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Identified differently expressed genes in renal cell carcinoma by using multiple microarray datasets running head: differently expressed genes in renal cell carcinoma

Y. CHENG, M. HONG[1], B. CHENG

Department of Urinary Surgery, Affiliated Hospital of Luzhou Medical College in Sichuan Province, Luzhou, China
[1]Department of Operating Room, Affiliated Hospital of Luzhou Medical College in Sichuan Province, Luzhou, China

Abstract. – OBJECTIVE: The purpose of this study was to identify differentially expressed genes and analysis biological processes related to renal cell carcinoma.

METHODS: A meta-analysis was performed using the Rank Product package of Gene Expression Omnibus datasets of renal cell carcinoma. Then Gene Ontology enrichment analyses and pathway analysis were performed based on Gene Ontology website and Kyoto Encyclopedia of Genes and Genomes. Protein-protein interaction network was constructed used Cytoscape software.

RESULTS: We identified a total of 1992 differentially expressed genes Rank Product package of renal cell carcinoma, 840 of them were not involved in individual DEGs. Gene Ontology enrichment analyses showed that those 840 genes enriched in terms such as response to hormone stimulus, endogenous stimulus, biological adhesion, and cell proliferation. Pathway analysis showed that significant pathways included pyruvate metabolism, glycerolipid metabolism, complement and coagulation cascades and so on. Protein-protein interaction network indicated that MT2A, MYC, CENPF and NEK2 has high degree which participated many interactions.

CONCLUSIONS: Our study displayed genes that were consistently differentially expressed in renal cell carcinoma, and the biological pathways, protein-protein interaction network associated with those genes.

Key Words:
Renal cell carcinoma, Differentially expressed genes, Bioinformatics.

Introduction

Renal cell carcinoma (RCC) is characterized by a lack of early warning signs and high metastases[1,2]. It was the most common form of kidney cancer, accounted for approximately 3% of adult malignancy[3,4]. The incidence of RCC was increasing in the past few years[5]. The risk factors for its development are still under intense investigation[6].

RCC is a complex disease that many genes and signaling pathways are involved in its development[7]. Analysis of gene regulation mechanism can help us understand RCC. Gene regulation analysis used high-throughput experiment method such as microarray has increased in recently years. Many differential expression genes (DEGs) were identified by microarray. Currently, a significant amount of microarray data has been produced and deposited in publically-available data repositories, including Gene Expression Omnibus (GEO) and Array Express Archive[8,9]. These repositories allow researchers to advance the discovery of genetic and diagnostic signatures by data integration and bioinformatics analysis, which would provide insights into the biological mechanisms for RCC. Recently, Feng et al[10] screened 648 down-regulated and 681 up-regulated DEGs for RCC. Lenburg et al[11] identified 1,234 genes that were more than three-fold changed in renal tumors. However, the results were inconformity between studies because of small samples size.

To better understand the complex pathology associated with RCC and identify molecular networks involved in the disease, we took a systems biology approach to acquire and integrate changes of mRNA levels between biopsy samples from patients with RCC and normal people. Our approach is to build a more precise target network from the selected biomarkers for RCC,

Corresponding Author: Yong Cheng, MD; e-mail: yongcheng1231@126.com

then further to research those DEGs by functional enrichment analysis, pathway enrichment analysis, and protein-protein interaction (PPI). The result may provide information for the understand of RCC.

Materials and Methods

Identification of Gene Expression Datasets

In the current study, we focused our attention on the differently expressed genes between normal kidney and cancerous kidney. The experimental protocol of this study was shown in Figure 1. On this basic two microarray datasets were extracted from the NCBI GEO database. We excluded studies in which samples with other serious diseases such as diabetes and hepatitis. We also excluded animal studies and studies in which microarray data was uncertainty.

Integrated Analysis of DEGs

The identification of DEGs and meta analysis were performed by the Rank Product (RP) package[12]. The meta-analysis algorithm implemented in RankProd using two datasets with different origins (GEO access number: GSE781, GSE6344).

