Identification of hub genes and networks in cisplatin-induced acute kidney injury

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Abstract

Acute kidney injury induced by cisplatin poses a serious health hazard to patients. Thus, this study was undertaken to elucidate key signaling pathways and hub genes relevant for therapeutic intervention involved in cisplatin-induced acute kidney injury(CI-AKI) by bioinformatics. We identified differentially expressed genes(DEGs) by R language on GSE106993 and GSE153625 datasets, downloaded from Gene Expression Omnibus (GEO). GO enrichment analysis and KEGG analysis were used to identify the main functions of common differential genes. The STRING database was used to construct protein-protein interaction (PPI) networks and hub genes were selected by Cytoscape. TransmiR v2.0 database and miRWalk2.0 database were used to construct transcription factor (TF)/microRNA (miRNA)/mRNA networks. Chinese herbal medicines targeting hub genes were screened by the ETMC database. 817 up-regulated genes and 769 down-regulated genes were obtained in CI-AKI model. Tumor necrosis factor(TNF) signaling pathway, P53 signaling, and metabolic signaling pathway are important pathways in CI-AKI. 8 hub genes were identified through PPI (Trp53、Egf、Stat3、Jun、Casp3、Cdh1、Ptgs2、Cat). We also constructed TF/microRNA/mRNA regulatory networks, including 2 TFs, 4 miRNAs and 214 mRNAs. The results of ETMC database analysis showed that Sang-Ye and Ban-Xia could be used for the treatment of CI-AKI. In this study, we identified 8 hub genes and 3 important signaling pathways in CI-AKI model by bioinformatics analysis, which provide targets for the treatment of CI-AKI. And the two Chinese herbal medicines obtained from our research, Sang-Ye and Ban-Xia, are expected to be used for the treatment of CI-AKI. Meanwhile, the TF/miRNA/mRNA networks we constructed are helpful to the further study of the mechanism of CI-AKI.

Introduction

Acute kidney injury (AKI) manifests as renal failure in a short period of time, caused by multiple hazardous factors[1]. In addition, part of AKI may progress to chronic kidney injury or even end-stage kidney disease, posing a serious threat to patients and presenting a significant burden on their families[2]. Although multiple etiologies drive AKI, cisplatin is the frequent cause of AKI in patients undergoing chemotherapy.

Cisplatin is among the most commonly used and effective drugs in the treatment of malignancies (e.g., bladder cancer, head and neck tumor, small cell lung cancer)[3–5]. Nonetheless, the accumulation of cisplatin in the kidney leads to inflammation and necrosis of the renal tubules[6]. The mechanisms of cisplatin-induced acute kidney injury (CI-AKI) are diverse and remain incompletely defined.

The current study seeks to identify the key genes and signaling pathways in the process of CI-AKI based on mouse model and offer new ideas for kidney protection. As a consequence, we downloaded the sequencing data of CI-AKI mouse model through Gene Expression Omnibus (GEO). The DEGs between CI-AKI group and normal group were screened by bioinformatics analysis. Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) were used for functional and pathway enrichment analysis.

Protein-protein interaction (PPI) and Cytoscape software were used to identify hub genes and construct transcription factor (TF) / micro-RNA (miRNA) / mRNA regulatory network.

Materials And Methods

Data source.

GSE106993 and GSE153625 datas were downloaded from the GEO database (www.ncbi.nlm.nih.gov/geo/), respectively. Both sequencing platforms of GSE106993 and GSE153625 were GPL21103,Illumina HiSeq 4000 (Mus musculus). GSE106993 contains 4 mice in CI-AKI group and 4 mice in control group. GSE153625 includes 4 mice in CI-AKI group and 8 mice in control group. The mice in both groups are C57BL/6 mice of 19-21 weeks old, and the sequenced tissues are kidneys.

Identification of identify differentially expressed genes (DEGs).

Limma package(v3.32.7)in R language was used to identify differentially DEGs [7]. Differential genes were selected with logFC ≥ 1 and FDR ≤ 0.05.

