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Original Article

Identification of differentially expressed genes between male and female patients with acute myocardial infarction based on microarray data

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Abstract: Background: Coronary artery disease has been the most common cause of death and the prognosis still needs further improving. Differences in the incidence and prognosis of male and female patients with coronary artery disease have been observed. We constructed this study hoping to understand those differences at the level of gene expression and to help establish gender-specific therapies. Methods: We downloaded the series matrix file of GSE34198 from the Gene Expression Omnibus database and identified differentially expressed genes between male and female patients. Gene ontology, Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis, and GSEA analysis of differentially expressed genes were performed. The protein-protein interaction network was constructed of the differentially expressed genes and the hub genes were identified. Results: A total of 215 up-regulated genes and 353 down-regulated genes were identified. The differentially expressed pathways were mainly related to the function of ribosomes, virus, and related immune response as well as the cell growth and proliferation. The protein-protein interaction network of all differentially expressed genes contained 4 hub genes, *FOS*, *UTY*, *KDM6A,* and *SMARCA4*, whose function in acute myocardial infarction is related to the sex hormone and sex chromosomes. Conclusion: Our study provides a global view of the gene expression differences between male and female patients with acute myocardial infarction, including differentially expressed genes and related pathways. However, further studies are still needed to verify our results.

Keywords: Coronary artery disease, gender, gene ontology, pathway analysis, protein-protein interaction network

Introduction

Coronary artery disease (CAD), also referred to as ischemic heart disease, is the most common cause of death, especially in middle and high-income countries. The imbalance in the ratio of myocardial blood supply to myocardial oxygen demand in the heart caused by CAD leads to angina and other clinical symptoms. In many cases, there can be an acute drop in the blood flow to the heart, resulting in acute myocardial infarction (AMI) that can be fatal within several minutes [1].

Although great progress has been made in the management of AMI, there need to be better management and preventative strategies to improve the overall outcomes in individuals with AMI. There are some risk factors associated with prognosis, including gender, hypertension, diabetes mellitus and so on [2]. Notably, according to data from NHANES, the prevalence of CAD was higher for males than females for all age (7.4% vs 5.3%) [3]. In addition, the incidence of AMI in men is higher than that of women of the same age (3.8% vs 2.3%) [3]. 'Important sex differences in the pathophysiology, clinical presentation, and clinical outcomes have also been revealed in patients with CAD [4]. For example, under 70 years old, the initial presentation of CAD is often angina in women and AMI in men [5]. Therefore, the American Heart Association has urged us to pay attention to sex disparities in patients with AMI as the first step to personalized medicine [4].

Gene expression microarray has become a useful tool to identify differentially expressed genes (DEGs) and networks as prognosis associated biomarkers and therapy targets. Peripheral blood has become one of the most common materials in microarray analysis, because of its critical role in communication between organs and the simplicity of sample collection. Several studies have focused on the biomarkers in peripheral blood of patients with CAD [6, 7]. However, there has been no study on the gene expression differences between male and female patients with AMI based on microarray data. Here, we reanalyzed the public data in the Gene Expression Omnibus (GEO, available at: https://www.ncbi.nlm.nih.gov/geo/) microarray data repositories, GSE34198, to identify DEGs and differentially expressed pathways between male and female patients with AMI as well as the interaction of the proteins encoded by these genes. Such differences in gene expression may not only explain the differences between men and women in the incidence and the prognosis of AMI, but also will help to take the gender of the patients into consideration while planning a management to achieve better outcome.

Materials and methods

Affymetrix microarray data

Using the keywords "myocardial ischemia", "cardiac ischemia" and "coronary artery disease", eligible microarray gene expression datasets were searched in the Gene Expression Omnibus microarray data repositories, and selected GSE34198 for subsequent studies. Others were excluded because the phenotype data didn't contain gender information, the numbers of the samples were too small, the samples were obtained from the cell lines. Zdenek Valenta et al. submitted GSE34198, based on Illumina GPL6102 platform (Illumina human-6 v2.0 expression beadchip). There were 97 samples in total in the dataset, including 7 technical replicates, 45 patients and 45 controls. The diagnosis of the patients was based on the clinical criteria, ECG outcome and laboratory findings according to medical guidelines. The cases were less than 80 years old and had never been treated for cancer. The controls were matched to the patients based on gender, age, status of diabetes mellitus, and smoking status [7]. Venous blood samples were collected from both patients and controls. Notably, Valenta et al. had also divided patients into those who did (AMI: 41 patients, 13 females and 28 males) and did not survive the 6 months follow-up period following the AMI (AMID6: 4 patients, 2 females and 2 males) [7]. It requires at least 3 samples per group to have sufficient power to detect any differentially expressed genes, so we didn't adopt Valenta's groups (AMI and AMID6) and converged all patients into the same AMI group [8, 9]. Of those, 15 female patients and 30 male patients with AMI were finally enrolled in our study. Their basic characteristics are shown in **Table 1**. The comparisons between the two group were made using the log-rank test for categorical variables and k-test for continuous variables.

Data preprocessing

R software (available at: http://www.R-project.org/) and packages in Bioconductor (available at: http://www.bioconductor.org/) were used to analyze the data. First, the GEOquery package was used to download the series matrix files from the Gene Expression Omnibus database and acquired the express matrix and phenotypic data [10]. The probe-set expression levels were then converted into gene expression levels using the illuminaHumanv2.db package [11]. If multiple probes mapped to a gene, the mean of the probe effect size was selected. Missing values were filled based on the average of non-missing neighboring values of its neighbor using the k-nearest neighbors method [12].

Identification of DEGs

Differential expression analysis in GSE34198 was performed using the limma package [13]. After dividing the samples in the dataset into two groups based on the gender, the downloaded express matrix of each dataset was sent to limma to compute the *p*-value and log2 fold change of each gene and picked up the significantly DEGs under the threshold of p-value < 0.01 and |log2 fold change| > 1.5. Among them, those with log2 fold change > 1.5 were defined as upregulated genes while others were defined as downregulated genes.

