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Uncovering the genetic link between acute myocardial infarction and ulcerative colitis co-morbidity through a systems biology approach

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Background:

Cardiovascular diseases especially acute myocardial infarction are the leading cause of disability and death. Atherosclerosis is the pathological basis of AMI, and chronic inflammation can accelerate the process. Ulcerative colitis is a chronic inflammatory disease associated with immunity with possible risks contributing to AMI development. However, controversy continues to surround the relationship between these two diseases. The present study unravels the pathogenesis of AMI and UC, which may provide a new perspective on the clinical management of patients with these comorbidities.

Methods:

Download microarray datasets GSE66360 and GSE87473 from gene expression omnibus database. Identification of common differentially expressed genes (co-DEGs) in AMI and UC followed, the following analysis was carried out: enrichment analysis, protein-protein interaction network construction, hub gene identified and co-expression analysis.

Results:

Totally 267 co-DEGs (233 upregulated and 34 downregulated) were screened for further analysis. GO enrichment

analysis emphasizes the important role of chemokines and cytokines in these two diseases. In addition, lipopolysaccharide-mediated signaling pathway is closely related to both. KEGG enrichment analysis reveals that lipid and atherosclerosis, NF-κB, TNF and IL-17 signaling pathways are the core mechanisms involved in the progression of these two diseases. Finally, 11 hub genes were identified with cytoHubba, including TNF, IL1B, TLR2, CXCL8, STAT3, MMP9, ITGAX, CCL4, CSF1R, ICAM1, and CXCL1.

Conclusion:

This study reveals a co-pathogenesis mechanism of AMI and UC regulated for specific hub genes, which not only provides new ideas for further mechanistic studies, but also provides new perspectives on the clinical management of patients suffering from these comorbidities.

Keywords: acute myocardial infarction, ulcerative colitis, bioinformatics, differentially expressed genes, hub genes

INTRODUCTION

Cardiovascular diseases especially acute myocardial infarction (AMI) are the leading cause of disability and death (1-3). AMI is myocardial necrosis caused by coronary artery acute and persistent ischaemia and hypoxia (4). Atherosclerosis is the pathological basis of AMI, and chronic inflammation can accelerate the process (5). Although early treatment with reperfusion after AMI onset can improve clinical outcomes, the risk of recurrence and mortality remains high for up to one year after AMI onset (6). Additionally, reperfusion therapy not only causes increased damage to ischemic myocardial tissue but also implicates previously uninvolved myocardial tissue (7). Reperfusion-induced injury accounts for up to 50% of overall myocardial injury, often with serious adverse events (7). Therefore, preventing AMI is a top priority.

Ulcerative colitis (UC) is a type of inflammatory bowel disease that causes chronic inflammation of the intestinal tract (8). Its pathological mechanism is complex and influenced by multiple factors, such as genetic background, intestinal immune status, and intestinal microbial balance, and the risk of developing colon cancer is 2-3 folds greater than the general population. (9, 10). The age of onset of UC is bimodal, 2-3 years and 50-80 years, respectively (11). UC affects not only the gastrointestinal tract but also the heart, with pericarditis and myocarditis as the most common manifestations (12). Besides, UC patients are at a significantly increased risk for both venous thromboembolism and mesenteric ischemia (12).

Although UC has been reported to be a risk factor for AMI progression (13), the relationship between these two diseases remains controversial. Osterman MT. et al (14) concluded that patients with UC do not have an increased incidence of AMI. However, Choi YJ. et al (15) reported an increased risk of myocardial infarction in patients with UC and a trend toward younger age. UC causes systemic inflammatory responses and promotes hypercoagulation in the body (15). Furthermore, the disruption of the intestinal mucosal barrier leads to the transfer of lipopolysaccharides (LPS) and other endotoxins into the bloodstream, inducing the secretion of pro-inflammatory cytokines, and leading to endothelial disturbances, atherosclerosis, and acute cardiovascular events (16). Gut microecological dysregulation increases plaque vulnerability by affecting lipid metabolism and inflammatory response (17). Azimi T. et al (18) demonstrated that *Clostridium difficile*, *Escherichia coli*, and *Campylobacter* are closely associated with the development of UC. Chronic bacterial infections may contribute to

the formation of vulnerable plaques through enhanced T-cell activation and inflammatory responses (19). Therefore, the cardio-intestinal axis may be an important pathway for UC to promote the development of AMI. Due to inconsistent research findings on the relationship between AMI and UC, there is no standardized medical care for such patients. The present study explores the pathogenesis of AMI and UC, which may provide a new perspective on the clinical management of AMI patients with UC.

