Identification and Analysis of Key Genes Associated with Ulcerative Colitis by Integrated Bioinformatics Methods

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Research Article

Keywords: ulcerative colitis, bioinformatics, biomarkers, differentially expressed gene

Posted Date: November 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1019392/v1

Abstract

Background: Ulcerative colitis (UC) is a prevalent inflammatory bowel disease of the colonic mucosa. The exact mechanism of the disease still remains unclear. Here we tried to explore new biomarkers and potential therapeutic targets in UC through adopting integrated bioinformatics tools.

Results: By performing DEGs analysis, 59 upregulated and 39 downregulated DEGs were successfully identified from GSE3365, respectively. And they were mainly enriched in the terms of Cytokine-cytokine receptor interaction,Viral protein interaction with cytokine and cytokine receptor,Pantothenate and CoA biosynthesis,IL-17 signaling pathway and Chemokine signaling pathway. Based on the data of protein–protein interaction (PPI), the top 10 hub genes were ranked, including Growth-regulated alpha protein (CXCL1), C-C motif chemokine 2 (CCL2), C-X-C chemokine receptor type 1 (CXCR1), Low affinity immunoglobulin gamma Fc region receptor III-B (FCGR3B), C-X-C chemokine receptor type 2 (CXCR2), Prostaglandin G/H synthase 2 (PTGS2), Triggering receptor expressed on myeloid cells 1 (TREM1), Interleukin-1 receptor type 1 (IL1R1), fMet-Leu-Phe receptor (FPR1), and Band 3 anion transport protein (SLC4A1).What's more, the results of correlation analysis demonstrated that there was a positive correlation between the 10 hub DEGs.

Conclusion: Ten DEGs were identified as potential candidate diagnostic biomarkers for patients with UC in present study. However, further experiments are needed to confirm the functional pathways and hub genes associated with UC.

Background

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which is a main forms of inflammatory bowel disease.[1] The worldwide incidence of UC has been rising and, factoring morbidity and mortality related to UC, health care and societal costs are substantial.[2] Although our knowledge of the contribution of environmental factors, genetics, and the immune system on disease development continues to grow, the exact mechanism of disease still remains unclear. Studies have shown that the pathogenesis of ulcerative colitis may include elements of genetic susceptibility, immune dysregulation, environmental factors, and the microbiome.[3]

At present, common approaches for treating UC include non-surgical and surgical treatments.

Among them, non-surgical treatments can be classified as non-pharmacologic treatments and pharmacologic treatments.Moreover, pharmacologic treatments involves aminosalicylic acid preparations, glucocorticoids, immunosuppressive agents, or biologicals, which are currently regarded as the most effective immunosuppressive agents for the treatment of UC, such as anti-TNF monoclonal antibodies.[4, 5]And non-pharmacologic treatments include hyperbaric oxygen therapy, faecal bacteria transplantation and leukocyte adsorption therapy.[6-8] Treatments mentioned earlier have significantly

improved treatment outcomes,therefore, an accurate and timely diagnosis of UC is of great significance to start the appropriate treatment.

Recent studies show that various biomakers shows a high effciency and value in evaluating clinical activity in patients with UC, such as serum biomakers(B-cell-activating factor, Cathelicidin, Galectin-3, Leucine-rich alpha-2 glycoprotein, Matrix metalloproteinases, Soluble Receptor for advanced glycation end products, Matrix metalloproteinases, Alpha-1 anti-trypsin, Hyaluronan, Soluble triggering receptor expressed on myeloid cells, Serum Trefoil factor 3, Neutrophil gelatinase B-associated lipocalin, Soluble ST2 protein, Phospholipase A2,and MicroRNAs) and fecal biomakers (fecal myeloperoxidase, fecal lactoferrin and fecal calprotectin). [9, 10]Biomarkers help to gain an objective measurement of disease activity as symptoms are often subjective. If an ideal biomarker existed for UC, it would greatly facilitate the work of the gastroenterologist treating these patients.

In this study, the microarray data of GSE3365 were applied to identify the differentially expressed genes (DEGs) between UC and non-UC peripheral blood utilizing an integrated bioinformatics.Afterwards, in order to analyze the main biological functions regulated by DEGs, enrichment analysis was conducted. Meanwhile, through correlation analysis, protein–protein interaction (PPI) and modular analysis of upregulated DEGs, key genes related to the diagnosis and treatment of UC were identified. The detailed workflow is shown in Figure 1.

Results

1.Identification of DEGs

GSE3365 was selected and underwent DEGs analysis using “Limma” package in R 3.6.3 software.Three ninety-eight DEGs were identified either up- or downregulated in all,including 59 up- and 39 downregulated genes (|log2FC|>1 and adjust P-value<0.05). As shown in Figure 2A, all 98 DEGs were plotted that blue ones represented downregulation, red ones indicated upregulation, and gray ones were the rest of the DEGs. Furthermore, the expression levels of all the DEGs were presented in the heatmap (Fig. 2B), and these genes were well clustered between UC and control group.

2. Correlation analysis

The top 10 up- or downregulated DEGs were selected for correlation analysis(|log2FC|>1 and adjust P-value<0.05). Figure 2C shows a bitmap of the correlation analysis between the DEGs. Red and green denoted positive and negative correlation, respectively. And the darker the color, the higher the correlation coefficient. According to the classification for Spearman's correlation coefficient (ρ), the absolute value of 0 to 0.10, 0.10 to 0.39, 0.40 to 0.69, 0.70-0.89,and 0.90 to 1.00 represented “negligible” correlation, “weak” correlation, “moderate” correlation, “strong”correlation,and “very strong” correlation, respectively. Furthermore, “ρ=0” indicated “no correlation ” and “ρ=1.00” represented “perfect correlation.”[13]As listed

in Figure 2c, ZNF91 had a notable positive correlation with SETD5 (ρ=1.00). However, ZNF91 had a highly negative correlation with AQP9 (ρ=-0.40).ALAS2 had positive correlation with EPB42 (ρ=0.94) as well. Concurrently,ZNF91 and SETD5 also had relatively obvious positive correlation with CELF2 (ρ=0.85 and ρ=0.85).In addition, a stronger negative correlation existed between AQP9 and FCF1 (ρ=-0.53).