GO and KEGG pathway enrichment

Based on the Gene ontology database [14] (GO, available at: http://www.geneontology.org/), functional enrichment studies of the significantly DEGs were performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, available at:

Table 1. Baseline characteristics of patients

Characteristic	Male patients (N = 30) n*	Female patients (N = 15) n*	*P* value
Age (year)	61.90 (7.46)	69.39 (10.49)	0.008
Height (cm)	171.93 (7.22)	155 (5.86)	< 0.001
Weight (kg)	92.85 (12.59)	68.08 (16.91)	< 0.001
Sbp (mmhg)	135.63 (14.34)	130.83 (20.98)	0.456
Dbp (mmhg)	80.38 (9.04)	73.83 (11.14)	0.137
Diabetes status			0.111
Yes	7 (23.3%)	7 (46.7%)	
No	23 (76.7%)	8 (53.3%)	
Smoking status			0.076
Yes	9 (30.0%)	1 (6.7%)	
No	21 (70.0%)	14 (93.3%)	
Acei			0.833
Yes	15 (50.0%)	7 (46.7%)	
No	15 (50.0%)	8 (53.3%)	
Betablockers			0.138
Yes	11 (36.7%)	9 (60.0%)	
No	19 (63.3%)	6 (40.0%)	
Diuretics			0.153
Yes	10 (33.3%)	2 (13.3%)	
No	20 (66.7%)	13 (86.7%)	
Ca blockers			0.180
Yes	12 (40.0%)	3 (20.0%)	
No	18 (60.0%)	12 (80.0%)	
Statins			0.128
Yes	9 (30.0%)	8 (53.3%)	
No	21 (70.0%)	7 (46.7%)	
Fibrates			0.041
Yes	0 (0.0%)	2 (13.3%)	
No	30 (100.0%)	12 (86.7%)	
Other medication			0.035
Yes	12 (40.0%)	11 (73.3%)	
No	18 (60.0%)	4 (26.7%)	

*For continuous variables: mean (sd).

https://david.ncifcrf.gov/) to investigate the functions of these gene signatures [15, 16]. The pathway analyses of these gene signatures based on Kyoto Encyclopedia of Genes and Genomes database (KEGG, available at: http://www.genome.jp/kegg/) were also performed [17] using DAVID. A *p* value less than 0.01 was selected as the threshold.

GSEA analysis

As a second generation method for pathway enrichments, GSEA derives a score from all genes that belong to a given gene set based on the expression matrix and group list input [18]. Thus, it eliminates the arbitrary in determining the threshold of significantly DEGs and has many advantages over GO and KEGG. Here, we performed GSEA analyses between male patients and female patients based on GO gene sets and curated gene sets downloaded from Molecular Signatures Database (available at: http://software.broadinstitute.org/gsea/msigdb) respectively [19]. Gene sets with gene ratio ≥ 0.9 and *p*-value < 0.01 in each analysis were recognized as significantly differentially expressed pathways and visualized in the dot plot generated using the ggplot2 packages in R software (available at: http://www.R-project.org/). The ES score plots of the top 3 significantly differentially expressed pathways in each analysis according to the net ES score were also shown.

PPI network construction

To comprehend the interaction of the proteins encoded by the DEGs is very important. Thus, we first obtained functional interactions between the DEGs using STRING database [20]. The protein-protein interaction (PPI) networks were visualized by Cytoscape (version 3.4.0) based on this information [21]. Only nodes with combined score > 0.400 and nodes degree ≥ 10 were reserved in the PPI networks. In the PPI network of all differentially genes, genes with nodes degree ≥ 25 were considered as hub genes.

Results

Identification of DEGs

According to our threshold in this research, 568 significant DEGs were detected in male patients compared with female patients, among which there were 215 upregulated genes and 353 downregulated genes (Supplementary Table 1). The ratio of upregulated gene counts to downregulated genes counts was 1:1.64.

GO enrichment

The results of GO and KEGG enrichment of the DEGs are shown in **Table 2**, respectively.

Table 2. Significantly enriched GO terms and KEGG pathway

Category	GO ID/ KEGG ID	GO term/ KEGG pathway	Total gene counts	Gene counts	*p* value
Biological Process	GO:0032728	Positive regulation of interferon-beta production	31	6	< 0.001
	GO:0009416	Response to light stimulus	275	5	0.0012
	GO:0009615	Response to virus	247	11	0.0013
	GO:0030308	Negative regulation of cell growth	168	11	0.0027
	GO:0032727	Positive regulation of interferon-alpha production	22	4	0.0043
	GO:0050806	Positive regulation of synaptic transmission	312	4	0.0055
	GO:0045184	Establishment of protein localization	1860	6	0.0056
	GO:0019060	Intracellular transport of viral protein in host cell	6	3	0.0079
	GO:0042384	Cilium assembly	283	10	0.0099
Cell Component	GO:0005737	Cytoplasm	10415	179	0.0015
	GO:0005829	Cytosol	2982	119	0.0031
	GO:0005654	Nucleoplasm	2392	100	0.0074
	GO:0043657	Host cell	19	3	0.0075
Molecular Function	GO:0005515	Protein binding	8578	297	< 0.001
	GO:0004386	Helicase activity	142	9	0.0031
	GO:0044822	Poly(A) RNA binding	1617	49	0.0044
KEGG	hsa03018	RNA degradation	78	8	0.0076

According to GO analysis, differentially expressed genes between male and female patients were significantly enriched in positive regulation of interferon-beta production, response to light stimulus, response to virus, negative regulation of cell growth, positive regulation of interferon-alpha production, positive regulation of synaptic transmission, establishment of protein localization, intracellular transport of viral protein in host cell and cilium assembly in Biological Process category, cytoplasm, cytosol, nucleoplasm and host cell in Cell Component category, as well as protein binding, helicase activity, poly(A) RNA binding in Molecular Function category. RNA degradation pathway was also significantly differentially expressed between male and female patients according to the results of KEGG enrichment. Supplementary Table 2 demonstrates DEGs in each GO terms and KEGG pathways.

GSEA analysis

The results of GSEA analyses based on GO gene sets and curated gene sets are shown in **Figures 1** and **2**, respectively. The top 3 significantly differentially expressed pathways identified in the analysis based on GO gene sets included GO T CELL MEDIATED IMMUNITY (NES = 1.86, *p*-value < 0.001), GO RRNA BINDING (NES = 1.81, *p*-value = 0.006) and GO SULFUR COMPOUND TRANSPORT (NES = 1.81, *p*-value = 0.004), while those identified in the analysis based on curated gene sets were HOWLIN CITED1 TARGETS 1 UP (NES = -2.04, *p*-value < 0.001), AMIT EGF RESPONSE 40 HELA (NES = -1.98, *p*-value < 0.001) and CHEN ETV5 TARGETS SERTOLI (NES = -1.95, *p*-value = 0.002).