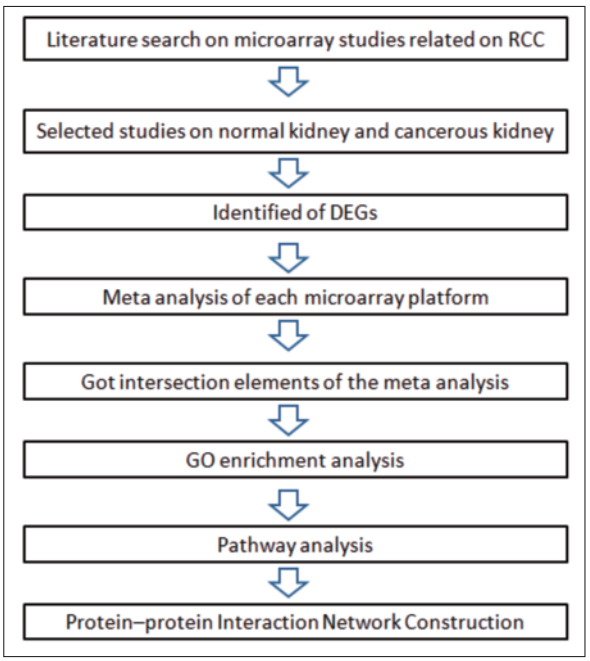

Figure 1. Experimental protocol of this study.

Each study have two experimental conditions (treatment versus control). For each gene g in k replicates i, each examining n_i gene, one can calculate the corresponding combined probability as a rank product , which is the position of gene g in the list of genes in the ith replicate sorted by decreasing fold change (FC).

By the Rank Product method, a list of up- or down-regulated genes were selected based on the estimated percentage of false-positives (PFP) predictions, which corresponded to determining the false discovery rate (FDR) in SAM. Genes with a PFP ≤ 0.05 were considered differentially expressed between cases and controls.

Functional and Pathway Enrichment Analysis

To further investigate the functions of the DEGs, we performed GO enrichment analysis and pathway analysis based on Gene Ontology database (http://www.geneontology.org/) and KEGG database (www.genome.jp/kegg/) by DAVID[13].

Protein-protein Interaction Network Construction

The protein-protein interaction (PPI) data were downloaded from STRING (http://string.embl.de/). Then the DEGs were imported into the interaction network and interactions were screened with both end nodes having DEGs. The networks were identified using Cytoscape software.

Results

Studies Included and Integrated Analysis of DEGs

Two gene expression datasets were extracted from the NCBI GEO database (GEO access number: GSE781, GSE6344). Both of the two studies detected the genes expression by two platforms: GPL 96 (HG-U133A) and GPL 97 (HG-U133B). Therefore, we first identified DEGs of each platform, and performed the meta-analysis for the different platforms. We got the union of genes from the meta-analysis of the two platforms.

We identified 905 DEGs and 355 DEGs from the two platforms of GSE 781 datasets, and identified 1461 DEGs and 918 DEGs from the two platforms of GSE 6344 datasets. The following meta analysis identified 700 up-regulation DEGs and 700 down-regulation DEGs of the platforms

GPL 96 (HG-U133A), and identified 503 up-regulation DEGs and 505 down-regulation DEGs of the platforms GPL 97 (HG-U133B). There were 840 gained genes and 411 lost genes in this meta analysis (Figure 2). Lost genes are genes that identified as DEGs in any individual analysis, but not in the meta analysis.

Functional and Pathway Enrichment Analysis

To further investigate the functions of the new identified 840 genes, we performed GO analysis and pathway analysis. The top 10 GO terms and pathway terms were show in Table I and Table II.

Interaction Network of the DEGs

By using Cytoscape software, the interaction networks were identified. The networks of up-regulated genes and down-regulated genes were shown in Figure 3 and Figure 4 respectively. The genes that degree greater than 10 in PPI network were show in Table III.

