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ORIGINAL ARTICLE

Selecting key genes associated with ovarian cancer based on differential expression network

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Summary

Purpose: *The purpose in this study was to select key genes related to ovarian cancer.*

Methods: *The gene expression profiles of E-GEOD-6008, E-GEOD-26712, E-GEOD-27651, E-GEOD-14001 were obtained from ArrayExpress database (http://www.ebi.ac.uk/arrayexpress/). Following data recruitment and preprocessing, differentially expressed genes (DEGs) were characterized using Significance Analysis of Microarrays (SAM). Then, a differential expression network (DEN) was constructed using Cytoscape 2.1 software based on differential and non-differential interactions. Pathway analysis was performed based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database using Pathway Analysis with the nodes contained in the main DEN. Centrality analysis on the DEN was conducted to selected HUB genes. And last, western blot was performed on the selected genes in an independent sample set.*

Results: *A total of 370 samples (347 ovarian tumors and 23 controls) were selected. In all, 490 DEGs were obtained, which contained 59 upregulated and 431 downregulated genes. A DEN including 875 gene pairs (1028 nodes) was constructed. There were 7 pathways by analyzing the nodes contained in the main DEN. Five HUB genes were gained, and three (UBC, ELAVL1, SIRT1) were both HUB genes and disease genes. Meanwhile, SIRT1 and NEDD4 were downregulated genes. Verification experiments indicated that the expression of SIRT1 and ELAVL1 in the disease group and the normal group were significantly changed.*

Conclusions: *This study showed that SIRT1 could be chosen as a potential biomarker for promoting detection of ovarian cancer, so as to further understand the molecular pathogenesis of this disease.*

Key words*: centrality analysis, differential expression network, HUB genes, ovarian cancer, pathway analysis*

Introduction

Ovarian cancer is a malignancy with an estimated 21,980 new cases and 14,270 deaths in 2014 in the United States [1]. These neoplasms are classified into distinct morphologic categories based on the appearance of the epithelium into tumors of serous, mucinous, endometrioid, clear cell, transitional, squamous, mixed and undifferentiated type [2]. Epithelial ovarian cancer is composed of a diverse group of tumors that can be derived from the ovary, fallopian tube or endometrium [3]. Despite advances in the disease detection and cytotoxic therapies, fewer than 40% of women with ovarian cancer are cured, and more than 60% patients present with advanced disease because of the silent tumor progression .

It is well known that the development and progression of tumors are related to accumulated molecular genetic or genomic changes [5]. Gene expression profiling had been widely used for cancer research. Tomas et al. [6] pointed out that

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gene expression profiling can identify a prognostic signature accounting for these distinct clinical outcomes. It has been reported that FGF9 is a key factor contributing to the cancer phenotype of ovarian endometrioid adenocarcinomas carrying Wnt/ß-catenin pathway defects [7]. It was indicated that the anterior gradient homolog 3 (AGR3) gene could serve as a prognostic marker for survival in patients with low- and high-grade serous ovarian carcinomas [8]. PAX2 was found to be one of the most upregulated genes in low-grade ovarian serous carcinoma [9]. Genomewide association studies had identified four susceptibility loci for epithelial ovarian cancer with another two loci being close to genomewide significance [10]. Despite the expanded efforts to study the genetic bases of ovarian cancer, the molecular mechanisms of the development and progression are still unclear.

The cross validation of datasets would significantly reduce these false findings and increased sensitivity [11]. Meanwhile, a large number of network approach for researching cancers were sprung up, such as biomolecular networks protein-protein interaction (PPI) network, gene regulatory networks [12,13], gene coexpression networks [14], statistical epistasis networks [15], weighted interaction network [16], and so on. DEN is a brand new network-based approach, which not only covers differential genes (DG) or differential network (DN), but also includes disease-related non-differential interactions which are missed in DN [17]. It was indicated that if the Spearman correlation coefficient was strongly correlated (>0.7) in one condition, but not in other conditions, then this edge was defined as differential interaction. If the edge was not differential interaction, but two endpoints (linked genes or coded proteins) of the edge were both differentially expressed, then this edge was noted as 'non-differential interactions' [17].

In the present study, we employed the DEN method, so as to select key genes related to ovarian cancer as far as possible accurately. Firstly, we conducted recruitment and preprocessing of the four groups of gene expression profiles obtained from ArrayExpress database. Then, immediately DEGs were screened. Following this the DEN which contained not only differential interactions, but also contained non-differential interactions was constructed. Pathway analysis was performed based on the KEGG database using nodes contained in the main DEN. We gained HUB genes via analyzing the degree centrality of the DEN. Meanwhile, in order to further prove the accuracy of our experiment, we conducted molecular biology experiments and western blot on the HUB genes that we gained.