3. Functional enrichment analysis of DEGs

To obtain a deeper insight into the biological functions of DEGs,GO annotation and KEGG pathway enrichment analyses were performed. The top 10 enriched GO terms were shown in

Figures 3 and 4. The GO terms were comprised of 3 parts: cellular component (CC), biological process (BP), and molecular function (MF).[14]DEGs of BP were involved in leukocyte migration, acute inflammatory response, neutrophil migration, granulocyte migration, and neutrophil degranulation.CC analysis revealed that DEGs were markedly enriched ecretory granule membrane, external side of plasma membrane , anchored component of membrane ,blood microparticle,and tertiary granule.For MF analysis, the significantly enriched terms were chemokine activity and chemokine receptor binding.Besides, the enriched KEGG pathways as presented in Figure 5, including Cytokine-cytokine receptor interaction,Viral protein interaction with cytokine and cytokine receptor,Pantothenate and CoA biosynthesis,IL-17 signaling pathway and Chemokine signaling pathway.

4. PPI network construction and module analysis

The STRING database was used to identify the PPI pairs. As indicated in Figure 6A, 51 nodes (DEGs) and 218 edges (interactions) were established in the constructed PPI network.

Depending on the degree value, the top 10 hub DEGs were determined. The results shown that CXCL1 and CCL2 were the most crucial genes with the highest degree=26, followed by CXCR1 and FCGR3B at degree=24, C-X-C chemokine receptor type 2 (CXCR2) at degree=22, Prostaglandin G/H synthase 2 (PTGS2) at degree=20, Triggering receptor expressed on myeloid cells 1 (TREM1) at degree=18, Interleukin-1 receptor type 1 (IL1R1) at degree=18, fMet-Leu-Phe receptor (FPR1) at degree=16, and Band 3 anion transport protein (SLC4A1) at degree=14 (Table 1).

Table 1

The information of top 10 hub genes based on their degree value.

Gene name	Protein name	Expression level	Degree	Enriched significant modules
CXCL1	Growth-regulated alpha protein	UP	26	module 3
CCL2	C-C motif chemokine 2	UP	26	module 2
CXCR1	C-X-C chemokine receptor type 1	UP	24	module 3
FCGR3B	Low affinity immunoglobulin gamma Fc region receptor III-B	UP	24	None
CXCR2	C-X-C chemokine receptor type 2	UP	22	module 2
PTGS2	Prostaglandin G/H synthase 2	UP	20	module 3
TREM1	Triggering receptor expressed on myeloid cells 1	UP	18	None
IL1R1	Interleukin-1 receptor type 1	UP	18	None
FPR1	fMet-Leu-Phe receptor	UP	16	module 2
SLC4A1	Band 3 anion transport protein	UP	14	module 1

Furthermore, the 3 significant modules (score>4.0) were extracted from the PPI network. Module 1 contained 6 gene nodes, including SELENBP1,SNCA, ALAS2, CA1,EPB42 and SLC4A1 with 28 edges (Fig. 6B). Module 2 contained 4 genes nodes and 12 edges, including Interleukin-1 receptor type 2 (IL1R2), C-C motif chemokine 2 (CCL2), Interleukin-1 receptor type 1 (IL1R1) and C-X-C chemokine receptor type 2 (CXCR2) (Fig. 6C). Module 3 contained 7 genes nodes and 24 edges, including PTGS2, Vascular non-inflammatory molecule 2 (VNN2), Low affinity immunoglobulin gamma Fc region receptor III-B (FCGR3B), C-C motif chemokine 7 (CCL7),CXCL1,CXCR1 and Aquaporin-9 (AQP9) (Fig. 6D). Notably, only one hub DEGs of SLC4A1 was found in module 1. Three hub DEGs of CCL2, CXCR2 and FPR1 were enriched in module 2. Three hub DEGs of CXCL1, CXCR1 and PTGS2 were enriched in module 3. However, FCGR3B ,IL1R1 and TREM1 were not shown in significant modules.

5. Expression level analysis of hub genes

The interaction network between the 10 hub DEGs was constructed by Cytoscape version 3.8.2 plug-in “cytoHubba”based on their degree (Fig. 7A). As demonstrated in Figure 7B, the hub genes expression levels of FPR1,CXCR2,CXCL1,CCL2,CXCR1,FCGR3B,IL1R1,SLC4A1,TREM1,and PTGS2 were markedly upregulated in UC peripheral blood compared to those in non-UC peripheral blood. Furthermore, correlation analysis between the expression levels of the 10 hub genes (FPR1,CXCR2,CXCL1,CCL2,CXCR1,FCGR3B,IL1R1,SLC4A1,TREM1,and PTGS2) was performed by adopting Spearman's correlation analysis. The results demonstrated that there was a positive correlation

between the 10 hub genes expression (Fig. 7C). Obviously, CXCR2 had a noteworthy positive correlation with FCGR3B (ρ=0.87).