Discussion

RCC is a complex disease, the pathogenesis of it is not clear. Identify the most important genes is contribute to understand the pathogenesis. We first combined the DEGs of microarray data by meta-analysis, then analysed new identified genes by functional enrichment analysis, pathway enrichment analysis, and PPI.

For the DEGs, the topological information as well as the fold change and p-values of genes are valuable parameters for evaluation of the importance of a gene. Among those parameters, we used the topological information as the main parameter. We found that *CDC42*, *STAT1* and *MYC* were most noticeable genes in the PPI network of up-regulation genes, while *CDH1* and *EGR1* for the down-regulation genes.

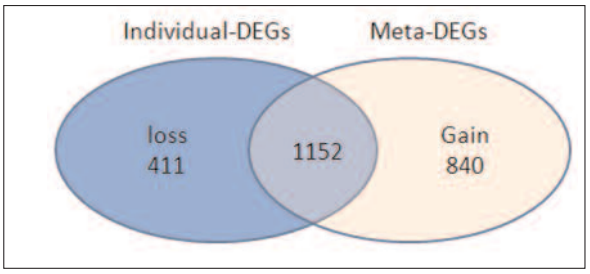

Figure 2. Venn diagram showing overlap between DEGs identified from the meta analysis (Meta-DEGs) and those from each individual data analysis (individual-DEGs).

CDC42 (cell division cycle 42) has the highest degree in the PPI network of up-regulation genes, which participated in 28 interactions. *CDC42* is a member of the Rho GTPase subfamily[14]. It is a highly conserved small GTPases that regulate the formation of a variety of actin structures and the assembly of associated integrin complexes[15,16]. It was reported that *CDC42* was essential for cell polarization in several organisms, and controlled cell polarity in a wide variety of cellular contexts[17,18].

STAT1 (Signal transducer and activator of transcription 1) also has the high degree in the PPI network of up-regulation genes, which participated in 21 interactions. *STAT1* interacts with p53 to enhance DNA damage-induced apoptosis[19]. It was reported that *STAT1* also associated with chronic lymphocytic leukemia and Alzheimer's disease[20,21].

MYC oncogenes included *c-myc, N-myc and L-myc*. The *MYC* proto-oncogene encodes a ubiquitous transcription factor (c-MYC) related to the control of cell proliferation and differentiation[22]. *MYC* overexpression exacerbated genomic instability and sensitizes cells to apoptotic stimuli[23]. Combined microarray analysis found altered apoptotic balance and distinct expression signatures of *MYC* family gene amplification in small cell lung cancer[24]. *MYC* were also associated with several kinds of cancer such as breast cancer, prostate cancer, gastrointestinal cancer and melanoma[25].

CDH1 (cadherin 1) has the highest degree in the PPI network of down-regulation genes, it participated in 22 interactions. *CDH1* is a conserved protein that identified as limiting, substrate-specific activators of APC-dependent proteolysis[26]. It was found that down-regulation *CDH1* was associated with poor differentiation and vascular invasion in colon cancer[27]. Several researches suggested that *CDH1* mutation was associated with gastric cancer and colorectal cancer[28,29]. Methylation of the *CDH1* promoter was thought as the second genetic hit in hereditary diffuse gastric cancer[30].

EGR1 (early growth response 1) is a primary response gene which encodes a zinc finger containing protein[31]. There was an unconformity in the expression of *EGR1* in different cancers. In a majority of prostate cancers, *EGR1* was overexpressed and promoted prostate tumor

Table I. The top 10 GO terms from 840 gain genes.