Methods

Bioinformatics analysis

Data recruitment and preprocessing

The gene expression profiles of E-GEOD-6008, E-GEOD-26712, E-GEOD-27651 and E-GEOD-14001 were obtained from ArrayExpress database (http://www.ebi.ac.uk/arrayexpress/). E-GEOD-6008 was existed in Affymetrix HG-U133A platform, the data were gained from 99 individual ovarian tumors (37 endometrioid, 41 serous, 13 mucinous, and 8 clear cell carcinomas) and 4 individual normal ovary samples [7]. E-GEOD-26712 was completed for an extensive set of 185 primary ovarian tumors and 10 normal ovarian surface epithelium using the Affymetrix human U133A microarray [6]. E-GEOD-27651, existed in Affymetrix HG-U133Plus2 platform, was generated from 6 human ovarian surface epithelia, 8 serous borderline ovarian tumors, 13 low-grade serous ovarian carcinomas, and 22 high- grade serous ovarian carcinomas [8]. E-GEOD-14001 was existed in Affymetrix HG-U133Plus2 platform, the data were gained from 3 normal human ovarian surface epithelia and from 10 low-grade and 10 high-grade serous ovarian carcinoma samples to perform gene expression profiling [9]. In all, a total of 370 samples (347 ovarian tumors and 23 controls) were selected. All of the microarray data and annotation files of healthy human beings and ovarian cancers were downloaded for further analysis.

We carried out background correction and normalization by robust multichip average (RMA) method [18] and quantile based algorithm [19] so as to eliminate the influence of nonspecific hybridization. Micro Array Suite 5.0 (MAS 5.0) algorithm was used to revise perfect match and mismatch value [20], which value was selected by the median method. Meanwhile, the gene expression value was transformed to a comparable level. Also, genefilter package was used to discard the probe if it couldn't match any genes and average the expression value over probes as the gene expression value if the gene had multiple probes [21].

After preprocessing, there were 12493, 12493, 20102 and 20102 probes in the gene expression profiles of E-GEOD-6008, E-GEOD-26712, E-GEOD-27651, and E-GEOD-14001, respectively.

Identifying DEGs

The propensity of many diseases can be reflected in a difference of gene expression levels in particular cell types and this has been well confirmed [22]. For this reason, genes showing different expression levels in control crowds and case strains are likely related to the disease. Distance-weighted discrimination (DWD)

is a classification (discrimination) method, which was realized from a high-dimensional analysis of the support vector machine (SVM) [23]. After having preprocessed all of the four profiles, we chose DWD to combine these four data and conduct comprehensive analysis of them. Furthermore, Significance Analysis of Microarrays (SAM) [24] was used to calculate gene expression values, so as to select out DEGs. For genes with scores greater than an adjustable threshold, SAM uses permutations of the repeated measurements to estimate the percentage of genes identified by chance, the false discovery rate (FDR). In this study, the threshold value FDR <0.05 and a delta cut-off value of >6.029 was used.

PPI network

The original PPI network was integrated from Biological General Repository for Interaction Datasets (BioGrid, http://thebiogrid.org/). In the BioGrid, there were 15,750 genes and 248,584 interactions of human beings in all. Based on the four transcript data, the PPI network including 10,629 genes and 186,800 relationships was then constructed.

Calculating Spearman correlation coefficients of gene relationships

Spearman correlation coefficient is a popular method to describe the interaction strength between genes [25]. After having extracted the gene expression values under different conditions (controls and ovarian cancer) separately, the Spearman correlation coefficient of each edge was computed, which denoted as A1 and A2, respectively. Meanwhile, the absolute value of the difference between the two Spearman correlation coefficient was denoted as |A1-A2|.

Determining the threshold of p value

Two models (one for the normal group, the other for disease group) were built randomly so as to determine how to choose the gene relationships for further research, each model containing 200,000 gene relationships, the gene relationships of which were randomly captured from the genes that contained in the original PPI network. The Spearman correlation coefficients of edges in two models (A1,A2) were calculated respectively. The absolute values of their correlation coefficients (|A1-A2|) were obtained. Setting the absolute value of the correlation coefficients in descending order, we found that when the threshold of p value was set at 0.05, the absolute value of the correlation coefficient was 0.839. Consequently, we conducted the Spearman value of the 186,800 relationships that we obtained from BioGrid in descending order and selected out those gene relationships whose absolute value of the correlation coefficient was greater than 0.839, as well as at least one of the Spearman correlation coefficients was greater than 0.7.

Constructing DEN

The differential interactions were obtained by setting the threshold of |A1-A2| greater than 0.839, as well as at least one of A1 or A2 was greater than 0.7. And for those gene relationships whose |A1-A2| was less than or equal to 0.839 but both of the nodes were all DEGs were non-differential interactions. The network was constructed using Cytoscape 2.1 software after having selected out all of the differential and non-differential interactions.