Discussion

Despite advances in diagnosis and treatments of UC, successful screening techniques and accurate diagnosis might favor early recognition, diagnosis, and therapeutic interventions.[15]

In the present study, integrated bioinformatics analysis was used to identify the potential key genes related to UC. By performing DEGs analysis, 59 upregulated and 39 downregulated DEGs were successfully identified (|log2FC|>1 and adjust P-value<0.05), respectively. To obtain a deeper insight into the biological functions of DEGs, GO annotation and KEGG pathway enrichment analyses were performed. Based on the data of PPI, the top 10 hub genes were ranked, including FPR1,CXCR2,CXCL1,CCL2,CXCR1,FCGR3B,IL1R1,SLC4A1,TREM1,and PTGS2. Notably, only one hub DEGs of SLC4A1 was found in module 1. Three hub DEGs of CCL2, CXCR2 and FPR1 were enriched in module 2. Three hub DEGs of CXCL1, CXCR1 and PTGS2 were enriched in module 3. However, FCGR3B ,IL1R1 and TREM1 were not shown in significant modules.

Accordingly, the expression level and correlation of 10 hub genes were analyzed. The 10 hub genes expression levels were markedly upregulated in UC peripheral blood compared to those in non-UC peripheral blood. Obviously, CXCR2 had a notable positive correlation with FCGR3B (ρ=0.87).

GO analysis showed that the DEGs were enriched in leukocyte migration，granulocyte migration， neutrophil activation, neutrophil degranulation，and acute inflammatory response. KEGG pathway annotation analysis revealed that DEGs were mainly involved in Cytokine-cytokine receptor interaction,Viral protein interaction with cytokine and cytokine receptor, IL-17 signaling pathway and Chemokine signaling pathway. Cytokines are soluble extracellular proteins or glycoproteins that are crucial intercellular regulators and mobilizers of cells engaged in innate as well as adaptive inflammatory host defenses, cell growth, differentiation, cell death, angiogenesis, and development and repair processes aimed at the restoration of homeostasis. Cytokines can be grouped by structure into different families，such as CC subfamily, CXC subfamily, interleukin(IL) family, TNF family, TGF-β family and so on.In this study, 4 hub DEGs, namely CXCL1，IL1R1，CXCR1，CXCL8, and CCL2, enriched in Cytokine-cytokine receptor interaction.

Interleukin 17 (IL-17) is a highly versatile pro-inflammatory cytokine crucial for a variety of processes including host defense, tissue repair, inflammatory disease pathogenesis and cancer progression.[16] Similarly, 3 hub DEGs, namely CXCL1, PTGS2, and CCL2, enriched in IL-17 signaling pathway.

Recent evidence suggests that CXC chemokines are not only critical for inflammation, but also mediate the recruitment of inflammatory leukocytes.[17, 18] Experimental studies have shown that CXCL chemokines were involved in the pathogenesis of UC while ELR positive CXCL chemokines are highly expressed in an animal model of ulcerative colitis.[19] CXCL1 is regarded as a key IL-17-induced neutrophil

chemoattractant. [20]Meantime, Anti-CXCL1 Ab relieves the progression of DSS-induced acute ulcerative colitis by suppressing proinflammatory expression and neutrophil infiltration.[21]Studies show that CXCR2 was remarkably upregulated in experimental UC and might reflect the degree of inflammation in patients with UC.[22, 23]In addition, the CXCL1-CXCR2 axis mediates neutrophil recruitment.[24] CCL2 is also known as monocyte chemoattractant protein-1 (MCP-1),raised level of MCP-1 has been widely demonstrated in the intestinal mucosa of patients with ulcerative colitis.[25] Kouichi Asano et al conducted that FCGR3B may play a crucial role in the pathogenesis of UC.[26]

Previous studies have shown that triggering receptor expressed on myeloid cells-1 (TREM1) has recently been shown to be upregulated in the intestines of patients with inflammatory bowel disease (IBD). [27]Besides, A study from China showed that higher levels of TREM-1 expression in peripheral blood mononuclear cells (PBMCs) were significantly correlated with disease activity,which could be a potential serum biomarker for monitoring disease activity in Chinese patients with UC.[28]Experiment confirmed the important pathogenic role of mouse Fpr1 in experimental colitis, the outcome effected mainly through regulation of immune cell recruitment and modulation of local cell activation and survival.[29] FPR1 can be identified as a mucosal marker of histological inflammation in patients with UC.[30]

Limitations

Some limitations exist in this study. First, the sample size of the data set used in this study is relatively small. Second, although we have identified some enriched pathways and core DEGs, the hierarchical processes between them have not yet been completely elucidated. However, further studies with larger sample sizes are still needed in order to identify potential biomarkers associated with UC.

Conclusions

In conclusion, the present study identified IL1B, CXCL1,CXCL8, TNF, FPR2, JUN, PPBP, MMP9, TLR2, and FCER1 as key genes in the pathogenesis of AMI by integrated analysis of microarray datasets. The results of this study further provide useful evidence for investigation into molecular mechanisms, selection of biomarkers, and treatment targets exploration of UC. However, further vitro and in vivo analyses experiments are needed to confirm the functional pathways and hub genes associated with UC.

Methods

1. Gene expression profile data

The gene expression profile data of GSE3365,downloaded from GEO database (https://www.ncbi.nlm.nih.gov/gds/),were used to screen DEGs in UC. Sixty-eight specimens (42 UC samples and 26 control samples) were contained in the data series of GSE3365. Molecular classification

of ulcerative colitis patients using transcriptional profiles in peripheral blood mononuclear cells.And the gene expression was detected by GPL96 [HG-U133A] Affymetrix Human Genome U133A Array.

2. Screening of DEGs and correlation analysis

Using the “Limma” package in R 3.6.3 software[11],normalization, log 2 conversion and DEGs screening of GSE3365 matrix data were performed. |log2FC|>1 and adjust P-value<0.05 were regarded as the statistical significance threshold level of DEGs samples.In addition, to get a better understanding of DEGs,correlation analysis was applied using Spearman's correlation coefficient and the visualized by adopting “ggplot2” and “ComplexHeatmap”R package[12].