ID	Term	*p* value	Gene
GO:0009725	Response to hormone stimulus	2.10E-05	ALPL, RBP4, ERBB4, ENPP1, PGF, ARNT2, PTGS1, GNG12, UQCRFS1, AGXT, TGFB1, PRSS8, ALDH1A2, REN, SERPINA1, GNG2, THBS1, NEFL, GNG7, GHR, SPP1, PLD1, BCKDHB, STAT1, ABCG1, SREBF2, BTG2, DUSP1, HMGCS2, CCND2, PDGFRA, ALDH2, FABP3, AVPR1A, IGFBP2
GO:0009719	Response to endogenous stimulus	1.50E-04	ALPL, RBP4, ERBB4, ENPP1, PGF, ARNT2, PTGS1, GNG12, UQCRFS1, AGXT, TGFB1, PRSS8, ALDH1A2, REN, SERPINA1, GNG2, THBS1, NEFL, GNG7, GHR, SPP1, PLD1, BCKDHB, STAT1, ABCG1, SREBF2, BTG2, DUSP1, HMGCS2, CCND2, PDGFRA, ALDH2, FABP3, AVPR1A, IGFBP2
GO:0007584	Response to nutrient	1.70E-04	ALPL, MUC1, RBP4, SLC8A1, KYNU, STC2, BCKDHB, STAT1, TGFB1, ALDH1A2, DUSP1, HMGCS2, GSN, TIE1, ALOX5, IGFBP2
GO:0001501	Skeletal system development	2.40E-04	ALPL, RBP4, AEBP1, CASR, ENAM, JAG2, POSTN, ATP6V1B1, TGFB1, CHST11, MYC, RUNX2, WWOX, GHR, SPP1, SPARC, GAS1, SIX4, COL5A2, ANXA2, CHRDL1, HOXB6, HOXD4, PDGFRA, TFAP2A, FOXC1, BMPR1B, PLEKHA1, CDH11, IGFBP5
GO:0010033	Response to organic substance	2.50E-04	KYNU, PGF, ARNT2, PTGS1, ILDR2, UQCRFS1, AGXT, TGFB1, EDNRA, GSN, SERPINA1, GNG2, MYC, GNG7, GHR, EGR1, PLD1, HSP90AA1, BTG2, CCND2, PDGFRA, AMFR, ALPL, RBP4, CYP1B1, ERBB4, ENPP1, CDH1, GNG12, ATP5G3, PRSS8, ALDH1A2, PLIN2, REN, COL6A2, HSPA6, THBS1, NEFL, SPP1, SLC8A1, BCKDHB, STAT1, ABCG1, SREBF2, CORO1A, HMGCS2, DUSP1, SMPD1, AVPR1A, ALDH2, FABP3, CLEC7A, IGFBP2,