PPI network and hub-genes

The PPI networks of all DEGs, are shown in **Figure 3**. There were 39 nodes and 137 edges in the PPI network of all DEGs. Supplementary Table 3 demonstrates the significantly differentially expressed GO terms and KEGG pathways that contained the nodes in PPI network. The heatmap of the nodes in PPI network is shown in **Figure 4**. The PPI network of all differentially genes contained 4 hub genes according to our criterion, including *FOS*, *UTY*, *KDM6A,* and *SMARCA4*.

Discussion

Currently, CAD has become the leading cause of death in the world due to the unhealthy lifestyles. There are significant differences in the incidence, prognosis pathophysiology, clinical presentation, and clinical outcomes of AMI between men and women [4]. However, the management of AMI are same for male and female patients, which mainly includes revascularization (thrombolytic therapy, primary PCI and CABG Surgery) and medical therapy (anti-

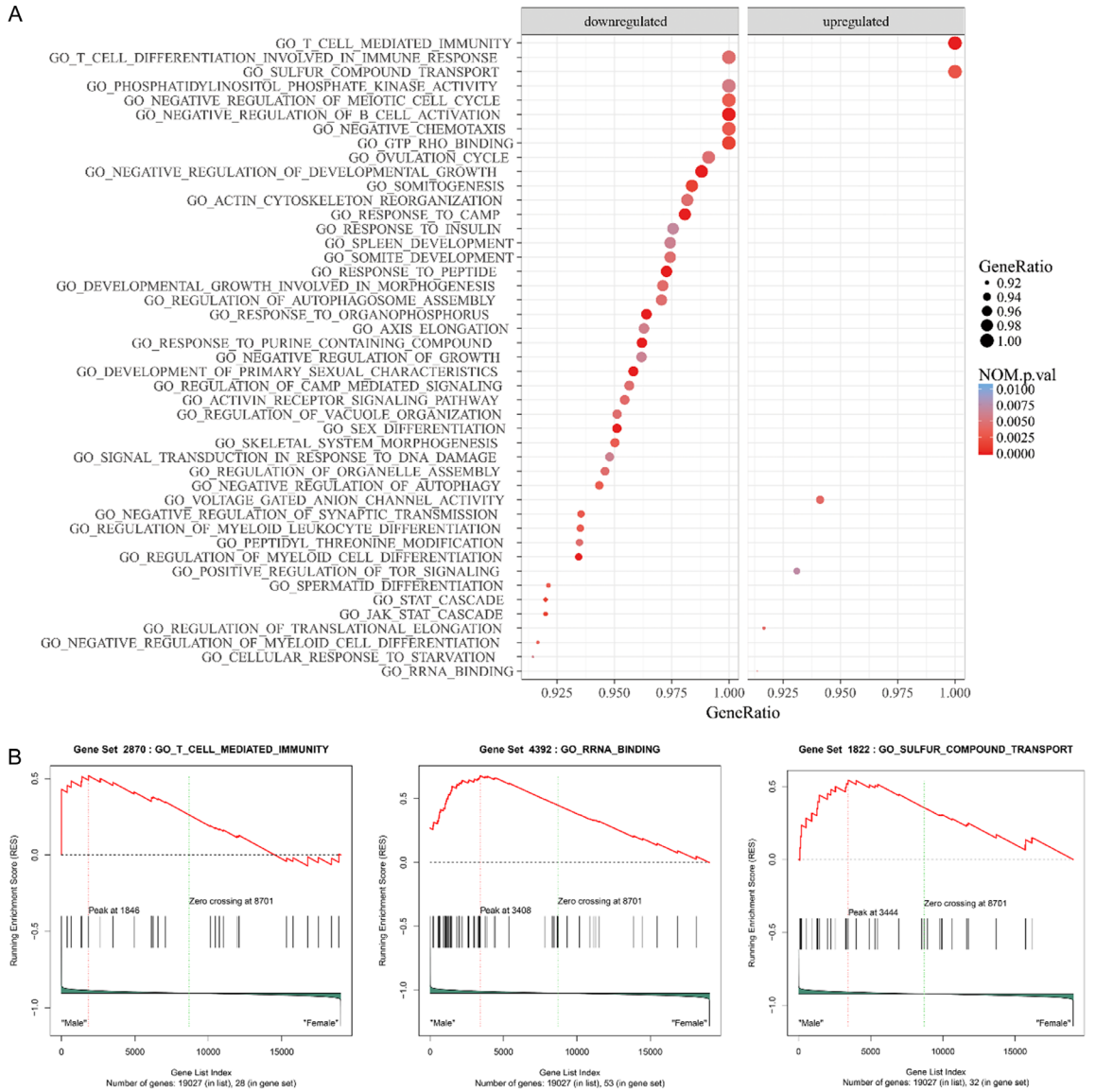

Figure 1. Significantly differentially expressed pathways identified by GSEA analyses based on GO gene sets. A. The dot plot of significantly differentially expressed pathways identified by analysis based on GO gene sets; B. The ES score plots of the top 3 significantly differentially expressed pathways identified by analysis based on GO gene sets.

platelet agents, β-blockers, ACE inhibitors, angiotensin receptor blockers, and statins) [22]. Treated by similar therapy, male and female patients achieved different outcome [23]. Therefore, the American Heart Association has urged us to pay attention to sex disparities in patients with AMI in 2016 [4].

In this study, the gene expression profile GSE34198 was re-analyzed to identify DEGs and differentially expressed pathways between male and female patients with AMI. The baseline characteristics shown in **Table 1** were similar between the two groups, so it was reasonable for us to perform this analysis. A total of 568 DEGs were detected in male patients compared to female patients with AMI, including 215 upregulated genes and 353 downregulated genes.