3. Functional enrichment analysis of DEGs

The statistically significant DEGs were further analyzed in R 3.6.3 software with the “clusterProfiler” and “ggplot2” package,to conduct the Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses.Adjust P-value<.05 was considered as the cut-off criteria.

4. PPI network construction and module analysis

In order to obtain directly or indirectly interacting proteins related to DEGs, the STRING version 11.5 database (https://string-db.org/) was used. At the same time, the confidence

score was set as >0.4 and species limited to “Homo sapiens.”Subsequently, the Cytoscape version 3.8.2 (http://www.cytoscape.org/) plug-in the molecular complex detection (MCODE)

was used to identify the key modules from PPI network.And modules with MCODE score ≥4.0 were presented.

5. Expression level analysis of hub genes

By using the “ggplot2” package in R 3.6.3 software to show the difference in expression of hub genes in healthy subjects and ulcerative colitis patient.

Abbreviations

UC=ulcerative colitis ,BP = biological process, CC= cellular component, GO=gene ontology,KEGG= kyoto encyclopedia of genes and genomes, DEG= differentially expressed genes,PPI=protein–protein interaction, GEO = gene expression omnibus, MCODE = molecular complex detection, ZNF91= zinc finger protein 91,SETD5=SET domain-containing protein 5,AQP9= aquaporin-9,ALAS2= 5-aminolevulinic acid synthase 2,EPB42 = rythrocyte membrane protein band 4.2,CELF2= CUGBP Elav-like family member

2,FCF1= rRNA-processing protein FCF1, SELENBP1= methanethiol oxidase,SNCA= alpha-synuclein, CA1= Carbonic anhydrase 1, SLC4A1= solute carrier family 4 member 1, CXCL1=Growth-regulated alpha protein , CCL2= C-C motif chemokine 2, CXCR1=C-X-C chemokine receptor type 1, FCGR3B =Low affinity immunoglobulin gamma Fc region receptor III-B, CXCR2=C-X-C chemokine receptor type 2 , PTGS2=Prostaglandin G/H synthase 2 , TREM1=Triggering receptor expressed on myeloid cells 1 , IL1R1=Interleukin-1 receptor type 1 , FPR1=fMet-Leu-Phe receptor, TNF= tumor necrosis factor,TGF-β= transforming growth factor beta,IL-17= Interleukin 17, PBMC=peripheral blood mononuclear cell.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Funding

Not applicable.

Authors’ contributions

YXY and LJJ conceived and designed the study. CHC, CXM, and XY collected the data and performed the data analysis, and YXY wrote the manuscript. All authors were responsible for reviewing data.

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Figures

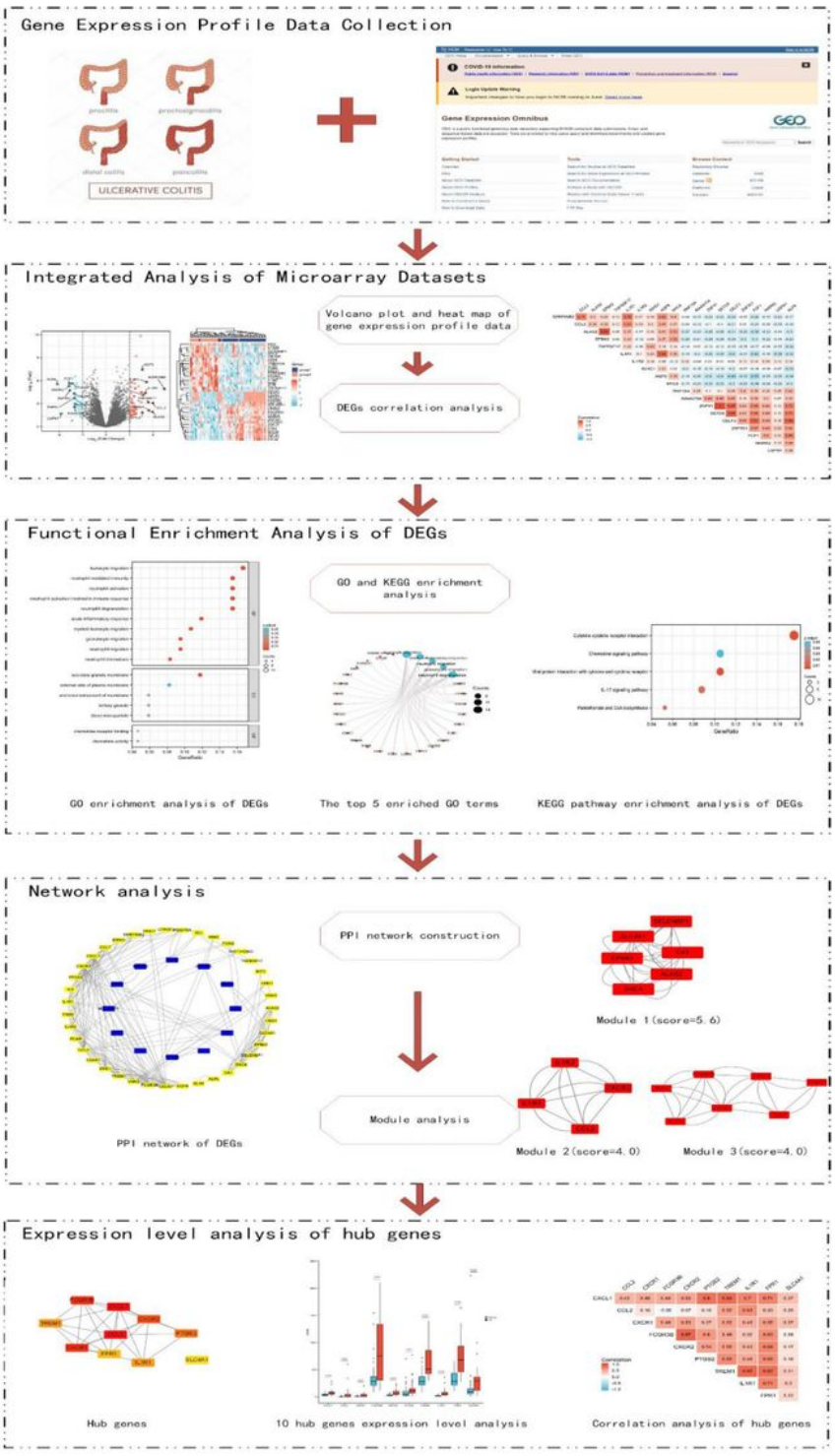

Figure 1

The detailed workflow for identification of key potential genes associated with ulcerative colitis.