GO:0009991	Response to extracellular stimulus	3.60E-04	ALPL, MUC1, RBP4, LDHA, KYNU, SLC8A1, STC2, BCKDHB, STAT1, PPARGC1A, TGFB1, ALDH1A2, DUSP1, HMGCS2, GSN, SFRP2, AVPR1A, TIE1, ALOX5, IGFBP2, SST, SPP1
GO:0048545	Response to steroid hormone stimulus	3.90E-04	ALPL, ERBB4, BCKDHB, PTGS1, ARNT2, AGXT, TGFB1, PRSS8, ALDH1A2, DUSP1, CCND2, PDGFRA, AVPR1A, ALDH2, SERPINA1, THBS1, IGFBP2, SST, NEFL, SPP1
GO:0022610	Biological adhesion	4.10E-04	AEBP1, CADM4, NRP1, FERMT3, NELL1, FERMT1, POSTN, L1CAM, CXCL12, VNN1, TYRO3, F8, PCDH9, CDHR5, RND3, SLC26A6, CX3CR1, CNTN3, CHL1, DCBLD2, PCDHB14, IL32, CDH1, SPOCK1, CLDN11, CDH5, CDH6, VCAM1, SEMA5A, IGSF11, ANXA9, ITGB6, COL6A2, EMB, THBS1, ANGPTL3, SPP1, NLGN1, NFASC, SDSL, NID1, EMILIN2, ITGA9, CORO1A, FBLN5, FREM1, CDON, NPHS1, CLEC7A, PERP, BMPR1B,
GO:0009611	Response to wounding	4.60E-04	DCBLD2, ACVRL1, NRP1, CYSLTR1, MASP1, CLU, C1R, PXK, BDKRB2, TGFB1, TLR8, CCL20, GSN, PROZ, ITGB6, MGLL, VNN1, SERPINA1, THBS1, SCNN1B, TFPI2, NEFL, SPP1, BLNK, F11, PLAT, KLK6, KLF6, CEBPB, F8, SERPING1, PROC, IL20RB, FBLN5, CX3CR1, PDGFRA, PLLP, CLEC7A, ALOX5, BMPR1B, PROS1, PLAU
GO:0042127	Regulation of cell proliferation	6.50E-04	NAMPT, HMX2, NRP1, ACVRL1, PGF, ARNT2, PTGS1, JAG2, TNFSF15, TGFB1, EDNRA, GPC3, CHST11, MYC, CCDC88A, PPP1CB, VASH1, MYCN, CD86, IL20RB, BTG2, CCND2, BTG1, NCK1, PDGFRA, FGFR2, RBP4, LST1, ERBB4, IFITM1, CLU, BDKRB2, CDH5, VCAM1, ALDH1A2, REG1A, BCL11B, INPP5D, PPAP2A, THBS1, RUNX2, TCIRG1, SPHK2, SPARC, GAS1, STAT1, KDR, CORO1A, AVPR1A, FABP3, ATP5A1, SST, PLAU, KCTD11, FABP6, IGFBP5