In order to confirm that the gene expression differences between the male and female patients with AMI detected in this study were different from those between normal male and female, we compared the differentially expressed genes and pathways between the male and

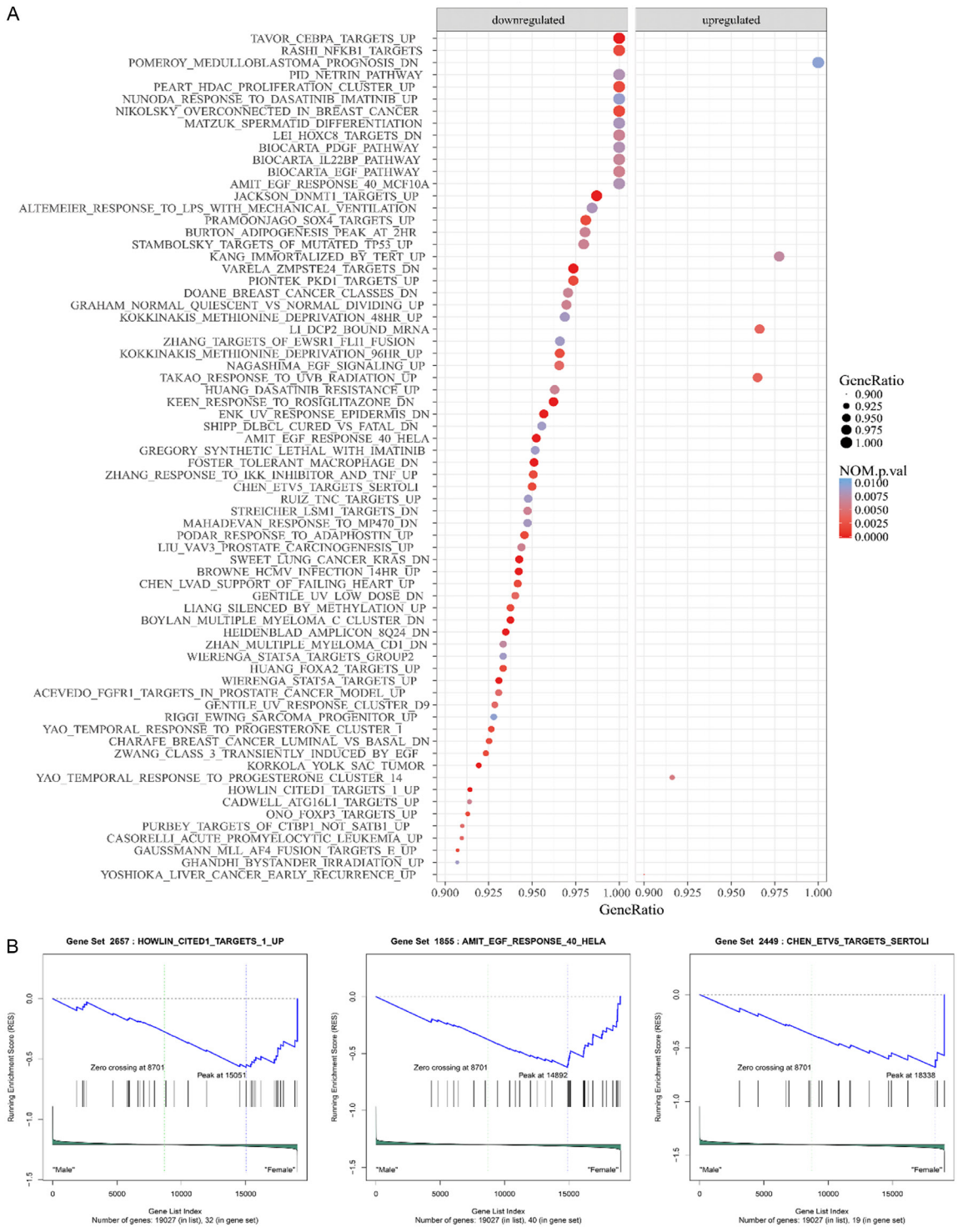

Figure 2. Significantly differentially expressed pathways identified by GSEA analyses based on curated gene sets. A. The dot plot of significantly differentially expressed pathways identified by analysis based on curated gene sets; B. The ES score plots of the top 3 significantly differentially expressed pathways identified by analysis based on curated gene sets.

female patients with those between normal male and female. Our results shown in **Table 3** show that only a little part of genes and pathways were overlapping. It suggests that the

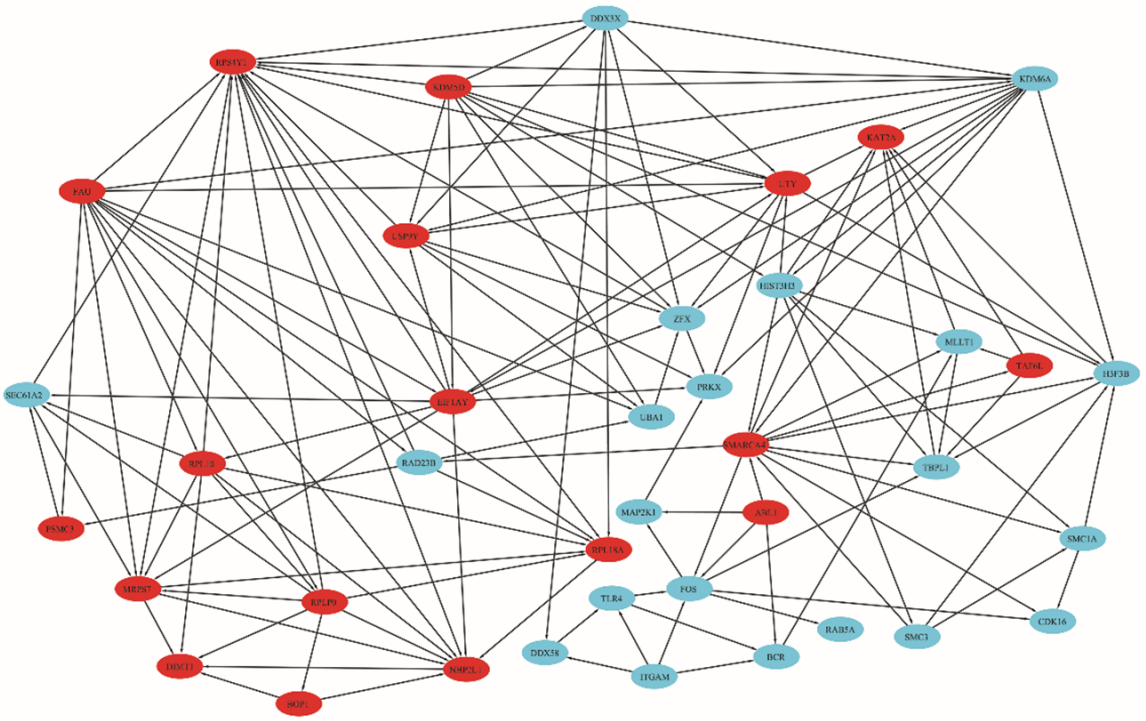

Figure 3. PPI network of all DEGs. The upregulated genes were shown in red while downregulated ones are shown in blue.