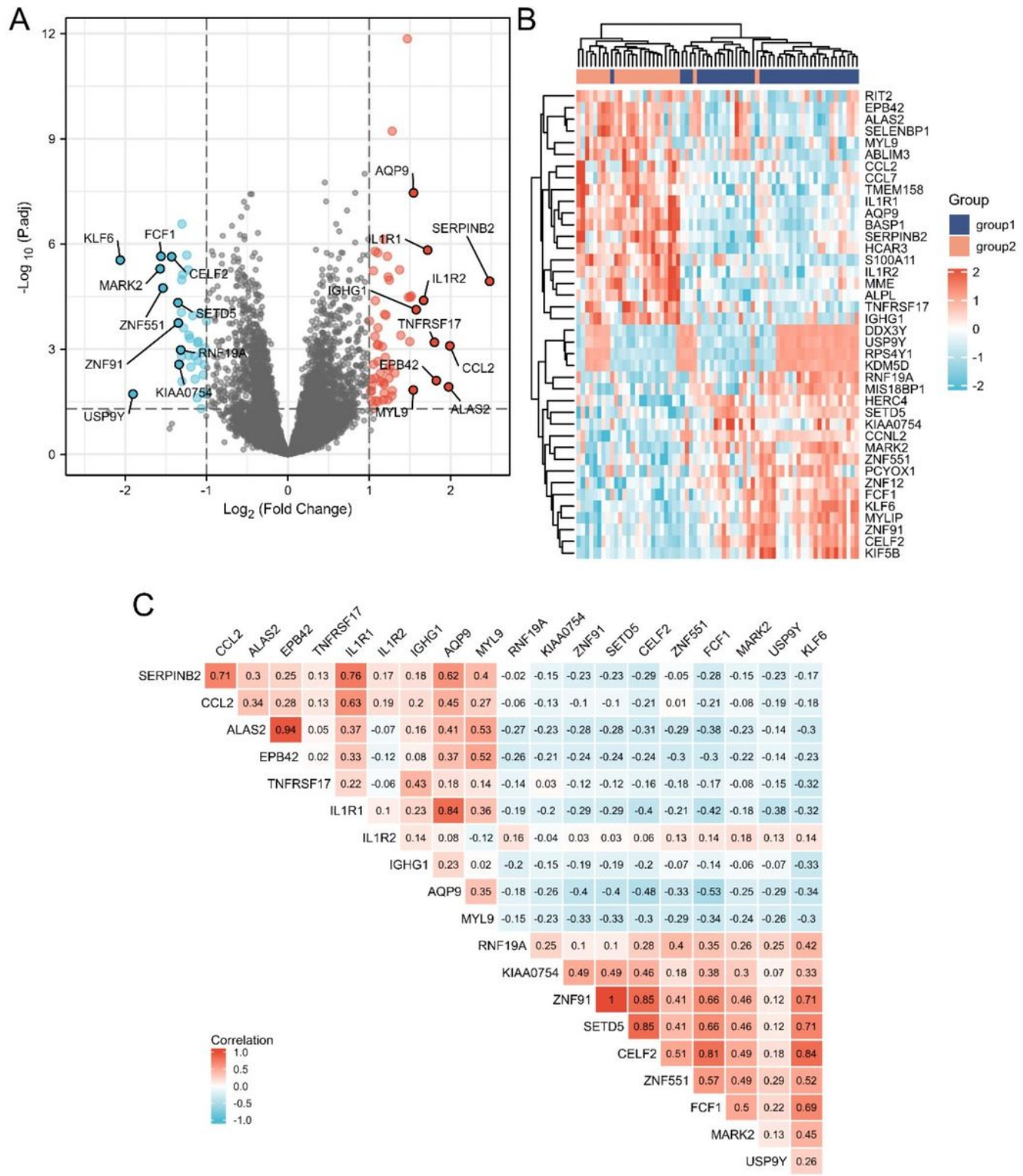

Figure 2

(A) Volcano plot of GSE3365. Blue ones represented downregulation, red ones indicated upregulation, and gray ones were the rest of the DEGs. (B)Heat map of DEGs. Each column represents one dataset and each row indicates one gene. Blue represents downregulated genes and red represents upregulated genes. (C) Bitmap of the correlation analysis between the top 10 up- or downregulated DEGs. Red and blue denoted positive and negative correlation,respectively. DEGs: differentially expressed genes.