GO and KEGG enrichment analysis.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were conducted by DAVID (https://david.ncifcrf.gov/) bioinformatics resources.

Identification of hub genes

The PPI of DEGs was constructed by STRING database (https://string-db.org/). Interactions with a score of >0.4 were pasted into Cytoscape software. Moreover, the cytohubba plugin was used to identify the hub genes in PPI network.

TF/miRNA/mRNA network.

The miRNAs regulated by transcription factors was predicted by TransmiR v2.0 database(http://www.cuilab.cn/transmir) [8] and intersected with differential miRNAs to obtain candidate miRNAs. In addition, the target mRNAs of candidate miRNAs were predicted by miRWalk2.0 online software (http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/)[9] (common target genes were predicted by miRWalk, miRanda, RNA22 and Targetscan), and intersected with differential mRNAs (negative correlation between mRNA and miRNA expression).

Prediction of Chinese Herbal Medicine targeting key genes

The Chinese herbal medicines targeting hub genes were screened by ETMC database (http://www.tcmip.cn/ETCM/index.php/Home/Index/)[10].

Results

Identification of DEGs in CI-AKI mouse model.

1387 up-regulated genes and 1182 down-regulated genes in CI-AKI group were obtained from GSE106993 (Fig. 1A). 1751 up-regulated genes and 1442 down-regulated genes in CI-AKI group were obtained from GSE153625 (Fig. 1B). Through intersection, we obtained 817 up-regulated genes and 769 down-regulated genes in CI-AKI group (Fig. 1C, D).

Enrichment Analysis of DEGs in CI-AKI mouse model.

The results of GO and KEGG enrichment analysis are presented in Fig. 2 and Table 1. GO terms related biological process were mainly involved in oxidation-reduction process and metabolic process (Fig. 2A). Cell component were mainly enriched in extracellular exosome and mitochondrion (Fig. 2B). The molecular function were primarily associated with oxidoreductase activity and catalytic activity (Fig. 2C). Subgroup analyses showed that up-regulated genes were mainly enriched inflammatory response, apoptotic process, cytoplasm and protein binding. Down-regulated genes were primarily associated oxidation-reduction process, metabolic process, mitochondrion, oxidoreductase activity and catalytic activity.

KEGG pathway enrichment analysis were mainly involved in metabolic pathways, tumor necrosis factor (TNF) signaling pathway and P53 signaling pathway (Fig. 2C). Metabolic pathways were mainly enriched by down-regulated genes. Meanwhile, TNF signal pathway and P53 signal pathway were obtained by up-regulated genes.

Identification of hub genes in CI-AKI process.

STRING database and Cytoscape software were adopted to construct the PPI of DEGs and investigate the interactions of DEGs. Plugin Cytohubba was used to acquire hub genes. With the intersection of the top ten genes from Degree, Closeness and Betweenness, we got 8 hub genes: Trp53、Egf、Stat3、Jun、Casp3、Cdh1、Ptgs2、Cat (Table 2), and constructed the interaction network (Fig. 3A).

Construction of TF/miRNA/mRNA Network.

We identified 27 differentially expressed miRNAs in CI-AKI group by reannotating DEGs in GSE106993(Table 3). At the same time, three transcription factors(Trp53,Stat3,Jun) and their target miRNAs were identified by TransmiR v2.0. A total of 4 overlapping miRNAs were obtained from differentially expressed miRNAs and target miRNAs. Unfortunately, there was no target miRNA found for Trp53. Finally, we predicted the target genes of 4 overlapping miRNAs by miRWalk2.0 and intersected with DEGs, and obtained 214 overlapping mRNAs (Fig. 3B).

Screening of Chinese Herbal Medicine targeting hub genes.

It was found that five hub genes can be used as targets for the treatment of Chinese herbal medicine through ETMC database. Two Chinese herbal medicines targeting multiple key genes, Sang-Ye and Ban-

Xia, may be used to treat CI-AKI(Table 4).