Functional enrichment analysis of the nodes contained in main DEN

KEGG is an effort to link genomic information with higher order functional information by computerizing current knowledge on cellular processes and by standardizing gene annotations [26]. In this study, the KEGG database was applied to investigate the enrichment analysis of the nodes containing in main DEN involved in the occurrence and development of ovarian cancer. The database for Annotation, Visualization and Integrated Discovery (DAVID) [27] was used to perform the KEGG pathway enrichment analysis with the p value < 0.01 and gene count > 5.

Centrality analysis

Centrality analysis is a network analysis method to investigate biological networks, such as gene regulatory, protein interaction and metabolic networks so as to identify interesting elements of a network [28,29]. Centrality measures mainly contain degree centrality, closeness centrality and shortest path betweenness centrality, in which degree is the simplest topological index [30]. Nodes with high degree (highly connected) are called "HUBS", which interact with several other genes, suggesting a central role in the interaction network [31]. In this work, the degree of the genes which were equal or greater than 11 were considered as HUB genes.

Disease genes contained in the DEN

Genecards is a database of human genes that provides genomic, proteomic, transcriptomic, genetic and functional information on all known and predicted human genes [32]. In this study, we downloaded all of the disease genes that associated with ovarian cancer from Genecards database (http://www.genecards.org/). There were 3231 disease genes associated with ovarian cancer in all in the database. The disease genes included in the DEN were ascertained by comprehensive statistical analysis.

Experimental verification

Materials

In this study, 10 ovarian cancer samples (3 endome-

trioid, 3 serous, 2 mucinous, 2 fiber intraepithelial neoplasia) (7 newly diagnosed and 3 retreatment) were derived from the patients who were operated from January 2014 to December 2015 in our hospital. The normal groups were taken from the distal tissue of the tumor tissue at a 2 cm distance. The patients selected did not show statistical significance (p>0.05) in age, gender, medical history or geographical. The antibodies used in the experiments were purchased from Santa Cruz Biotechnology, Inc. Taq polymerase, dNTP, ultra-pure water and DNA marker were purchased from Takara Company and Beijing Ding States Biological Technology Company. The total cellular RNA extraction kit was purchased from Invitrogen Company. All of the other reagents were of analytical grade.

RT-PCR

The total RNA was extracted using RNA extraction kit following the manufacturers' recommendations. The cDNA was synthesized according to the following reaction system: 4.0 μL RNA and 3.0 μL Oligodt18 were mixed evenly, then put it into 70℃ water bath for 5 min, and put on ice immediately after denaturation; then 2.0 μL RNasin (40 U/μL), 8.0 μL 5 × reverse transcriptase buffer, 8.0 μL dNTPs and 2.0 μL AMV reverse transcriptase (5 U/μL) were added, mixed evenly and then put it into 37℃ water bath for 60 min. Meanwhile, we repackaged the AMV reverse enzyme which had been inactivated at 95℃ for 5 min and saved them under -20℃.

Different cDNA was taken as templates, and β-actin was taken as reference according to the following reaction system for PCR amplification, respectively. The gene primer sequences (5'-3') were as follows: UBC: F-TCGGCCTTAGAACCCCAGTA/R-GAGATCCCTCCGCAGAATCG; SF3A2: F-CCCAGTCTGCTAAAGCCCTA/R-TGCTCGTACGCAGACATGAA; ELAVL1: F-GGTCGTGCGCGCTGAG/R-TTCAGCGTGTTGATCGCTCT; SIRT1: F-AACAGGTTGCGGGAATCCAA/R-TGGGTGGCAACTCTGACAAA; NEDD4: F-GGAGGACGAGGAAAATTCACGA/R-CCCAGCCAGGCTCTAATTCC; β-actin: F- AAGTACTCCGTGTGGATCGG/R-TCAAGTTGGGGGGACAAAAAG.

PCR reaction system was as follows: 10.0 μL 10×PCR Buffer, 1.0 μL TaqDNA polymerase (5 U/μL), 3.0 μL upstream primers, 3.0 μL downstream primers and 8.0 μL dNTPs. The PCR reaction conditions were as follows: UBC:95℃ 1 min; 30 cycles of 95℃ 1 min, 55℃ 30 s, 72℃ 30 s; 72℃ 10 min; SF3A2: 95℃ 5 min; 30 cycles of 94℃ 30 s, 55℃ 40 s, 72℃30 s; 72℃ 10 min; ELAVL1: 95℃ 1 min; 35 cycles of 94℃ 30 s, 56℃ 30 s, 72℃ 1 min; 72℃ 7 min; SIRT1: 95℃ 1 min; 30 cycles of 94℃ 30 s, 54℃ 30 s, 72℃ 30 s; 72℃ 7 min; NEDD4: 95℃ 1 min; 35 cycles of 94℃ 30 s, 55℃ 30 s, 72℃ 1 min; 72℃ 7 min; β-actin: 95 ℃ 1 min; 30 cycles of 94℃ 10 s, 51℃ 1 min, 72℃ 30 s; 72 ℃ 7 min. The experiment was repeated thrice and plotted using the average value of the data.