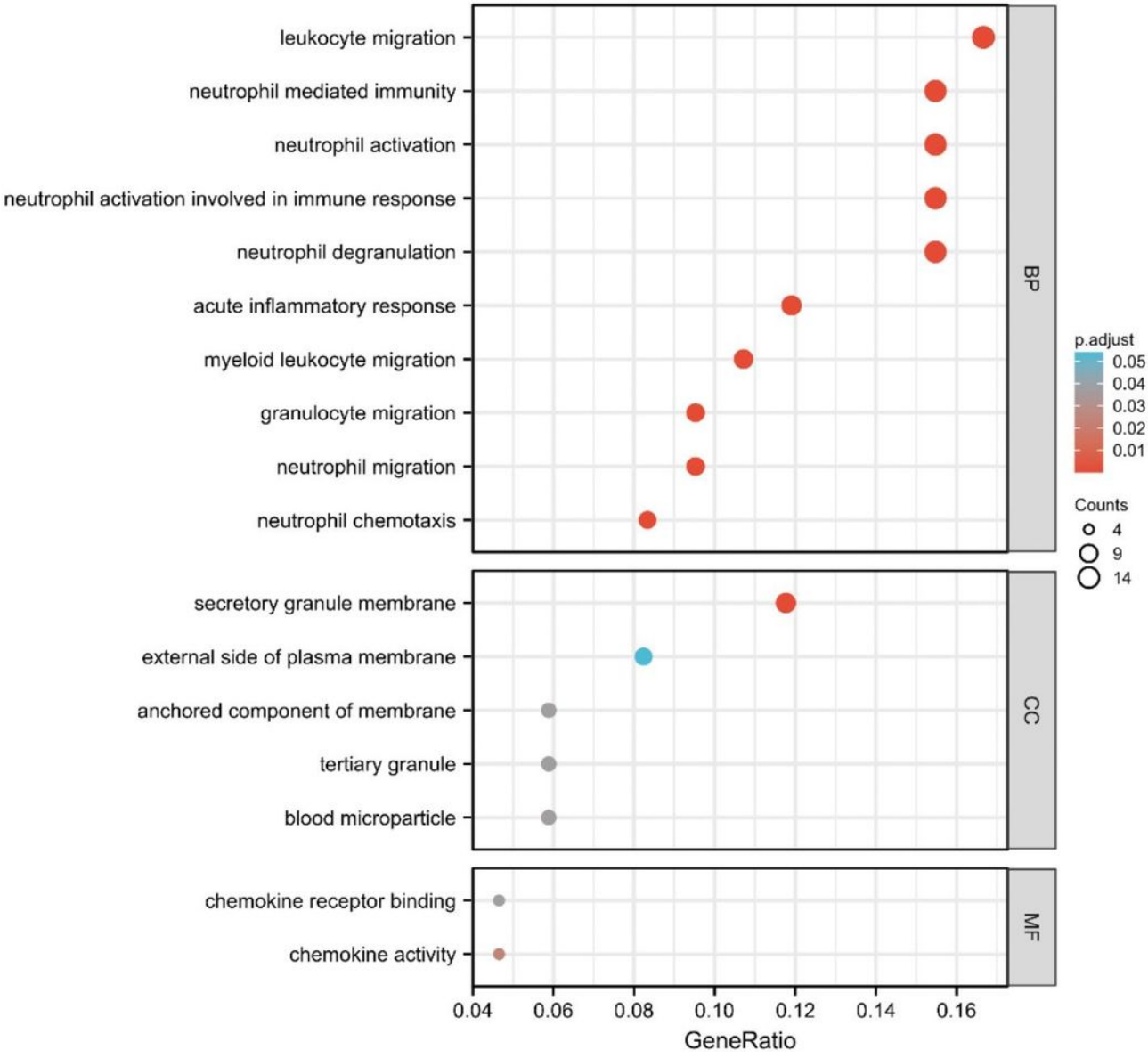

Figure 3

GO enrichment analysis of DEGs (P-value<.01 and q-value<0.05). DEGs: differentially expressed genes; GO: Gene Ontology.