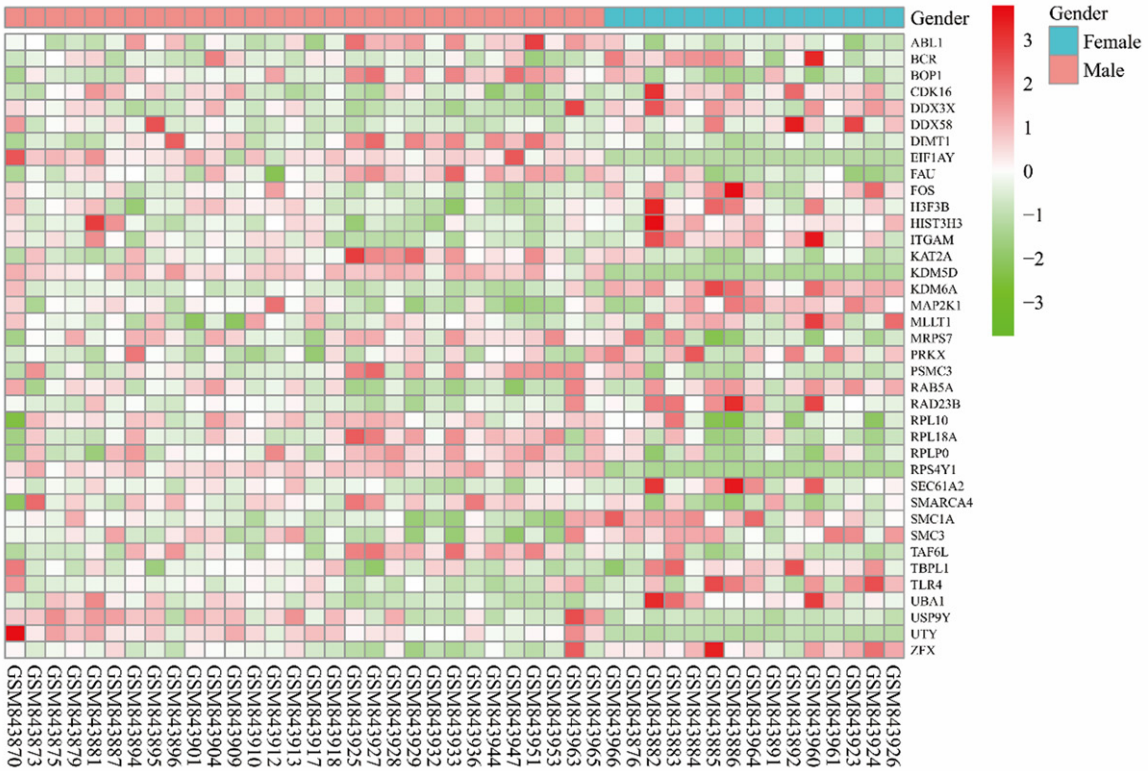

Figure 4. Heatmap of nodes in PPI network.

Table 3. Number of differentially expressed genes and pathways

Items	Numbers in control group	Numbers in patients group	Numbers of overlapping ones
Differentially Expressed Genes	333	568	59
GO Enrichment	7	16	0
GO BP	3	9	0
GO MF	2	3	0
GO CC	2	4	0
KEGG Analysis	5	1	0
GSEA	369	115	13
Curated gene sets	43	70	7
GO gene sets	326	45	6
Nodes of PPI network	22	39	9

gene expression differences we detected may help us illustrate gender differences better and provide some evidence for gender-specific target therapy, even though to date we have not found any of present drugs mentioned above targets the hub genes and pathways detected by us.

Most of the significantly up-regulated pathways were related to the function of the ribosomes, including biosynthesis, transportation and localization of the proteins. Several studies have reported that ribosomes increase significantly in cardiomyocytes of the MI rats and may contribute to the reparation and compensatory hypertrophy [24]. In recent studies, the role of ribosomal biogenesis in reducing cardiomyocyte apoptosis as well as protecting and repairing the myocardium has been proved, and function of ribosome has been used as a marker for myocardial reparation and stem cell activation [25, 26]. From our perspective, the differentially expressed pathways related to the function of ribosome indicates that male patients possess stronger repair and compensatory capacity than female patients in the early stage of CAD, which is corresponding to the phenomenon that the initial presentation of CAD is often angina in women under 70 years old and MI in men at the same age. However, some studies have argued that the numbers of ribosomes were decreased or highly variable in AMI patients and the expression of pathways related to the ribosome were down-regulated or uncertain [9, 27-29]. The possible explanation for this conflict is that patients or animal models with different stages and severity of the disease were enrolled in different studies. Thus, further studies regarding the role of ribosome in AMI are still needed. Furthermore, several pathways associated with virus, interferon, and related immune response like positive regulation of interferon-beta production, response to virus, positive regulation of interferon-alpha production, intracellular transport of viral protein, and GO T cell mediated immunity in host cell have been observed to be differentially expressed. Some researchers suggested that activated T cell can produce interferon and other pro-inflammatory mediators to upregulate macrophages to adhere to the endothelium and migrate into the intima, which can intensify the inflammatory response and thus worsen disease development [30, 31]. However, the conclusions are still conflicting [32-34]. Two pathways pertaining to the cell growth and proliferation including negative regulation of cell growth and Amit EGF response 40 HeLa were also differentially expressed. They may be related to abnormal proliferation of the smooth muscle cells of the media and the regeneration of the cardiomyocytes that are of great importance in the progression and recovery of CAD.

Four hub genes were identified in the PPI network according to our threshold, including *FOS*, *UTY*, *KDM6A*, and *SMARCA4*. Among them, *FOS* has been reported to be up-regulated in the smooth muscle cells in atherosclerotic plaque and related to abnormal proliferation of the smooth muscle cells of the media [35] as well as the vascular calcification [36]. As a transcription factor related to immune response, *FOS* also facilitates the expression of tissue factor that promote the inflammatory process, which plays a crucial role in myocardial lesions and is involved in the pathogenesis of AMI as well [37, 38]. When considering the gender differences in AMI, some researchers attribute them to sex hormones, especially estrogen. Hormonal influence on the expression of FOS has been observed. Estrogen can downregulate the expression of FOS and protect the heart in female patients [39]. Interestingly, FOS was overexpressed among our female patients, the average age of whom were 61.9 years. Postmenopausal females have insuffi-

cient estrogen, so its impact on FOS were reversal, which is corresponding to our results. In addition, estrogen can provide female with protection in many other aspects. For example, ER-β can mediate PI3K/Akt and anti-apoptotic signaling in the myocardium which upregulated Bcl-2 and downregulated Bax, caspase-3 and caspase-8. It can also suppress apoptosis of myocardiocytes [40]. Furthermore, estrogens can stimulate the expression of endothelial NO synthase (eNOS). Through releasing of nitric oxide, coronary arteries can be relaxed and endothelial function of peripheral resistance arteries can be restored directly [41]. Higher content of eNOS also suppresses L-type calcium channels and thus prevents calcium overload, one of the main causes of ischemia/reperfusion injury [42]. Notably, the action of estrogen is controlled by Class II histone deacetylases which works through direct interaction with estrogen receptor repressing MEF2 to decrease the expression of estrogen receptor [43].