Western blot

Firstly, proteins were extracted according to the extraction method of cytoplasmic protein which was reported by Yoon et al [33]. Then, SDS-PAGE gel (12%) was used to separate the proteins. After electrophoresis, the proteins were power-transfered (4℃, constant current 300 mA, 2 hrs) to nitrocellulose membranes, then the membranes were closed in TBST solution (Tris buffer containing 0.1% Tween-20) with 5% non-fat dry milk at room temperature, then stayed in TBST solution containing the first antibody (1: 10000 dilution) at 37℃ for 2 hrs. Collected the first antibody, and washed the membranes by TBST solution for three times. Then the membranes stayed in TBST solution containing HRP-labeled goat antirabbit IgG secondary antibody (1:5,000) for 2 hrs at room temperature. Washed the membranes by TBST solution for 15 min three times and then by ultra-pure water twice. Finally, substrates were added to the membranes to react for 3 min and exposed in the dark. The experiment was repeated thrice.

Data analysis

The Bio-Rad gel imaging analyzer was used to observe and photograph the results of 1.5% agarose gel electrophoresis so as to analyze the PCR products. The result that analyzed by Quantity One software of gel imaging system was shown by the relative content of the target gene and β-actin band. Image J was used to analyze the gray values of the protein bands and the results were represented with the relative content of target protein and GAPDH bands. Data between groups were analyzed with t-test by SPSS 19.0 ($p>0.05$: no difference; $0.001<p<0.05$: difference; $p<0.001$: significant difference).

Results

Bioinformatics analysis

Identifying DEGs

After having preprocessed all of the four profiles, DWD were chosen to combine these four data and conduct comprehensive analysis of them. There were 12491 genes remained in combined dataset after processing DWD. Furthermore, SAM of the samr software package was used to calculate gene expression values. In this condition, when we set the threshold value FDR<0.05 and a delta cut-off value of >6.029, we obtained 490 DEGs in all, which contained 59 upregulated and 431 downregulated genes.

Constructing DEN

As we introduced before, the DEN should be constructed by complementarily considering both differential and non-differential interactions. Here we got 744 differential interactions via conducting analysis on the absolute value of the Spear-