Discussion

Cisplatin has the advantages of strong penetration, good curative effect, wide action spectrum and synergistic effect with a variety of drugs[11]. As a consequence, it is widely used in the treatment of malignancies. Nevertheless, the nephrotoxicity of cisplatin seriously limits the clinical use of[12]. At present, the mechanism of CI-AKI is not completely clear.

1586 common differential genes were obtained from GSE106993 and GSE153625, including 817 up-regulated genes and 769 down-regulated genes. GO enrichment analysis showed that up-regulated genes were mainly related to inflammation and apoptosis. Meanwhile, oxidation-reduction processes and related molecular functions were enriched by down-regulated genes. KEGG enrichment analysis showed that TNF pathway and P53 signal pathway associated genes were up-regulated during CI-AKI. However, the genes related to metabolic pathway were down-regulated.

Inflammation is a complex biological process that runs through all stages of CI-AKI[13]. Necrotic cells induce the release of pro-inflammatory factors and chemokines, recruiting a variety of inflammatory cell infiltration, resulting in more cell death, forming a vicious circle of cell death-inflammation[14]. TNF signal pathway is an important inflammatory signal pathway, and TNF- α is the key gene of TNF signal pathway. TNF- α forms complex I with tumor necrosis factor receptor 1 and tumor necrosis factor receptor 2 activates the transcription of nuclear factor κ B (NF- κ B). And then, NF- κ B promotes the expression of inflammation-related genes[15]. Inflammation is intimately associated with apoptosis. TNF- α not only induces inflammation, but also activates death receptor pathway and promotes apoptosis[16]. Some studies have shown that P53 signal pathway is involved in the process of apoptosis induced by TNF- α[17]. P53 can activate mitochondrial apoptosis pathway and induce cell apoptosis by changing the permeability of mitochondrial[18]. Mitochondria is not only the source of energy for eukaryotes, but also participates in the regulation of various functions of organism. We enriched a number of mitochondrial-related biological processes, cellular components and molecular functions in the down-regulated genes, which suggested that there is mitochondrial dysfunction in the process of CI-AKI. Mitochondrial dysfunction increases ROS production which aggravates mitochondrial dysfunction and releases large amounts of cytokines which induce inflammatory responses[19]. Therefore, inflammation, apoptosis and mitochondrial dysfunction play important roles in development of CI-AKI. Meanwhile, there are cross-talks between inflammation, apoptosis, and mitochondrial dysfunction.

8 hub genes were obtained through PPI network. Previous studies have shown that human homologous genes of 8 hub genes play important roles in the process of CI-AKI. It was found that the expression of P53 was up-regulated in the early stage of CI-AKI, and inhibition of P53 could improve the symptoms of CI-AKI[20]. P53 participates in the process of CI-AKI through a variety of forms. On the one hand, it regulates various ways of cell death, such as apoptosis, necrosis, iron death, etc., on the other hand, it affects the process of autophagy[18, 21–23]. STAT3 is an important Inflammation gene, which can

