24]. The threshold value with |PCC| > 0.90 and p-value < 0.01 was set to select the significant co-expressed gene pairs. Then the co-expressed networks were visualized by Cytoscape package and subnetworks were scored by plugin MCODE.

Results

Differentially expressed genes (DEGs)

In order to analyse the DEGs between ovarian cancer epithelia tissues and normal ovarian surface epithelial tissues, the authors download the gene expression profiles of GSE14407 from GEO. After analysis, they obtained total of 1,442 DEGs including 1,187 upregulated ones and 255 downregulated ones.

GO analysis and pathway enrichment analysis

To investigate the DEGs in function level, the authors carried out GO analysis and KEGG pathway analysis. In GO analysis, the DEGs were mainly classified into three categories including biological process (BP), cell component (CC), and molecular function (MF). As shown in Table 1, the over-represented GO terms of upregulated DEGs were mainly related with proteolysis, protein localization, regulation of cell death, and regulation of programmed cell death. The upregulated DEGs were mainly enriched in pathways of complement and coagulation cascades, amino sugar and nucleotide sugar metabolism, and fatty acid metabolism (Table 2). The downregulated DEGs enriched GO terms included DNA binding, purine nucleotide binding, and ATP binding (Table 1) and the mainly involved pathways were cell cycle, oocyte meiosis, pathways in cancer, and p53 signaling pathway (Table 2).

PPI network analysis

The PPI network was constructed using the protein pairs with confidence score > 0.4 (Figure 1). After MCODE analysis, the authors obtained three sub-networks: subnetwork 1, subnetwork 2, and subnetwork 3 (Figure 2). Thirty-seven nodes in PPI networks were found to be with the maximum connective degree (24) such as abnormal spindle-like microcephaly-associated protein (ASPM), Aurora kinase (AURKA), Cyclin-A2 (CCNA2), G2/mitotic-specific cyclin-B1 (CCNB1), and Cyclin-dependent kinase 1

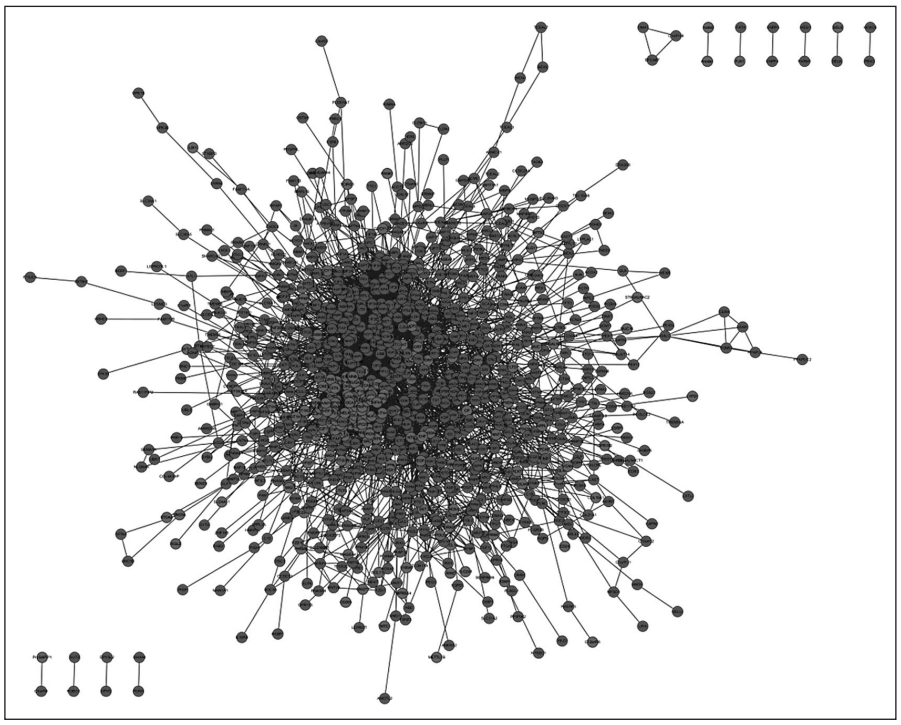

Figure 1. — PPI network of DEGs (red: upregulated genes; green: downregulated genes).