MATRIALS AND METHODS

Data Source

Relevant datasets were searched on the gene expression omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) database (20) using keywords “acute myocardial infarction” and “ulcerative colitis”, respectively. The inclusion criteria were: 1) Homo sapiens (Top Organism); 2) expression profiling by an array (Study type); 3) total number of samples in a single microarray dataset >50; 4) single microarray dataset from the same sequencing platform. We downloaded 4 microarray datasets from GEO, including GSE66360-GPL570 (21) and GSE62646-GPL6244 (22) for AMI and GSE87473-GPL13158 (23) and GSE59071-GPL6244 (24) for UC. The GSE66360 and GSE87473 datasets were used for mechanistic analysis of differentially expressed genes (DEGs), and GSE62646 and GSE59071 were used for further screening of hub genes. GSE66360 contained 49 AMI and 50 normal (NL) samples; GSE62646 included 84 AMI and 14 NL samples; GSE87473 contained 106 UC-active and 21 NL samples; GSE59071 included 74 UC-active, 23 UC-inactive, and 11 NL samples. Download datasets from the GEO database via the R GEOquery package and pre-process them with Rstudio (25). Genes were annotated using the gene SYMBOL. Since the data used in this study were obtained from public databases, no local ethics committee approval or informed consent was required.

Identification of DEGs

We analyzed the GSE66360 and GSE87473 datasets separately by using the R limma package (26). Filtering criteria ($|logFC| > 0.585$ and adjusted $P < 0.05$) were set to obtain DEGs between the disease and normal groups, and volcanoes of DEGs were plotted by the R ggplot2 package (27, 28). Among these DEGs, $logFC > 0.585$ or $logFC < -0.585$ indicated that they were upregulated or downregulated in the disease group, respectively(28, 29). We used the R VennDiagram package to plot Venn diagrams of up- and downregulated genes between the datasets GSE66360 and GSE87473, separately, to obtain co-DEGs common to both diseases (30).

Functional Enrichment Analyses of co-DEGs

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were used to evaluate functional annotation of the key module genes. GO terms include biological process, cellular component, and molecular function (31). KEGG as a knowledge base for systematic analysis of gene function, linking genomic information to higher-order functional information (32). We performed enrichment analysis by the R clusterProfiler package (33).

PPI Network Construction and Module Analysis

The STRING (https://cn.string-db.org/) database (34) is designed to integrate all known and predicted associations between proteins. The co-DEGs were input into the STRING database, "Homo sapiens" was selected, the minimum required interaction score was set to ≥0.4, and the free nodes were hidden. The downloaded results were input into Cytoscape software in a tab-separated values (TSV) format for further analysis (35). The key modules were obtained using the MCODE plugin in Cytoscape with default settings. Then, enrichment analysis was performed on the module genes.

Screening and Analysis of Hub Genes

The cytoHubba plugin in Cytoscape was used to filter hub genes (36). Here, we used four algorithms (degree, closeness, EPC, and MCC) and took the genes of the first 20 intersections of these four algorithms to further analyze. The co-expression network of these hub genes were constructed via the GeneMANIA (http://genemania.org/) (37) database, setting the species to human.

Validation of Hub Genes Expression

We further validated hub gene expression in GSE62646 and GSE59071 datasets, setting P-value < 0.05 to be considered significantly different.

Prediction and Verification of TFs

The TRRUST (https://www.grnpedia.org/trrust) database (38) was used to predict transcriptional regulatory networks. Setting the species as human, the co-hub genes that are stably expressed in the datasets GSE66360, GSE87473, GSE62646 and GSE59071 were imported into the TRRUST database to obtain the associated transcription factors (TFs). Transcription factor regulatory networks were constructed by Cytoscape. Subsequently, the expression of these TFs was further validated by the datasets GSE66360 and GSE87473.

RESULTS

Identification of DEGs

Figure 1 shows the diagram of the study design and workflow. After normalization of microarray data, 670 upregulated and 405 downregulated DEGs in GSE66360 and 1323 upregulated and 1138 downregulated DEGs in GSE87473 were identified (**Figure 2A, B**). The upregulated and downregulated DEGs were intersected separately to identify co-DEGs for the AMI and UC, of which 233 co-DEGs were upregulated and 34 were downregulated (**Figure 2C, D**).