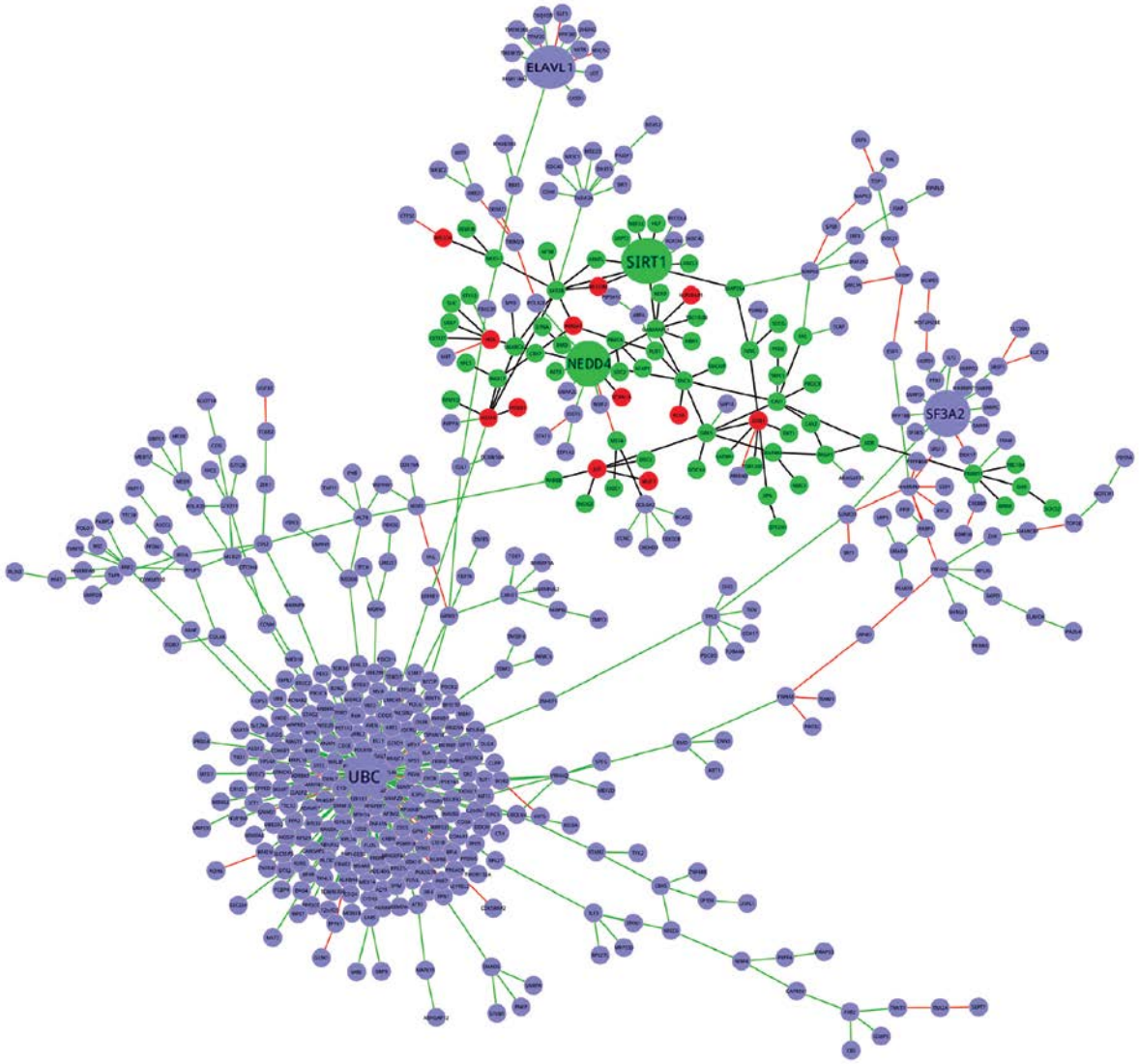

Figure 1. The main differential expression network involved in ovarian cancer. HUB genes were enlarged. Red nodes and green nodes represent upregulated and downregulated genes in ovarian cancer, respectively, and blue nodes represent non-DEGs. Red edges represent overexpressed differential interactions, while green edges represent downexpressed differential interactions in ovarian cancer compared to normal ovary, respectively, and black edges represent non-differential interactions.

Table 1. The KEGG pathway of the nodes contained in the main DEN

ID	*Term*	*Count*	*p value*
hsa03420	Nucleotide excision repair	13	$2x10^{-7}$
hsa04120	Ubiquitin mediated proteolysis	22	$3x10^{-7}$
hsa03040	Spliceosome	18	$2.4x10^{-5}$
hsa05211	Renal cell carcinoma	12	$1.8x10^{-4}$
hsa04114	Oocyte meiosis	13	$2.6x10^{-3}$
hsa03002	Basal transcription factors	7	$3.4x10^{-3}$
hsa04720	Long-term potentiation	9	$8.5x10^{-3}$

man correlation coefficients of gene pairs in two conditions. Furthermore, there were 131 gene pairs whose nodes were both DEGs but the absolute value of the Spearman correlation coefficients in two conditions was less or equal to 0.839. In other words, there were 131 non-differential interactions. Therefore, the DEN, including 875 gene pairs (1028 nodes), was constructed. However, there were some gene pairs not containing in the main DEN. By conducting statistical analysis on the major network (Figure 1), there were 506 genes and 532 edges containing in it.

KEGG pathways analysis

In order to gain further insights into the function of the nodes contained in the main DEN, DA-

VID was applied to identify the significant dysregulated KEGG pathways. By setting the threshold p value <0.01 and gene count >5, 7 pathways were obtained (Table 1). They were Ubiquitin mediated proteolysis, Spliceosome, Nucleotide excision repair, Renal cell carcinoma, Oocyte meiosis, Basal transcription factors and Long-term potentiation.

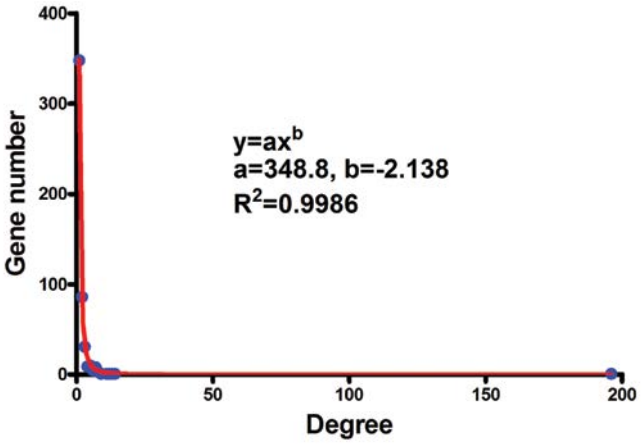

Figure 2. The scattergram of gene degree distribution in the main differential expression network. The degree distribution presented a power law, indicating the character of scale-free network.

Disease genes including in the DEN

By comprehensive statistical analysis, 335 disease genes among the 3231 disease genes in all that we obtained from the Genecards database were included in the DEN we built above.