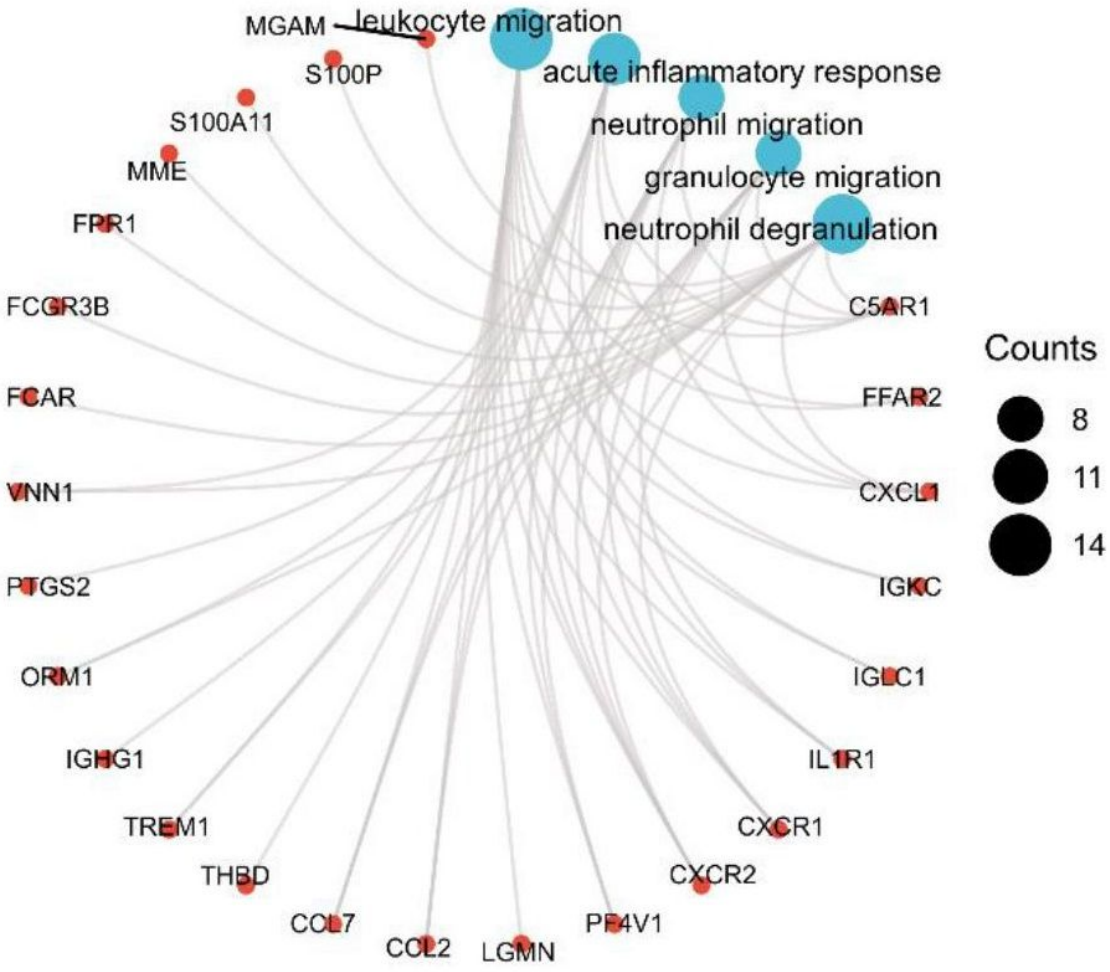

Figure 4

The top 5 enriched GO terms. GO: Gene Ontology.

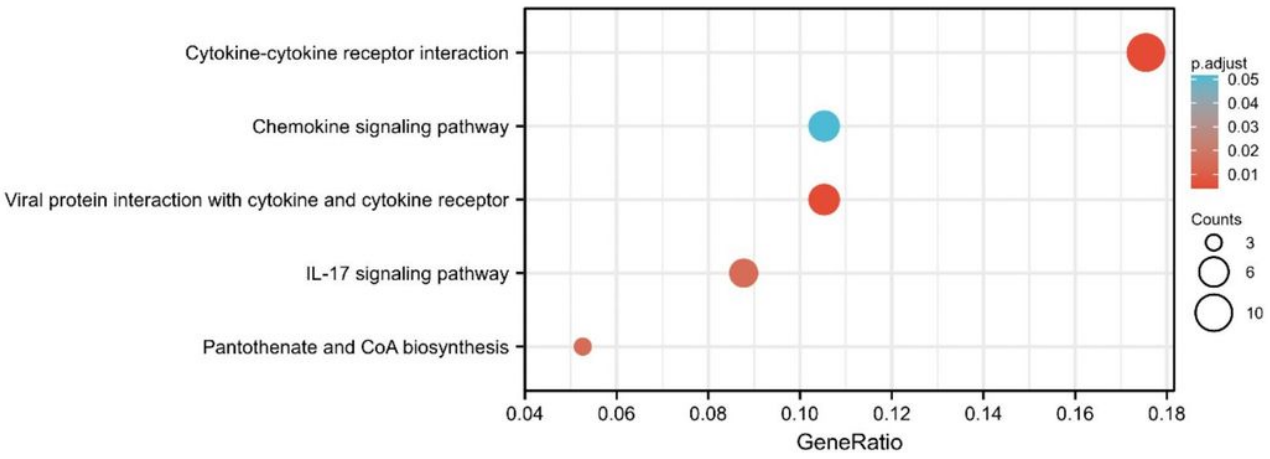

Figure 5

KEGG pathway enrichment analysis of DEGs (P-value<.05 and q-value<0.05). DEGs: differentially expressed genes; KEGG: Kyoto Encyclopedia of Genes and Genomes.