Functional Enrichment Analyses of co-DEGs

Functional enrichment analyses were performed for 267 co-DEGs (**Figure 3A, B**). GO enrichment analysis emphasized the following biological processes such as response to lipopolysaccharide, response to molecule of bacterial origin, positive regulation of cytokine production, and leukocyte migration (**Figure 3A**). KEGG enrichment analysis emphasized the importance of osteoclast differentiation, lipid and atherosclerosis, NF-kappa B, TNF and IL-17 signaling pathways (**Figure 3B**, **Table 1**). Taken together, these results suggest that inflammation and immune response are common core mechanisms of UC and AMI.

PPI Network Construction and Module Analysis

PPI network analysis of co-DEGs was performed using the STRING database (**Figure 3C**). The results were imported into Cytoscape in a TSV format to construct a PPI network. The PPI network comprised 205 nodes and 1782 edges (**Figure 3D**). The more connections between nodes and the higher the relevance, the higher the node's ranking in the PPI network. (**Figure 3C, D**). In addition, five tightly linked gene modules were screened via the MCODE plugin in Cytoscape (**Figure 4A-E**). Furthermore, modular genes were integrated, and GO and KEGG analyses were performed (**Figure 4F, G**). GO enrichment analysis showed that modular genes were mainly enriched in biological processes such as response to molecule of bacterial origin, response to lipopolysaccharide, and leukocyte migration (**Figure 4F**). KEGG enrichment analysis revealed that modular genes were mainly involved in osteoclast differentiation, lipid and atherosclerosis, NF-κB, TNF, and IL-17 signaling pathways (**Figure 4G**). Overall, we found that AMI and UC had many common pathogenic mechanisms, which may be mediated by specific hub genes.

Screening and Analysis Hub Genes

Top 20 genes were screened in the cytoHubba plugin with the degree, closeness, EPC, and MCC algorithms, respectively. (**Table 2**). The R ggplot2 package was used to plot the venn diagram to identify hub genes. (**Figure 5A**). Eleven hub genes were screened, including TNF, IL1B, TLR2, CXCL8, STAT3, MMP9, ITGAX, CCL4, CSF1R, ICAM1, and CXCL1 **(Table 3)**. The GeneMANIA database was utilized to structure hub gene co-expression networks (37). Co-expression network analysis showed complicated PPI networks with co-expression (72.67%), co-localization (14.25%), physical interactions (5.40%), pathway (2.98%), shared protein domains (2.47%), predicted (1.86%), and genetic interactions (0.37%) (**Figure 5B**). GO analysis revealed the key association of hub genes with biological processes, such as leukocyte migration, cellular response to lipopolysaccharide, cellular response to molecule of bacterial origin, cytokine-mediated signaling pathway, and cytokine receptor binding **(Figure 6A)**. These results emphasize the importance of lipopolysaccharides and cytokines in both AMI and UC. In addition, KEGG results suggested the hub genes involved notably in lipid and atherosclerosis, rheumatoid arthritis, AGE-RAGE signaling pathway in diabetic complications，NF-kappa B，IL-17，and toll-like receptor signaling pathways **(Figure 6B)**.

Validation of Hub Genes Expression

We additionally selected two datasets including AMI and UC, respectively, and validated the reliability of the 11 hub genes. In the dataset GSE62646, 7 hub genes were significantly differentially expressed in the AMI versus

normal group, including TNF, STAT3, CCL1, ITGAX, CSF1R, ICAM1, and CCL4 **(Figure 7)**. Interestingly, CCL4 was downregulated in AMI, contrary to the previous expression trend, which may be due to insufficient sample size, sequencing technology, sample variation, etc. The remaining 6 hub genes with significant differences were all significantly upregulated in the AMI group consistent with the previous expression trend. In the GSE59071 dataset, all 11 hub genes were significantly upregulated in the UC-active group compared with the normal group **(Figure 8)**. We defined the 6 hub genes that were stably upregulated in all datasets as co-hub genes, including TNF, STAT3, ITGAX, CSF1R, ICAM1, and CCL1.