regulate the release of inflammatory mediators and participate in inflammatory response, but also induce cell apoptosis through mitochondrial pathway[24, 25]. Inhibiting the expression of STAT3 can significantly improve the apoptosis and inflammatory response induced by cisplatin and sepsis[26, 27]. C-Jun is an important component of nuclear transcriptional activation protein, which can regulate the expression of death and inflammation-related genes[28, 29]. C-Jun is activated in a variety of kidney diseases, inhibition of C-Jun activation can improve kidney inflammatory response[30]. Caspase3 is the ultimate executor of apoptosis, which is regulated by many apoptotic pathways, such as TNF pathway and P53 pathway [16, 18]. Cadherin 1 (CDH1) is a member of the cadherin family and encodes E-cadherin, which is an important marker of epithelial-mesenchymal transformation. Studies have shown that E-cadherin is down-expressed in tubular cells with acute kidney injury, and up-regulation of E-cadherin can alleviate the inflammatory response and apoptosis in the process of CI-AKI [31]. Interestingly, it was found that CDH1 is up-regulated in CI-AKI, so what is the significance of CDH1 up-regulation? The latest study found that E-cadherin can not only regulate cell adhesion, migration and proliferation, but also limit apoptosis induced by ROS and improve cell viability [32]. This suggests that the up-regulation of CDH1 in the early stage of CI-AKI may have a protective effect on the kidney. EGF is a cytokine with multiple functions, which can bind to EGF receptors, activate downstream pathways, and regulate cell proliferation, apoptosis and differentiation[33]. Studies have shown that the expression of EGF is low in tubular cells after ischemia-reperfusion injury, and exogenous EGF contributes to the recovery of kidney function [34, 35]. However, the decrease of EGF is not linear. In CI-AKI model, it was found that the expression of EGF decreased at first, then increased, and finally decreased, suggesting that our body may repair itself by up-regulating EGF[36]. PTGS2, also known as COX-2, is an important mediator in the inflammatory process, which mediates a variety of inflammatory responses by promoting the expression of IL-6 through the regulation of prostaglandin E2 synthesis[37, 38]. Selective COX-2 inhibitors can reduce the injury of glomeruli and tubule, thereby alleviating the progression of acute kidney injury [39, 40]. CAT is an important member of the antioxidant system, which can break down hydrogen peroxide into water and carbon dioxide. The expression of CAT is low in CI-AKI model. In addition, up-regulation of CAT can protect kidney function [41].

MiRNA is a kind of non-coding RNA (19-25 nucleotide length) that regulates gene expression after transcription[42]. It is involved in many biological processes of acute kidney injury. In addition, it has been found that miR-449 is highly expressed in CI-AKI, and abnormal expression of miR-449 regulates apoptosis of kidney tubular epithelial cells through deacetylase 1/P53/Bcl2 associated X protein pathway[43]. The synthetic miR-500a-3p liposome could significantly reduce kidney injury[44]. The expression of miRNA is regulated in many ways, of which transcriptional regulation is the most common. P53-induced miR-199a-3p decreased the expression and phosphorylation of rapamycin and promoted apoptosis of kidney tubular epithelial cells[45]. In the study, we obtained several differentially expressed miRNA in the process of CI-AKI, and constructed TF/microRNA/mRNA regulatory networks, including 2 TFs, 4 miRNAs and 214 mRNAs, revealing the potential regulatory network in the process of CI-AKI.

Traditional Chinese medicine has been paid more and more attention, and the effect of traditional Chinese medicine in the treatment of acute kidney injury has been widely recognized in recent years. Zhi

Bai Di Huang Wan can reduce the apoptosis of tubular epithelial cells induced by gentamicin by inhibiting the activation of Caspase-3[46]. Resveratrol is a natural phenolic compound, which can reduce cisplatin-induced apoptosis of tubular epithelial cells by activating deacetylase 1 and deacetylating P53. We screened two traditional Chinese medicines, Sang-Ye and Ban-Xia, by targeting key genes. Sang-Ye is the dry leaf of mulberry, which has the effects of reducing lipid and anti-inflammation. Flavonoids from Sang-Ye can alleviate acute kidney injury induced by high uric acid[47]. The alkaloids extracted from Sang-Ye can reduce the production of ROS and reduce the acute kidney injury induced by oxidative stress[48]. Ban-Xia, which belongs to the Araceae family, is a valuable medical plant. Banxia Baishu Tianma Decoction regulates oxidative stress in hypertensive kidney injury by up-regulating the expression of Cu-Zn superoxide dismutase and catalase 2[49].

Conclusion

This study intends to screen the hub genes and pathways in the process of CI-AKI by bioinformatics. We got eight hub genes and three important pathways by analyzing DEGs in CI-AKI mouse model. At the same time, we constructed a TF/miRNA/mRNA regulatory network to reveal the potential regulatory mechanism of CI-AKI. Finally, two traditional Chinese medicines were screened to provide reference drugs for the treatment of CI-AKI by targeting hub genes.