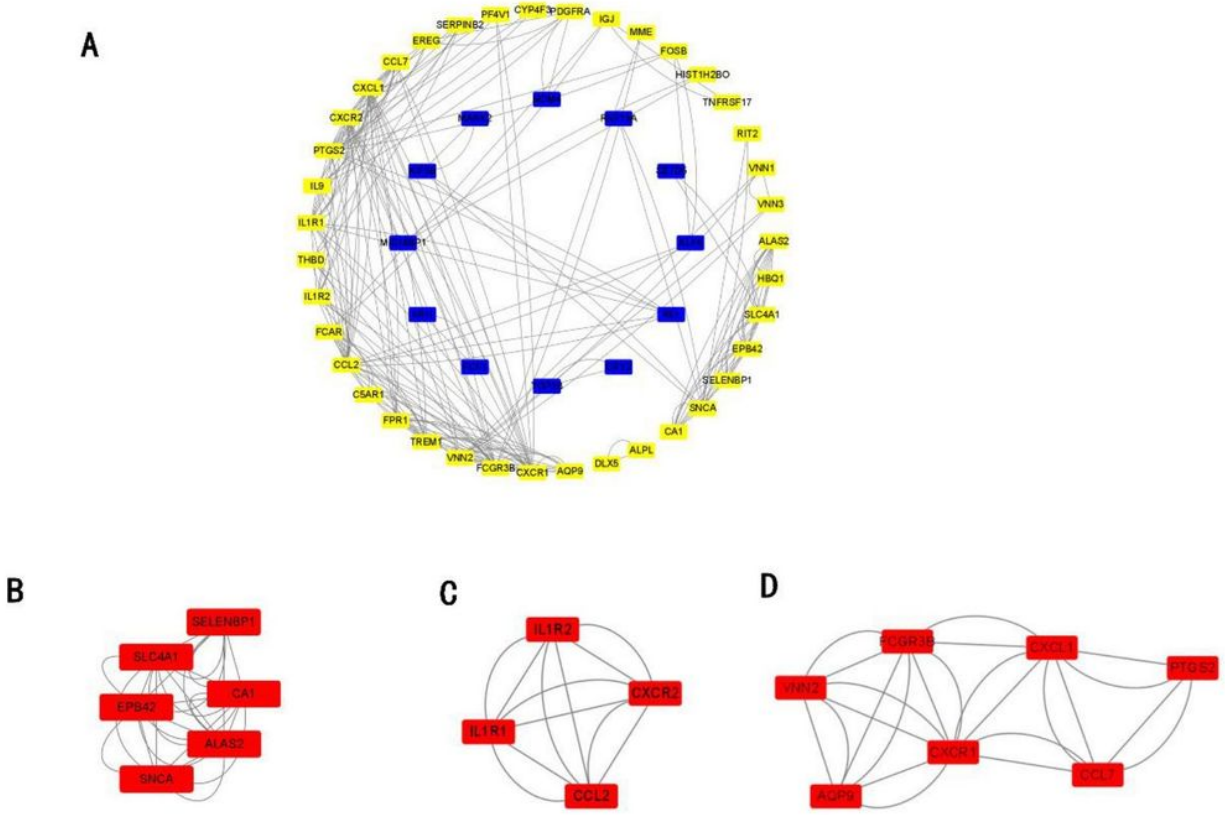

Figure 6

Analysis of DEGs PPI network and module analysis. (A) PPI network of DEGs. (B) Module 1 contained 6 gene nodes and 28 edges, MCODE score=5.6. (C) Module 2 contained 4 genes nodes and 12 edges, MCODE score=4.0. (D) Module 3 contained 7 genes nodes and 24 edges, MCODE score=4.0. Blue represents downregulated genes and yellow represents up-regulated genes in Figure 6A. Red represents up-regulated genes in Figure 6B,C,D.DEGs: differentially expressed genes; PPI: protein–protein interaction; MCODE: molecular complex detection.

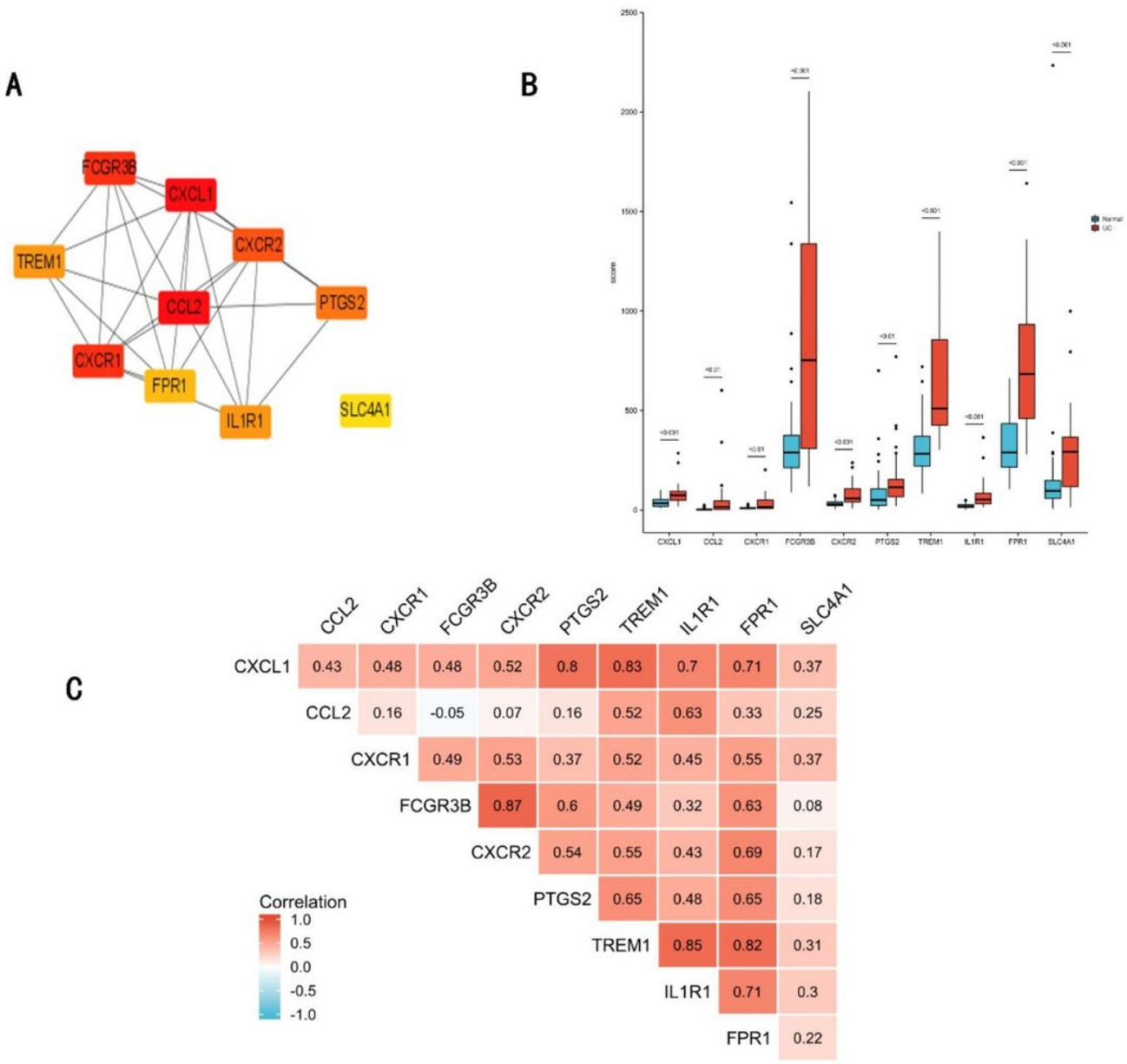

Figure 7

(A) The network of 10 hub genes. The 10 nodes are displayed from red (high degree value) to yellow (low degree value). (B) Analysis of 10 hub genes expression level in ulcerative colitis. (C) Bitmap of the correlation analysis between the 10 hub genes. Red and blue denoted positive and negative correlation, respectively.