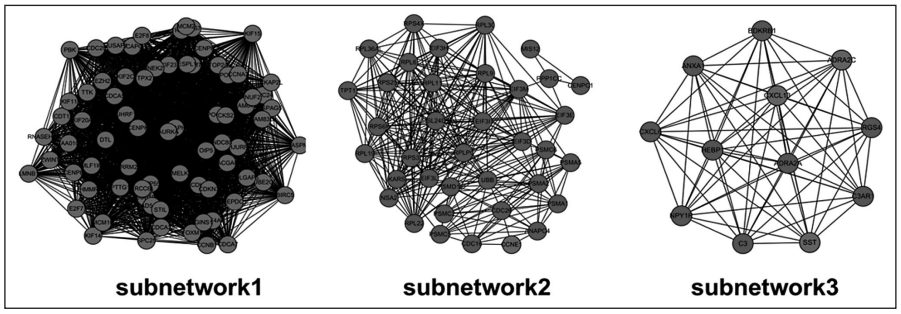

Figure 2. — Three sub-networks in PPI network by MCODE.

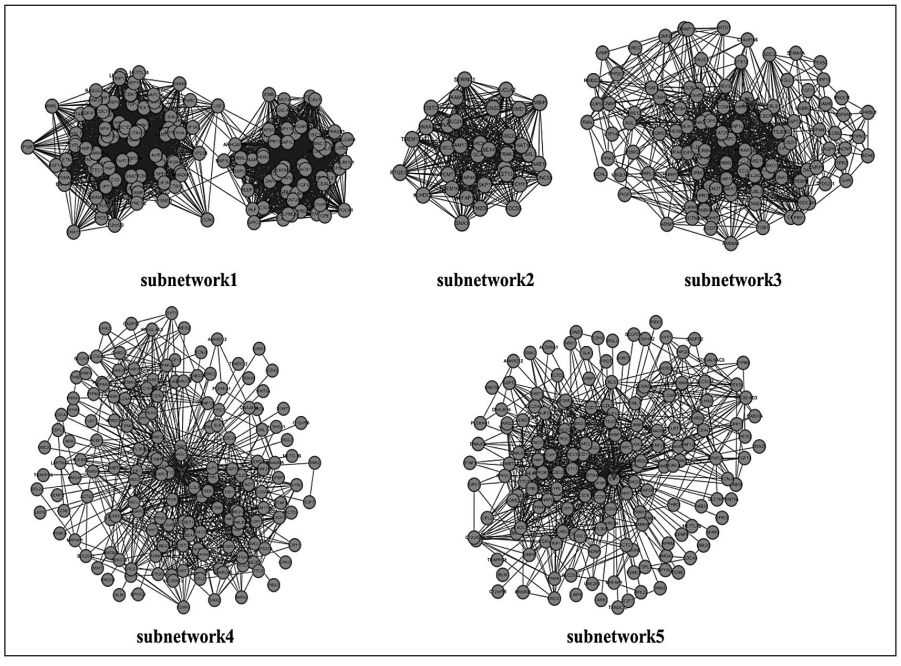

Figure 3. — Five modules of co-expressed network Sub-network 1-3 for 357 TFs; Sub-network 4-5 with ARNT and RIM3 as core nodes.

Table 3. — *The main biological process of 3 sub-network of PPI network.*

Subnetwork rank	Number of nodes	Main biological processes
1	75	cell cycle, cell division
2	37	translation, regulation of cellular protein metabolic process
3	12	cell surface receptor linked signal transduction, G-protein coupled receptor protein signaling pathway

Table 4. — *The main biological processes of different modules in co-expression network.*

Subnetwork rank	Number of nodes	Main biological processes
1	139	protein localization, regulation of cellular protein metabolic process
2	35	protein transport, establishment of protein localization
3	113	cell cycle, translation, cell cycle process
4	161	regulation of transcription, cell cycle
5	161	regulation of transcription, cell cycle

(CDK1). The three subnetworks involving biological processes were cell cycle, cell division; translation, regulation of cellular protein metabolic process, and cell surface receptor linked signal transduction, and G-protein coupled receptor protein signaling pathway, respectively (Table 3).

Co-expression network analysis

A total of 357 transcription factors with $|PCC| > 0.90$ and p-value < 0.01 were used for co-expressed network construction. In the co-expressed network, three sub-network with highest scores and were filtered by MCODE. Two transport factors with the highest connectivity were selected and the sub-networks with the two transport factors as core nodes and their first adjacent nodes were investigated for function analysis (Figure 3). The five modules mainly involved biological process were listed in Table 4.