Prediction and Verification of TFs

Using the TRRUST database, 11 TFs that may regulate the expression of these co-hub genes were identified **(Figure 9** and **Table 4)**. The reliability of the 11 TFs was verified in GSE66360 and GSE87473 datasets. In GSE66360, 8 TFs significantly differed between AMI and normal groups **(Figure 10)**. Six TFs (SPI1, RELA, NFKB1, JUN, CEBPD, and CEBPA) were upregulated and 2 (HDAC1 and STAT1) were downregulated in the AMI group compared with normal groups. In GSE87473, 6 TFs significantly differed between UC-active and normal groups **(Figure 11)**. Upregulated 5 TFs (STAT1, SPI1, RELA, NFKB1, CEBPD) and downregulated 1 TF (CEBPA) in the UC-active group compared to the normal group. Notably, CEBPA and STAT1 were expressed in AMI and UC in opposite trends, perhaps due to factors such as disease progression, cycle, tissue, and sample differences. SPI1, RELA, NFKB1, and CEBPD were stably upregulated in both AMI and UC-active. These TFs may be involved in disease progression through the regulation of TNF, STAT3, ITGAX, ICAM1, and CCL1.

DISCUSSION

UC belongs to inflammatory bowel disease, an immune-related chronic inflammatory disease of the intestine (8). Particularly, UC-active not only aggravates the systemic inflammatory response but also contributes to the hypercoagulable state of the body (15). AMI is myocardial necrosis caused by coronary artery acute and persistent ischaemia and hypoxia (4). Atherosclerotic plaque rupture is the most common cause of AMI (39). In addition to accelerating the progression of atherosclerosis, UC can also lead to the formation of vulnerable plaques by affecting intestinal microecology (19). UC patients have significantly higher thrombotic events and cardiovascular mortality (40). Kristensen SL. et al (41) similarly concluded that UC contributes to an increased risk of AMI, stroke, and cardiovascular death, especially in UC-active, with a further increase in the incidence of these adverse events. In addition, Ha C. et al (42) suggested that female UC patients are more likely to develop AMI than their male counterparts. However, Sinh P. et al (43) found that UC did not increase mortality in patients with AMI. Currently, there is no consensus on the relationship between AMI and UC remains controversial. The present study explored the pathogenesis of AMI and UC, which may provide a new perspective for the clinical management of AMI patients with UC. In addition, it provides novel ideas for further research on the molecular mechanisms of AMI combined with UC.

We identified 267 co-DEGs between the two diseases by bioinformatic methods. Finally, 6 co-hub genes were identified as stably upregulated in both AMI and UC, including TNF, STAT3, CCL1, ITGAX, CSF1R, and ICAM1. The results of enrichment analysis indicated UC may promote AMI through inflammatory and immune responses. GO enrichment analysis highlighted the importance of leukocyte migration, cytokine−mediated signaling pathway, cellular response to lipopolysaccharide, and positive regulation of NF-kappaB transcription factor activity.

Leukocyte migration is an early event of vascular inflammation progression and is closely related to atherosclerosis (44). In addition, chemokines and cytokines have been associated with chronic inflammation (45). Atherosclerosis is a pathological disease characterized by fibroproliferation, chronic inflammation, lipid accumulation, and immune disorders of the vessel wall (46). As atherosclerotic plaques progress to advanced stages, vulnerable plaques rupture, leading to the development of AMI. UC is characterized by a massive accumulation of immune cells, myeloid cells, and lymphocytes in the diseased intestine (47). The continuous activation of these cells, together with the production of inflammatory mediators, promotes UC recurrence, making it difficult to completely cure the disease (47). Therefore, blocking the migration of leukocytes to the intestine is the main strategy used to control the disease and relieve symptoms (47). LPS is a potent inducer of inflammation. Intestinal LPS can bind to LPS-binding protein and celiac particles and enter the body's circulation through the lymphatics, enhancing the inflammatory process (48). In addition, disruption of the intestinal mucosal barrier in UC patients leads to the transfer of LPS and other endotoxins into the bloodstream, inducing a pro-inflammatory cytokine response that leads to endothelial dysfunction, atherosclerosis, and acute cardiovascular events (16). KEGG enrichment analysis highlighted the importance of lipid and atherosclerosis, RA, NF-kappa B, IL-17, and toll-like receptor signaling pathways. Atherosclerosis is an inflammatory disease characterized by lipid accumulation in the arterial wall (49). Lipids and atherosclerosis are undoubtedly the pathological basis for the development of AMI. The pathogenesis of RA is associated with chronic inflammatory and immune system disorders (50). Numerous studies have reported a significantly increased risk of AMI and UC in RA patients (51, 52). NF-κB is involved in immunity, inflammation, cell proliferation, and apoptosis (53). In particular, overactivation of the NF-κB signaling pathway is closely associated with various inflammatory diseases (53).