Not only sex hormones, but sex chromosomes can also cause sex differences in patients with AMI. *KDM6A*, a gene on the human X chromosome, is one of two histone demethylases known as the X escapees. Therefore, expression of *KDM6A* is generally higher in female compared with male [44] and it has been thought to be responsible for more severe ischemia/reperfusion injury in female patients compared with male. Since the risk of MI is much higher in young men than women at the same age, it may be a very useful protection mechanism in men. *UTY* is a male-specific gene located on male-specific region of the human Y chromosome, and its down-regulation together with *PRKY* in macrophages was observed in haplogroup I [45]. UTY encodes one of the histocompatibility antigens recognized by T cells [46], while PRKX, functional homolog on the X chromosome, encodes one of cAMP-dependent kinases and is thought to be involved in maturation of macrophage and development of kidney [47]. They increase the risk of CAD through depressing adaptive immunity pathway and activating proinflammatory response pathway in haplogroup I.

As for *SMARCA4*, the relation between its genetic polymorphisms and CAD has been extensively studied [48, 49]. Some SNPs in the *SMARCA4* like rs11879293, rs12232780, rs4300767, rs10417578 and rs1122608 have been associated with a decreased risk of CAD. Recently Nakatochi et al. identified a DNA methylation site in *SMARCA4* (cg17218495) that is associated with MI [50]. That means the development of AMI may be influenced by changes in these methylation site in *SMARCA4*.

However, there are also some limitations in our study. First, the number of the samples enrolled was too small and no information on when the samples were collected is provided. Second, the characteristics of male and female patients other than gender was not strictly the same, and other covariates may also affect the patient's gene expression. Third, because of the limited sample size (< 3) in AIMD6 group who did not survive 6 months, all patients were regarded as the same AMI group rather than being divided into two groups based on 6-month follow up period as Valenta et al. did. That means we couldn't explore gender specific differences in both cases (AMI vs AMID6) in detail. Fourth, our study was only carried out based on bioinformatics methods and the experimental evidences to prove our conclusions was lacking. Moreover, the mechanisms of those pathways and hub genes identified in our study on AMI were not clearly understood so more studies are still needed to further understand the differences between men and women in terms of AMI.

In conclusion, our bioinformatics analysis of public microarray data, GSE34198, provides a global view of the gene expression differences between male and female patients with AMI, including DEGs and their interaction. The differentially expressed pathways are mainly involved in the function of ribosomes, virus, and related immune response as well as the cell growth and proliferation, and the function of the identified hub genes in AMI were related to the sex hormone and sex chromosomes. Our study can help explain differences between men and women in the incidence and the prognosis of AMI. This might be useful in clinical practice to establish gender-specific therapy for AMI. However, our study also has some limitation, so further studies are still needed to verify our results and clarify the relevant mechanisms.

Acknowledgements

Zhongxing Wang, Huaqiang Zhou and Kaibin Yang conceived and designed the study; Hua-

qiang Zhou and Kaibin Yang acquired and analyzed the data; Yuanzhe Zhang, Xiaoyue Wei, and Yiyan Song worked with the figures and tables; Zeting Qiu, Si Li, Qinchang Chen and Wulin Tan revised the paper; Huaqiang Zhou, Kaibin Yang and Shaowei Gao wrote the paper. All authors listed have approved the final article.

Disclosure of conflict of interest

None.

Abbreviations

CAD, Coronary artery disease; AMI, acute myocardial infarction; DEGs, differentially expressed genes; GEO, Gene Expression Omnibus; GO, Gene ontology database; DAVID, Database for Annotation, Visualization, and Integrated Discovery; KEGG, Kyoto Encyclopedia of Genes and Genomes database; PPI, protein protein interaction; eNOS, endothelial NO synthase.

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Supplementary Table 2. DEGs in each GO terms and KEGG pathways