Centrality analysis to gain HUB genes

We found that the degree distribution displayed approximating a power-law via conducting analysis on the nodes degree of the main DEN that we built above (Figure 2), suggesting that the DEN was a scale-free network [34]. Meanwhile, five HUB genes were obtained as we set the degree of the nodes containing in the main DEN in descending order, including UBC (degree=196), SF3A2 (degree=14), ELAVL1 (degree=13), SIRT1 (degree=12), and NEDD4 (degree=11). Thereinto, SIRT1 and NEDD4 were downregulated genes. Furthermore, UBC, ELAVL1, SIRT1 were also disease genes.

Experimental verification

In our study, RT-PCR and Western blot were implemented to confirm the mRNA and protein

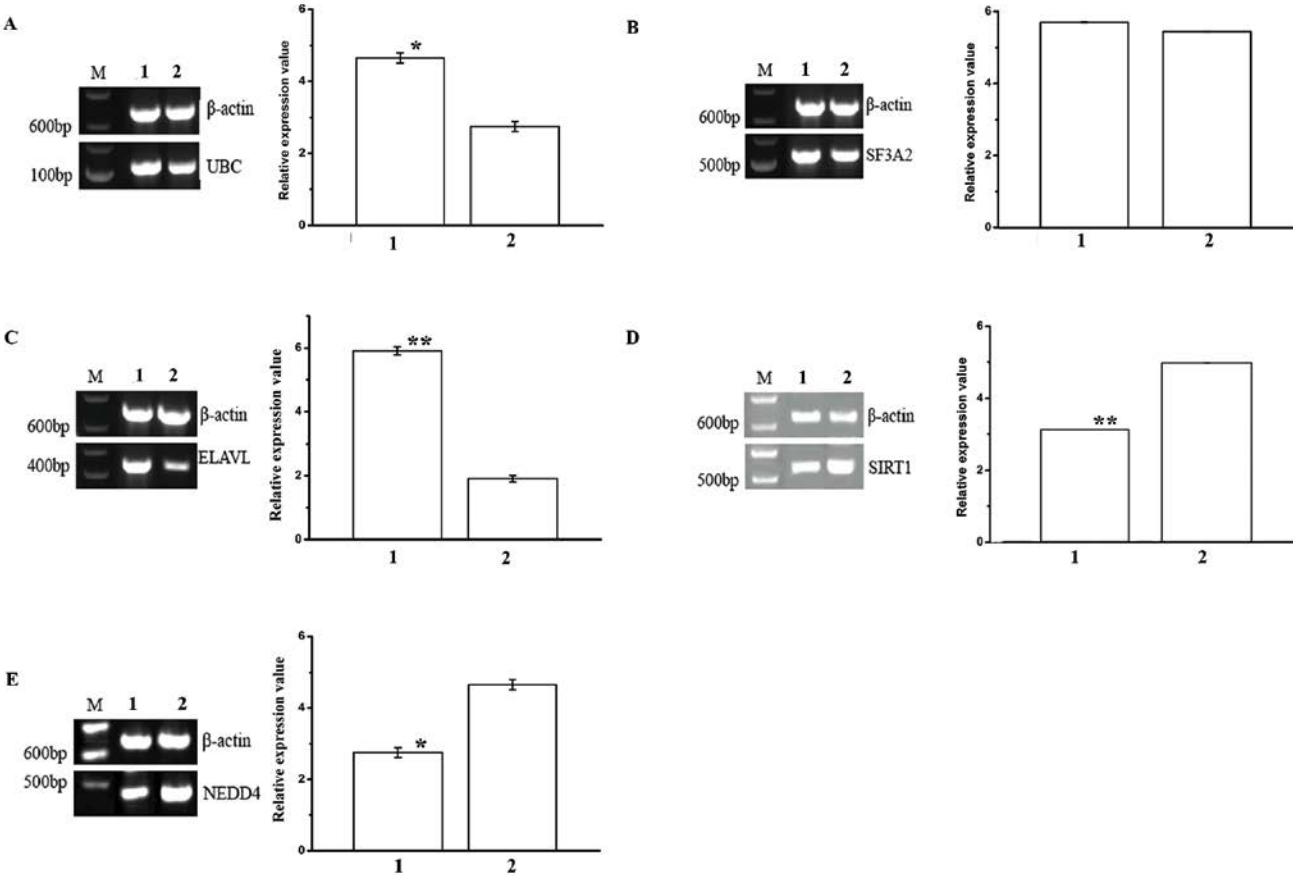

Figure 3. The variation of gene expressions of UBC **(A)**, SF3A2 **(B)**, ELAVL1 **(C)**, SIRT1 **(D)** and NEDD4 **(E)** via RT-PCR. The electrophoresis images came from representative cases and the histograms were obtained by mapping with the average data of the statistic data on the gray values of the protein bands. Arabic numeral 1 represents disease group, and arabic numeral 2 represents normal group. Two asterisks (**) indicate p<0.001, one asterisk (*) indicates 0.001<p<0.05, while no asterisk indicates p>0.05 when compared to the control.

expression levels of five HUB genes (UBC, SF3A2, ELAVL1, SIRT1, NEDD4). The relative expression of mRNAs and corresponding proteins are shown in Figure 3 and 4, respectively. We found that the expression of SIRT1 and NEDD4 were significantly downregulated in ovarian cancer compared with normal condition, and there was no difference in the expression of SF3A2 in two conditions, which were coincident with our bioinformatics results. The expression of UBC and ELAVL1 were significantly upregulated in ovarian cancer compared with normal condition from RT-PCT and Western blot analyses, however their expression levels were non-differential between ovarian cancer and normal subjects in the datasets.