Table II. The top 10 pathways analysis based on KEGG.

Term	*p* value	Count
Pyruvate metabolism	1.10E-03	9
Glycerolipid metabolism	2.40E-03	9
Complement and coagulation cascades	3.50E-03	11
Valine, leucine and isoleucine degradation	8.40E-03	8
Sphingolipid metabolism	1.70E-02	7
Tryptophan metabolism	1.90E-02	7
Axon guidance	2.10E-02	14
Propanoate metabolism	2.70E-02	6
Fc gamma R-mediated phagocytosis	3.10E-02	11
Butanoate metabolism	3.40E-02	6

progression[32]. However, in other tumor types such as breast cancers and glioblastomas, *EGR1* was expressed at low levels and inhibited tumor growth when overexpressed[32].

For the functional and pathway enrichment analysis, the most significant enriched term was the GO category of response to hormone stimulus with a p-value of 2.1×10^{-5}. Other significant GO categories included response to endogenous stimulus ($p = 1.5\times10^{-4}$) and response to nutrient ($p = 1.7\times10^{-4}$). Among the pathways enriched in KEGG analysis, pyruvate metabolism, glycerolipid metabolism, and complement and coagulation cascades were the most significant terms.

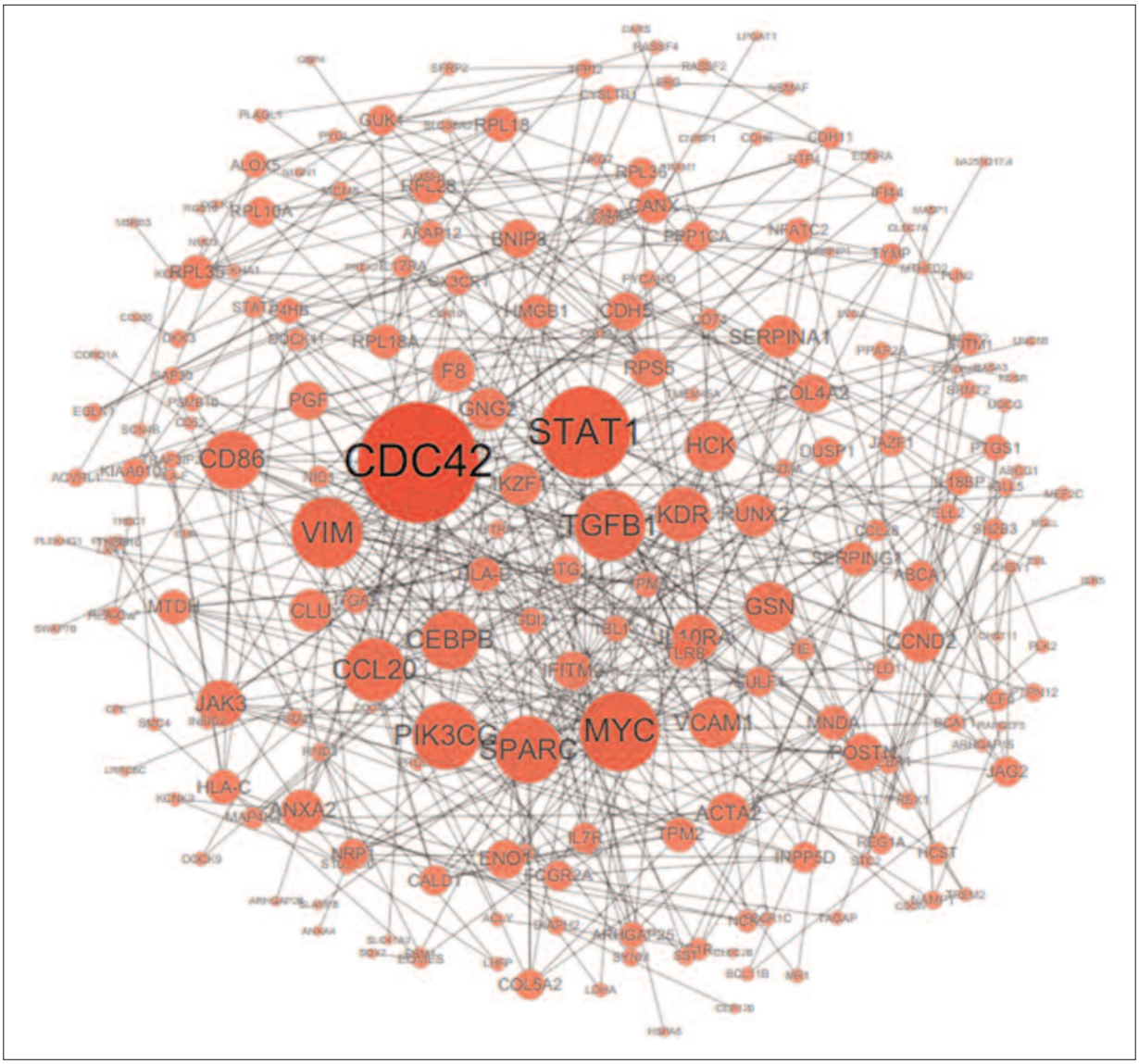

Figure 3. The PPI networks of up-regulated genes. The node stand for the protein (gene), edge stand for the interaction of proteins (genes). The size of the nodes represent the degree of node, the bigger nodes with higher degree.