Category	Term	Differentially expressed genes
GO BP	GO:0032728~positive regulation of interferon-beta production	DDX58, HMGB2, DDX3X, ZC3HAV1, TBK1, TLR4
	GO:0009416~response to light stimulus	FOS, SLC4A10, SLC1A3, DUSP1, POLG
	GO:0009615~response to virus	DDX58, IFIT2, CCDC130, IFIT1, DDX3X, ZC3HAV1, TBK1, XPR1, DHX36, IVNS1ABP, CHUK
	GO:0030308~negative regulation of cell growth	RTN4, ACVRL1, DDX3X, SFRP1, NAIF1, FRZB, GNG4, SMARCA4, ADAM15, SERTAD2, SLIT3
	GO:0032727~positive regulation of interferon-alpha production	DDX58, ZC3HAV1, TBK1, TLR4
	GO:0050806~positive regulation of synaptic transmission	SYT1, SLC1A3, CLSTN3, LGI1
	GO:0045184~establishment of protein localization	DERL1, RCC2, WDPCP, DZIP1, SMYD3, ABL1
	GO:0019060~intracellular transport of viral protein in host cell	IFIT1, DERL1, DYNLT1
	GO:0042384~cilium assembly	SNAP29, SCLT1, CEP162, WDPCP, IFT20, TTC26, DZIP1, CCDC113, RAB3IP, FUZ
GO CC	GO:0005737~cytoplasm	FAM200B, LDHA, ZC3HAV1, CHMP4B, TUFT1, TBK1, DZIP1, FAM110B, DSTYK, CCT2, TLR4, MED22, TXLNA, PRKX, MAGEC2, CRYGC, MCOLN3, RPLP0, PHTF1, DHX36, TGS1, CUTC, SDR9C7, TBPL1, NCBP3, NUDT16, GTPBP6, MADD, ZHX2, MLXIPL, PNPLA1, BASP1, KIAA0753, AHR, FAAP100, NABP1, CEP162, SPAG6, ARRB1, TNFAIP8, PUDP, CNTROB, SNTG1, HARS, SLU7, HAS2, CELF1, PIDD1, TRAPPC2, RAD23B, ZFAND5, COASY, MRPS16, HMGB2, MPLKIP, LITAF, TDRD6, LCE1B, BOP1, CCNG2, FUZ, FAM65A, T, ARG1, BLOC1S4, PSMB7, AGGF1, DDX3X, RASAL3, ZDHHC9, SCARB1, DNAAF5, ERCC6L, CRIP1, CARD9, OSGEP, MAP2K1, EPAS1, OSBPL9, SMYD3, SAP18, BRIP1, TOMM40, GCN1, AIM2, DDX6, FXR1, TNKS1BP1, DDX58, TNFSF11, SYNE2, PSMC3, UBA1, ETS2, DDX59, GRK5, FBXO34, ABL1, SMC1A, AHSA1, BTBD11, DNAL4, LRRC8E, RITA1, ELF2, EDC4, PAWR, CDK16, CCDC106, CHUK, NT5C, SERTAD2, RAMP2, ANKS1A, HERC6, FLNB, ECT2, NLRP2, C6ORF89, NAPRT, EML3, XPC, MAST2, TNFSF13B, TAF15, DACT2, BNIP2, WRAP53, CARD17, UBE2M, RAB5A, AICDA, FOXC1, TMSB4Y, MAPRE3, KPNA1, SRGAP1, CAPS, SNAP29, IRX3, USP9Y, EPB41L4A, IVNS1ABP, DTNBP1, TRIB1, DIMT1, EXOSC10, WDR18, MTMR1, WDPCP, POU2F2, SPATA2, TEKT2, MLLT1, AATF, MAGEA11, GPS1, DGKQ, GSTA5, LRRC41, OTULIN, SPATA5L1, ETF1, EXO5, SMC3, IRF9, IFIT2, ATXN2, MEF2D, NDOR1, IFIT1, DUSP1, CCDC113, MAPK8IP2, ATP6V0A1, SPG11, RBM14, GCA, ACTR10
	GO:0005829~cytosol	LDHA, STAR, CHMP4B, TBK1, CEP76, IL18, VPS54, DTYMK, DSTYK, RASGEF1A, CCT2, CNOT4, OPLAH, EIF1AX, RPLP0, AKR7A2, FAU, RPL10, DHX36, TGS1, LONRF1, CCNA1, MVB12B, BCR, MADD, MLXIPL, GCC2, CEP162, GAPVD1, RCC2, ARRB1, PUDP, HARS, PIDD1, NUP43, TRAPPC2, SNX5, PAH, ARG1, BLOC1S4, PSMB7, RASAL3, DNAJA1, KBTBD7, TNKS, ERCC6L, SEC61A2, CARD9, SPHK2, EPAS1, MAP2K1, GGH, GALT, TREX1, AIM2, DDX6, DDX58, TNKS1BP1, RPL18A, SFRP1, UBA1, PSMC3, MYH11, ABL1, SMC1A, AHSA1, SAT1, NBN, AP2S1, EDC4, RAB3IP, FOS, ZFAT, CHUK, PSMD8, NT5C, ARL2, ZDHHC8, HERC6, KIDINS220, ECT2, FLNB, NAPRT, BTG2, BNIP2, UBE2M, RAB5A, KLHL12, RPS4Y1, TMSB4Y, KPNA1, SRGAP1, PPP2R2A, CAB39L, WASH1, UROS, TXLNG, DTNBP1, PATL1, MTMR1, PHLDA1, SCLT1, WDTC1, DGKQ, SPSB1, AIMP2, ASMT, OTULIN, SIRT5, GJB6, SAMSN1, EXO5, ETF1, SMC3, IRF9, NDOR1, IFIT2, IFIT1, SPG11