Discussion

Ovarian cancer is the seventh leading cause of cancer-related death in women [35]. Because of the location of the ovaries, it is difficult to detect this disease at earlier stages [4]. Thus, most women, although initially responsive, eventually develop and succumb to drug-resistant metastases [36]. Therefore, new biomarkers for promoting early detection of ovarian cancer are essentially necessary for further understanding of the molecular pathogenesis. Understanding the etiologic heterogeneity of ovarian cancer may result in more tailored treatments and ultimately reduce morbidity and mortality from this disease.

In this study, we chose DEN to research the gene expression profiles of ovarian cancer, expected to select out key genes related to ovarian cancer, for further understanding of the molecular pathogenesis. We got five HUB genes: UBC, SF3A2, ELAVL1, SIRT1, and NEDD4. Thereinto, SIRT1 and NEDD4 were downregulated genes. And UBC, ELAVL1 and SIRT1 were also disease genes. However, the results of the experimental verification were not completely coincident with our bioinformatics results. The expression of UBC and ELAVL1 which were not DEGs according to our bioinformatics results were significantly upregulated in ovarian cancer compared with normal condition. The probable reasons were the following: firstly, the microarray data was obtained from ArrayExpress database but not generated

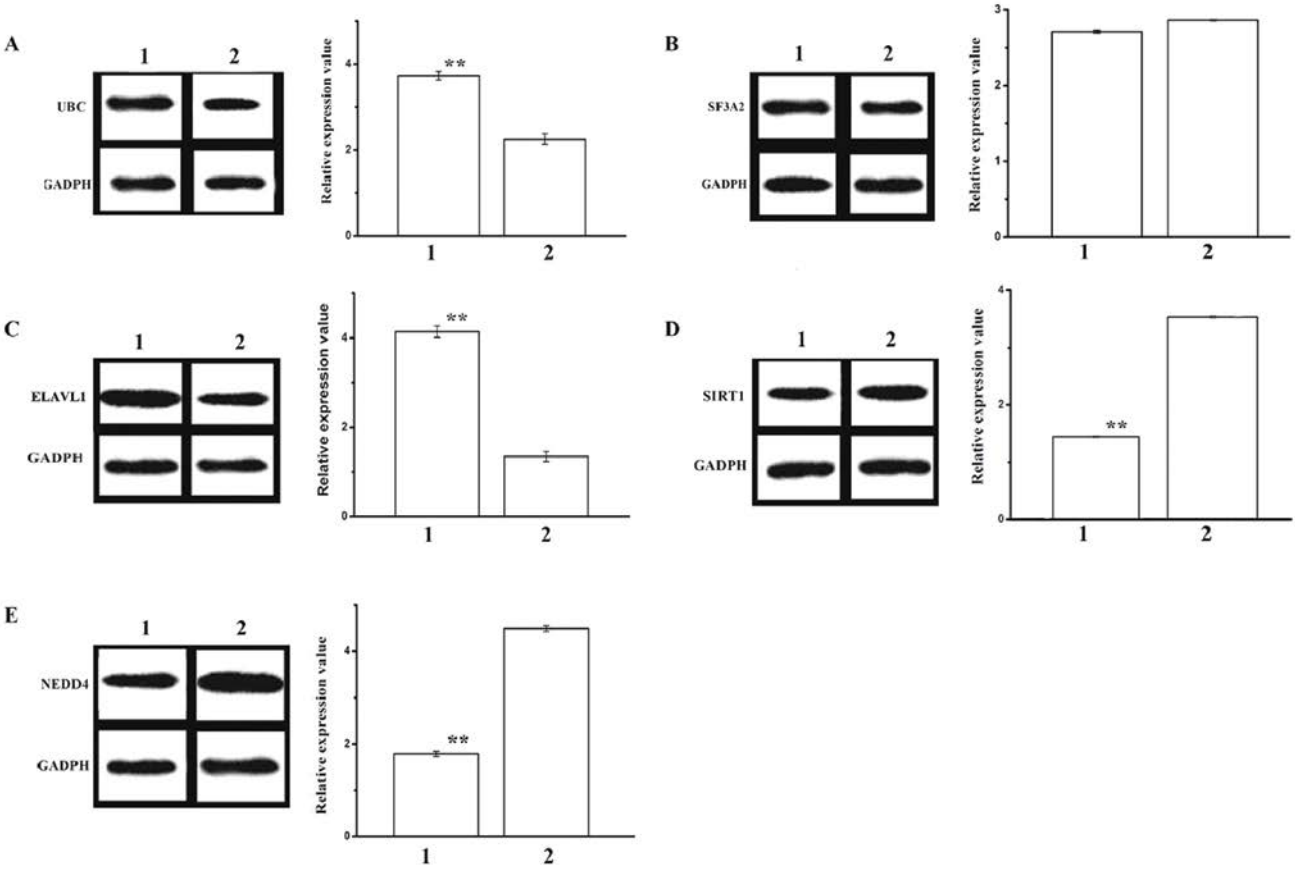

Figure 4. The variation of protein expressed by UBC **(A)**, SF3A2 **(B)**, ELAVL1 **(C)**, SIRT1 **(D)** or NEDD4 **(E)** via Western blot. The electrophoresis images came from representative cases and the histograms were obtained by mapping the average data of the statistic data on the gray values of the protein bands. Arabic numeral 1 represents disease group, and arabic numeral 2 represents normal group. Two asterisks (**) indicate $p<0.001$, one asterisk (*) indicates $0.001<p<0.05$, while no asterisk indicates $p>0.05$ when compared to the control.

by ourselves. Secondly, it might due to the small number of samples in the experimental groups. Finally, the criteria of differential expression between bioinformatics and experimental verification were different, one used SAM methods to identify DEGs under the threshold of FDR < 0.05 and a delta value > 6.029 and the other performed a t-test to decide the significant difference.

In our study, although the expression level of UBC was non-differential in two conditions using traditional differential expression method, it was screened out by DEN method, and its degree was the highest (degree=196), suggesting a central role in the network. Ubiquitin (Ub) is a small, highly conserved eukaryotic protein that plays a crucial role in diverse cellular signaling pathways, including targeting proteins for proteasomal degradation [37]. In eukaryotes, ubiquitin comes from the protein product of gene UBC and some other genes [38]. Meanwhile, ubiquitin-mediated proteolysis was a significantly correlated pathway identified by our KEGG enrichment analysis. It had been indicated that the disruption of UBC resulted in embryonic lethality with defective fetal development [39]. It was such an important HUB gene that was neglected by traditional methods via screening DEGs. It further proves the superiority of DEN method for screening key genes from another point, that DEN can fully explore all disease-related interactions including non-differential and differential interactions.