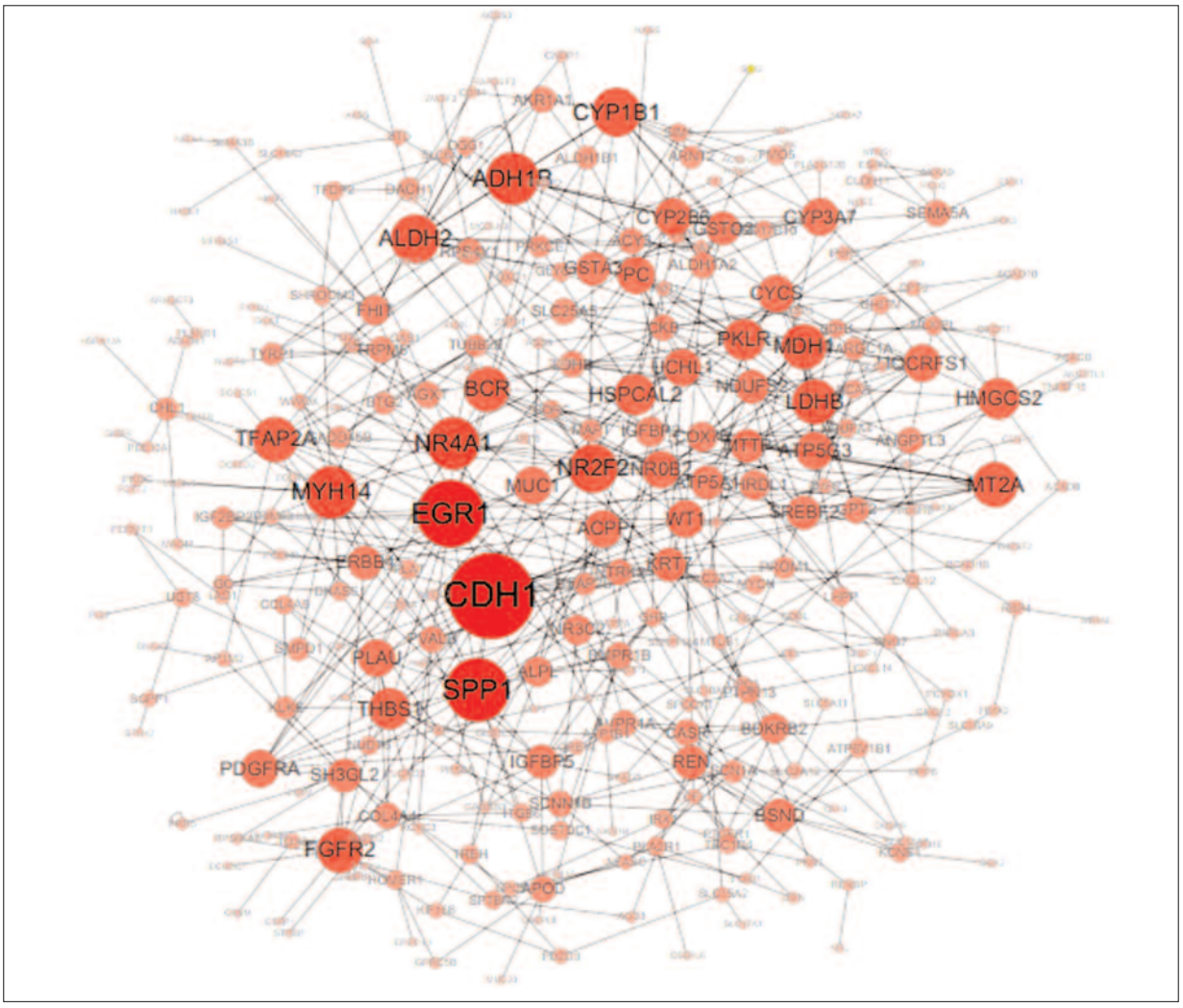

Figure 4. The PPI networks of down-regulated genes. The node stand for the protein (*gene*), edge stand for the interaction of proteins (*genes*). The size of the nodes represent the degree of node, the bigger nodes with higher degree.

Table III. The genes that degree greater than 10 in PPI network.

up-regulated genes	Down-regulated genes	Degree
CDC42	–	28
–	CDH1	22
STAT1	–	21
MYC	–	18
–	EGR1	17
TGFB1, VIM	SPP1	16
SPARC, PIK3CG	–	15
CCL20	–	14
CEBPB, CD86	NR4A1, ADH1B, MYH14	13
KDR	NR2F2, ALDH2, CYP1B1	12
HCK, GSN, VCAM1	MDH1, MT2A, LDHB, BCR, FGFR2, TFAP2A	11

The categories we identified deserve further studies and may merit further attention and validation, though it is impossible to discuss all the significant functional categories expressed differentially in RCC.

Conclusions

The detailed mechanism of RCC was not clear. Several genes related RCC were identified in our study, and the function and signaling pathways their participated were present systematically, such as *GSN, MYH14, ALDH2, and MDH1*. Those genes might play a role in RCC, more research should focus on them.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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