Declarations

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Authors' contributions

LZ conceived and supervised the study. LY designed the study. LY, JX and XL analyzed the data. YC and HZ confirmed the authenticity of the raw data. LY and JX wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Tables 1-4 not included with this version.

Figures

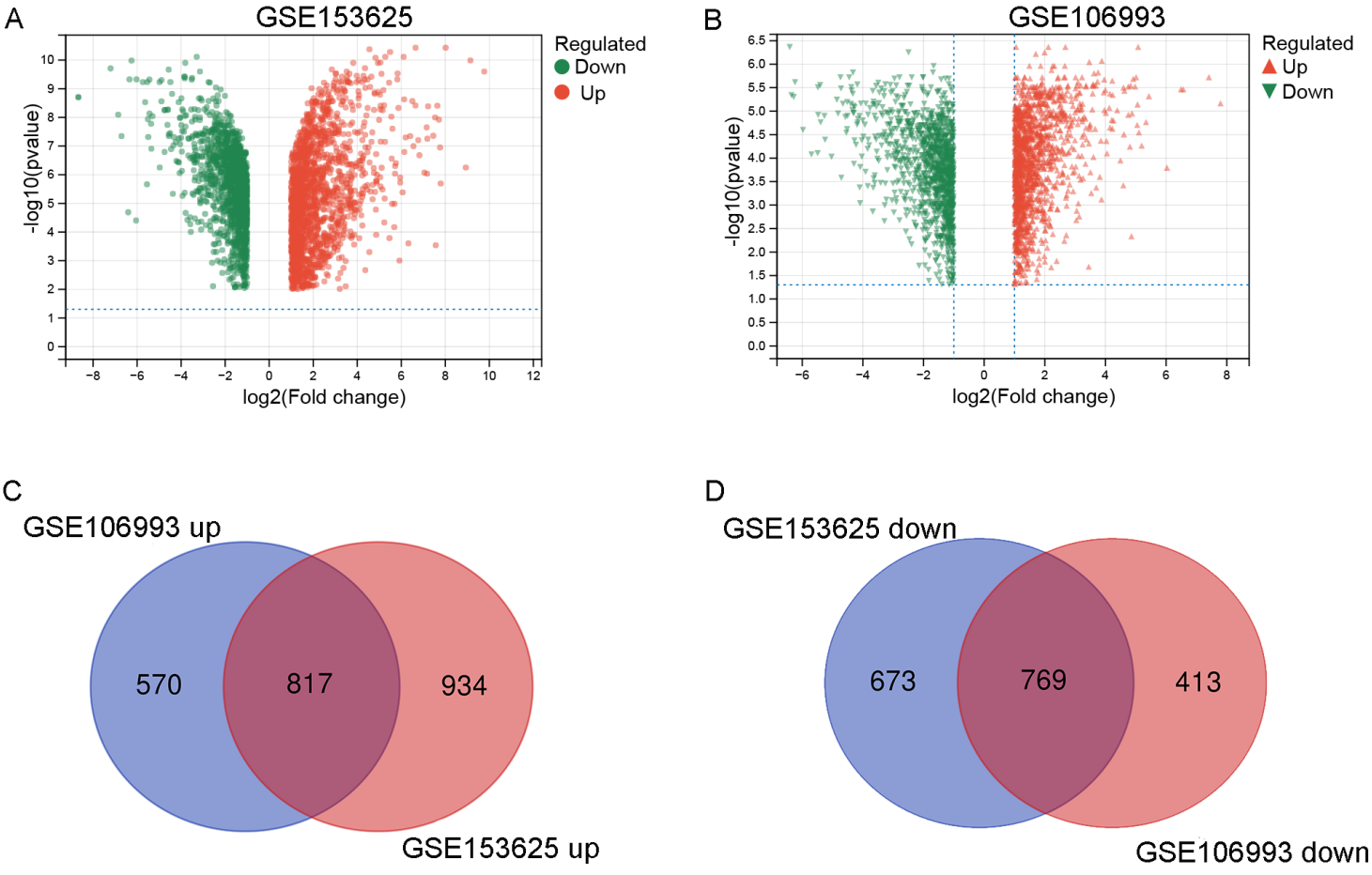

Figure 1

Differentially expressed genes in cisplatin-induced acute kidney injury group VS normal group. A, Volcano map of differentially expressed genes in GSE106993. B, Volcano map of differentially expressed genes in GSE153625. C, Differentially expressed genes upregulated in GSE106993 and GSE153625. D, Differentially expressed genes downregulated in GSE106993 and GSE153625.