Although ELAVL1 was not DEG, we could find that the expression of ELAVL1 in disease group and normal group was significantly changed via analyzing the results of verifying experiments. ELAVL1 belongs to a highly conserved family of genes encoding RNA-binding proteins and has been linked to cell growth and proliferation through its regulation of mRNA stability [40]. It was reported that variation in angiogenesis-related genes, such as ELAVL1, may be associated with ovarian cancer risk and more specifically may influence tumor invasiveness [41]. Meanwhile, ELAVL1 overexpression is a biomarker of poor survival, as a sign of tumor progression in an hostile microenvironment able to select the most aggressive cancer cells [42].

Meanwhile, it could be easily found that the expression of SIRT1 in the disease and normal group was significantly changed by analyzing the results of verifying experiments, which coincided with our bioinformatics results. Mammalian SIRT1 is a NAD^+-dependent deacetylase, which is involved in a wide spectrum of biological processes, including stress responses, cellular metabolism, and possibly, aging and tumorigenesis [43]. Researchers had uncovered a novel function of the longevity molecule SIRT1 as a potential marker and modulator of the drug resistance phenotype in ovarian cancer [44]. It was reported that expression of SIRT1 was significantly increased in malignant ovarian epithelial tumors compared to benign and borderline ovarian epithelial tumors ($p<0.001$) [45]. Li et al. [46] reported for the first time that BRCA1, a tumor suppressor gene involved in multiple cellular processes, was a positive regulator of SIRT1 levels and a negative regulator of NAD-related SIRT1 activity, which further correlated the physiological properties of BRCA1 with SIRT1-related metabolism in ovarian cancer cells. Meanwhile, it was reported that in serous ovarian carcinoma, the TP53 showed loss of function in precancerous ovarian lesions [47], while there were several reports indicating that there were some interactions between TP53 and SIRT1 [48,49]. In this case, the loss of SIRT1 expression could act as a candidate biomarker for promoting detection of ovarian cancer.

In the present research, SIRT1 was a significantly downregulated HUB disease gene, coinciding completely with the experimental verification of the bioinformatics results of SIRT1. Thus, we predict that SIRT1 can be chosen as a potential biomarker for promoting the detection of ovarian cancer, and also to further understand the molecular pathogenesis of ovarian cancer. Furthermore, we'll conduct an in-depth study on the relationship between SIRT1 and ovarian cancer.

Conflict of interests

The authors declare no confict of interests.

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