Discussion

Ovarian cancer is regarded as heterogeneous cancer, which remains the leading cause of death from gynecologic cancer [12]. With high mortality and low cure rates, highlighted attentions from all over the world have been focused on disclosing the potential mechanism of ovarian cancer progression. In order to better understand ovarian cancer, the present authors explored the molecular mechanism with the application of bioinformatics method.

The present results suggested that 1,442 genes were involved in the progression of ovarian cancer, including 1,187 upregulated genes and 255 downregulated genes. Co-regulation mechanism is an important approach to understand the development of cancers. Based on the DEGs identified in the present study, the authors further investigated the gene expression correlations with TF related regulatory pairs. Results showed that the main co-expression sub-networks were involved in cell cycle, regulation of transcription, and cellular protein metabolic process. To obtain information of genes communications from mass genomic data, they also constructed the PPI networks. The PPI networks also showed that the main biological processes of DEGs between ovarian cancer epithelia tissues and normal tissues included cell cycle, signal transduction and cellular protein metabolic. The similar results can be found in the GO and pathway analysis. The DEGs enriched GO terms related with cell cycle, proteolysis, and molecular binding.

Significant pathways and genes have been determined to be associated with the primary function modules. Pathway enrichment analysis suggested that p53 signaling pathway was significant in ovarian cancer. Protein 53 (p53) as a tumor suppressor protein has been reported to be excessively expressed in ovarian cancers [25]. The expression of p53 is implicated in the modulation of apoptosis which may result in inhibition of drug induced apoptosis [26]. Previous study has reported that the action of p53 is associated with drug resistance of ovarian cancer cells [27]. The activation of p53 was triggered in the caspase-dependent mitochondrial death pathway induced by drug and the expression of p53 protected tumor cells from apoptosis and delayed S-phrase arrest [26]. The critical role of p53 pathway contributing to drug resistance has been highlighted in the treatment of ovarian cancer. The p53 signaling pathway identified in the present work function in signal transduction and cell apoptosis process.

By co-expression network analysis, the transcription factors: aryl hydrocarbon receptor nuclear translocator (ARNT) was found to play key roles in regulation regions of ovarian cancer. ARNT gene encodes aryl hydrocarbon receptor nuclear translocator protein which is the composition of the aryl hydrocarbon receptor (AhR) complex. ARNT forms AhR complex in nucleus with activated AhR in response to aryl hydrocarbon receptor (AhR) ligands [28]. AhR·ARNT complex has a close association with the xenobiotic stress response. The heterodimer of AhR·ARNT functioned in regulating multiple gene expressions to respond to xenobiotic stress, including cytochrome P450 subfamily polypeptide 1 (CYP1A1) [29]. The overexpression of ARNT is positively related with CYP1A1 expression levels [30]. A series of evidences proved that CYP1A1 gene polymorphism played role in the development of epithelial ovarian cancer [31]. The accumulation of CYP1A1 elevated the risk of having ovarian cancers. Therefore, ARNT is a critical regulator in the development of ovarian cancer by inducing the associated genes.

PPI networks also indicated some significant genes with higher degrees such as ASPM, AURKA, CCNA2, CCNB1, and CDK1. ASPM encoding for a mitotic spindle protein is localized in the spindle poles during mitosis. The expression of ASPM was found to be upregulated in proliferating tissues and malignant cells [32]. *ASPM* expression is determined to be correlated with the grade and survival of epithelial ovarian cancer [33]. Different levels of ASPM expression were observed in ovarian tumor cells correlating with the grade of tumors. ASPM has been considered to be a potential molecular target in glioblastoma and also has potential application in other cancers [34]. AURKA severed as a member of serine/threonine kinases also played a key role mitosis process. The peak activity of AURKA is presented in the G2 phase to M phase transition of the cell cycle [35]. As outlined in previous reports, the overexpression of AURKA is a common and significant event in the progression of ovarian cancers [36]. The amplification of AURKA may be a premalignant marker for ovarian carcinogenesis. Other node proteins such as CCNA2, CCNB1, and CDK1 also showed significant effect on cell cycle process. Therefore, these genes played a primary role in regulating cell cycle.

In summary, this work provides a systematic overview to understand the mechanism underlying ovarian cancer progression. The differential expressions of genes result in changes of pathways and function modules. The critical nodes in networks and the significantly disturbed pathways showed potential targets for ovarian cancer treatment. Further studies should be conducted to explore the clinical application of the targets.

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