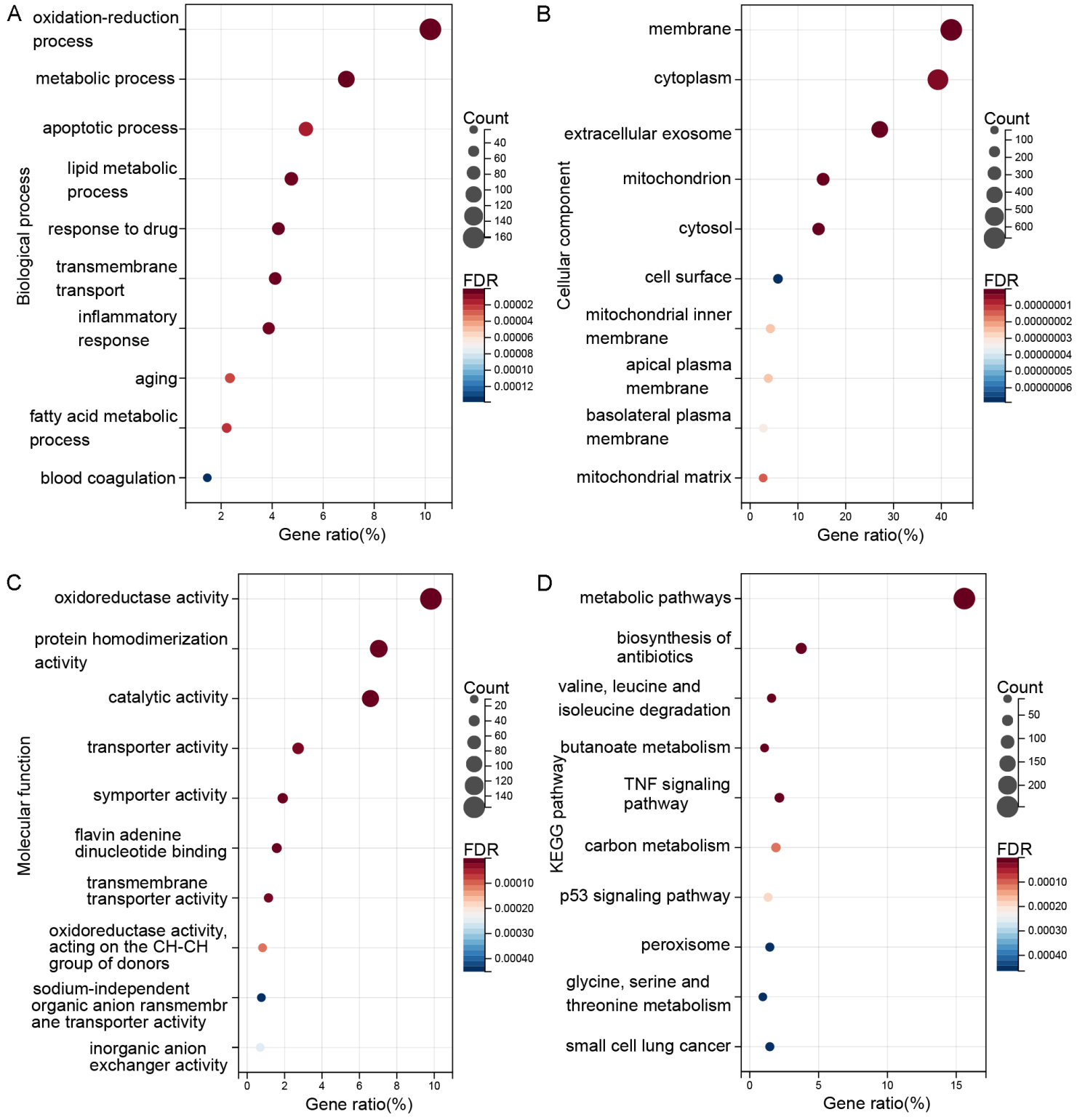

Figure 2

GO and KEGG pathway enrichment analysis of differentially expressed genes. A, Biological process enrichment analysis of differentially expressed genes. B, Cellular component enrichment analysis of differentially expressed genes. C, Molecular function enrichment analysis