	GO:0005654~nucleoplasm	FAM200B, DZIP1, CBX4, KDM1A, HOXC8, FAU, HIST3H3, TGS1, CCNA1, NUDT16, POLE, ZHX2, MLXIPL, SP140, AHR, NVL, NABP1, FAAP100, CEP162, ARRB1, SLU7, CELF1, PIDD1, SMARCA4, COASY, RAD23B, HMGB2, MPLKIP, LITAF, BOP1, PLAGL1, PSMB7, DDX49, ERCC6L, EPAS1, SMYD3, SAP18, BRIP1, TOMM40, MSL3, TNKS1BP1, SYNE2, PSMC3, ETS2, POLD2, H3F3B, FBXO34, ABL1, SMC1A, NCOR1, HIST1H3I, NBN, KDM6A, ELF1, ELF2, UTY, TIMM17A, EDC4, FOS, MCM8, DNAJC14, CCDC106, CHUK, PSMD8, KDM5D, ANKS1A, RRP36, SNAPC4, PRPF4, SENP2, XPC, TAF15, NAIF1, RPS4Y1, FOXC1, CPSF4, KPNA1, PPP2R2A, SNU13, IVNS1ABP, EXOSC10, DIMT1, WDR18, ERCC6, POU2F2, MLLT1, CC2D1B, MAGEA11, GPS1, KAT2A, PHF12, EXO5, SMC3, SF3A3, IRF9, MEF2D, ATXN2, CCDC113, ATP6V0A1, RBM14
	GO:0043657~host cell	IFIT1, DERL1, DYNLT1
GO MF	GO:0005515~protein binding	SYT1, LDHA, STAR, DZIP1, VPS54, CCT2, CD53, MED22, SLC52A2, PRKX, MAGEC2, IFT20, EIF1AX, RPLP0, EIF1AY, RPL10, DHX36, GNG4, CCNA1, TBPL1, MVB12B, BCR, POLG, ZHX2, PTPRS, TAF6L, GCC2, MRM3, FAAP100, CCDC130, CEP162, RCC2, F5, CNTROB, PIDD1, NUP43, SURF1, TRAPPC2, RAD23B, COASY, MAGEA8, CCDC92, BOP1, FAM19A4, TJAP1, HADHA, FUZ, AGGF1, KBTBD6, KBTBD7, TNKS, STX11, TCF25, MAP2K1, SPHK2, ATP11B, TREX1, FXR1, DDX6, FAM90A1, CD55, SYNE2, RPL18A, SFRP1, UBA1, CSRNP2, ETS2, IGFL1, H3F3B, GRK5, SPNS1, AHSA1, NCOR1, RTN4, ELF1, SPG7, ELF2, ACVRL1, AP2S1, GOLGA7, P4HA3, HIST1H1E, SLC25A6, FUNDC1, ERLIN1, SLC3A1, MAPK1IP1L, FLNB, NAPRT, MXD4, SENP2, MAST2, TAF15, BNIP2, RAB5A, NAIF1, ZSCAN16, AICDA, FOXC1, SEMA4D, TMSB4Y, C10ORF62, SRGAP1, PRPF38A, ADAM15, SNAP29, CAB39L, WASH1, SNU13, ABHD1, WDR18, CFAP58, COL7A1, SPATA2, MLLT1, APBA2, CC2D1B, AATF, PHLDA1, ZNF564, IL18R1, SLC8A1, DGKQ, SPSB1, AIMP2, AFF1, PHF12, ETF1, MARCH5, SF3A3, MRPL23, RASSF4, MEF2D, DUSP1, ATP6V0A1, LRP8, PXYLP1, RBM14, SPG11, ZC3HAV1, CHMP4B, CEP76, TUFT1, TBK1, TSPAN4, IL18, CBX4, TLR4, CSPG5, TXLNA, CNOT4, KDM1A, CRYGC, RALB, RABGEF1, AKR7A2, ASPH, LGI1, LONRF1, TGS1, HIST3H3, CUTC, NCBP3, SARAF, MADD, TNFRSF14, BASP1, KIAA0753, AHR, SP140, NVL, ASCL1, NABP1, ARRB1, FBXO18, CST5, CT55, TNFAIP8, SLU7, CELF1, PRPS2, SMARCA4, ZFAND5, TMEM199, HMGB2, MRPS16, MPLKIP, DERL1, LITAF, SNX5, LCE1B, ITGAM, ZNF330, PSMB7, BLOC1S4, TCERG1, DDX3X, PRR3, NUMB, FBXW4, DNAJA1, SCARB1, SSX3, B4GALT7, SRGN, ERCC6L, GABRD, CARD9, EPAS1, GALT, TOMM40, BRIP1, SAP18, AIM2, DDX58, MLK4, PSMC3, POLD2, MYH11, FBXO33, SMC1A, ABL1, FBXO34, DNAL4, HIST1H3I, ZKSCAN7, LRRC8E, SAT1, RITA1, NBN, EDC4, PAWR, RAB3IP, SLA, NDUFS7, FOS, MCM8, KIAA0040, LBP, CDK16, KIRREL2, CCDC106, CHUK, ARL2, RAMP2, ANKS1A, MIEF1, COX4I1, DYNLT1, ALK, PRPF4, ECT2, NLRP2, C6ORF89, XPC, TNFSF13B, BTG2, WRAP53, SLC41A3, UBE2M, TXNRD2, KLHL12, CPSF4, MAPRE3, KPNA1, PPP2R2A, GDAP2, ECHS1, PF4, DTNBP1, TRIB1, EXOSC10, PATL1, ERCC6, SHISA5, TOR1B, MAGEA11, SCNN1D, GPS1, KAT2A, WDTC1, OTULIN, TSPAN15, SMC3, ATXN7L3, IRF9, IFIT2, NDOR1, ATXN2, IFIT1, TMEM43, CCDC113, CSGALNACT2, MAPK8IP2, DSC2, GCA, ACTR10
	GO:0004386~helicase activity	DDX58, MCM8, ERCC6, DDX3X, FBXO18, DHX36, SMARCA4, ERCC6L, DDX6
	GO:0044822~poly(A) RNA binding	RTN4, HMGB2, ZC3HAV1, SNU13, BOP1, CNOT4, EXOSC10, DIMT1, PATL1, TRMT1L, TCERG1, PRR3, DDX49, DDX3X, RPLP0, EIF1AX, ZCCHC9, MRPL37, RPL10, FAU, AATF, DHX36, NCBP3, SPOUT1, HIST1H1E, RRP36, SAP18, MRPS7, ETF1, SAMSN1, GCN1, FLNB, SF3A3, FXR1, MRM3, DDX6, NVL, IFIT2, ATXN2, RPL18A, RCC2, TAF15, UBA1, CELF1, CPSF4, SMC1A, RBM14, ALKBH5, PRPF38A
KEGG	hsa03018:RNA degradation	NUDT16, EXOSC10, PATL1, BTG2, EDC4, DHX36, CNOT4, DDX6

Supplementary Table 3. Significantly differentially expressed GO terms and KEGG pathways that contained the nodes in PPI network

Nodes in protein-protein-interaction network	Category	Term
BOP1	CC	GO:0005737~cytoplasm
	CC	GO:0005654~nucleoplasm
	MF	GO:0005515~protein binding
	MF	GO:0044822~poly(A) RNA binding
USP9Y	CC	GO:0005737~cytoplasm
UTY	CC	GO:0005654~nucleoplasm
CDK16	MF	GO:0005515~protein binding
TAF6L	MF	GO:0005515~protein binding
DDX3X	MF	GO:0005515~protein binding
TLR4	MF	GO:0005516~protein binding
FOS	BP	GO:0009416~response to light stimulus
KAT2A	CC	GO:0005654~nucleoplasm
SEC61A2	CC	GO:0005829~cytosol
HIST3H3	CC	GO:0005654~nucleoplasm
KDM5D	CC	GO:0005655~nucleoplasm
SMARCA4	MF	GO:0005515~protein binding
RPLP0	MF	GO:0005516~protein binding
RPL18A	MF	GO:0044822~poly(A) RNA binding
PSMC3	CC	GO:0005737~cytoplasm
MRPS7	MF	GO:0044822~poly(A) RNA binding
TBPL1	CC	GO:0005737~cytoplasm
FAU	CC	GO:0005829~cytosol
MAP2K1	CC	GO:0005829~cytosol
RPS4Y1	CC	GO:0005830~cytosol
RAD23B	CC	GO:0005654~nucleoplasm
ABL1	CC	GO:0005655~nucleoplasm
BCR	MF	GO:0005515~protein binding
MLLT1	MF	GO:0005516~protein binding
DDX58	MF	GO:0004386~helicase activity
KDM6A	CC	GO:0005654~nucleoplasm
UBA1	MF	GO:0005515~protein binding
PRKX	MF	GO:0005516~protein binding
DIMT1	MF	GO:0044822~poly(A) RNA binding
RAB5A	CC	GO:0005737~cytoplasm
ITGAM	MF	GO:0005515~protein binding
H3F3B	MF	GO:0005516~protein binding
RPL10	MF	GO:0044822~poly(A) RNA binding
SMC3	CC	GO:0005737~cytoplasm
EIF1AY	MF	GO:0005519~protein binding
SMC1A	MF	GO:0044822~poly(A) RNA binding