of differentially expressed genes . D, KEGG pathway enrichment analysis of differentially expressed genes.

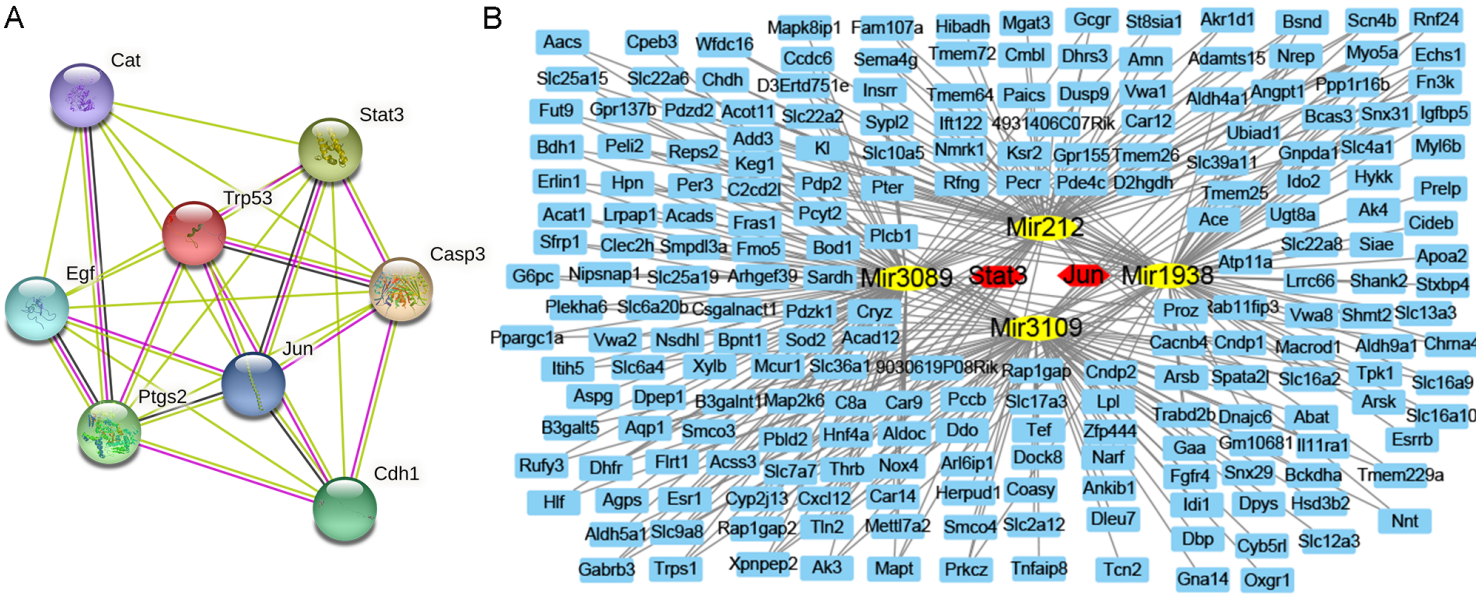

Figure 3

Gene interaction network. A, Protein-protein interaction network of 8 hub genes. B, TF/miRNA/mRNA network. Red is transcription factor. Yellow is miRNA. Blue is mRNA.