IL-17 is expressed by different leukocyte subsets, such as gamma-delta (γδ) T cells, natural killer (NK) cells, NK T cells, and neutrophils (54). IL-17 exacerbates the inflammatory response of plaque tissues and promotes thrombosis and vulnerable plaque formation (54). TLRs are clonal transmembrane signaling receptors that link intrinsic and specific immunity (55). They are mainly found in the macrophages, dendritic cells, NK cells, and lymphocytes (56). TLRs are activated by binding to damage-associated molecular patterns, microbial-associated molecular patterns, and pathogen-associated molecular patterns to regulate inflammation and immune response (57).

Eleven TFs that may regulate co-hub gene expression were identified using the TRRUST database. However, the colony-stimulating factor 1 receptor (CSF1R) was outside the transcriptional regulatory network. This may be because some of the data were not included in the TRRUST database. CSF1R is a type I single-transmembrane protein that is abundantly enriched in myeloid cells. CSF1R binds to its endogenous ligands (CSF1 and IL-34) and activates downstream signaling pathways, including PI3K/AKT, JAK/STATs, and MAPK, thereby regulating the proliferation, differentiation, migration, and activation of target immune cells (58). Xiang C et al.(58) ssuggested that targeting CSF-1R is a potential target for regulating inflammatory diseases. Furthermore, through further validation, 4 TFs (SPI1, RELA, NFKB1, and CEBPD) were found to be stably upregulated in AMI compared with UC. They are synergistically engaged in regulating co-hub genes (TNF, STAT3, ITGAX, ICAM1, and CCL1).

TNF acts as a pleiotropic cytokine, which not only directly induces the expression of inflammation-related genes but also induces cell death and indirectly drives inflammation and immune responses (59). Luo X. et al (60) proposed TNF-α as a novel biomarker to predict plaque rupture in patients with ST-elevation myocardial infarction. Thus, inhibition of TNF-α may reduce the inflammatory load of the body and stabilize plaque, especially in patients with multiple inflammatory diseases. TNF-α antagonists are important drugs in the treatment of UC (61). However, long-term inhibition of TNF-α increases the risk of opportunistic infections and skin cancer in patients (62). To overcome such limitations, inhibition of TNF-α downstream inflammation-related pathways is the alternative. TNF activates caspase protease, JNK, and NF-κB signaling pathways, regulating apoptosis,

inflammation, and immune processes (63). Reduced DNA methylation levels in diseased tissue during AMI induces SPI1 overexpression and overactivates the TNF-α/NF-κB signaling pathway, exacerbating myocardial tissue inflammation (64). The NF-κB family has five members, including NFKB1, NFKB2, RELA, c-REL, and RELB (65). These proteins dimerize to form functional NF-κB. Among them, the NFKB1 gene promoter -94insertion/deletion ATTG polymorphism was associated with the risk and severity of acute coronary syndromes (66). Chen YE. et al (67) found that inhibition of the inflammatory pathway associated with v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA) is an effective target for the treatment of UC. In addition, inhibition of the RELA/TNF-α signaling pathway in AMI protects cardiac function through anti-inflammatory effects (68).

CCAAT enhancer binding protein delta (CEBPD) belongs to the CEBP family and is a TF that regulates many biological processes, especially inflammation and immune responses (69, 70). CEBPD can be activated by inflammatory factors such as IL-6, IFN-α, IFN-γ, and IL1B to participate in inflammation and immune regulation (69). CEBPD is considered to be an inflammatory enhancer in aortic endothelial cells and exacerbates tissue damage in concert with TNF-α (71). CEBPD was found to aggravate tissue damage by inducing inflammatory gene expression in liver tissue, lung tissue, and brain glial cells (72). Moreover, CEBPD promotes macrophage polarization toward M1 and exacerbates tissue inflammation (73). Our results showed that CEBPD and TNF were stably upregulated in patients with AMI and UC. Thus, the CEBPD/TNF axis may be a potential mechanism for the treatment of AMI and UC. However, this should be supported by *in vivo* and *in vitro* models.

STAT3 is an important regulator of cell proliferation, differentiation, apoptosis, angiogenesis, inflammation, and immune response (74). STAT proteins are activated by a variety of protein kinases, including Janus kinase, growth factor receptor, non-receptor tyrosine kinase, and G protein-coupled receptor (75). Among them, STAT3 is involved in the process of atherosclerosis through the regulation of endothelial cell function, macrophage polarization, inflammation, and immune response (76). STAT3 has four isoforms with different functions, including STAT3-α, STAT3-β, STAT3-γ, and STAT3-δ (76). STAT3-α-mediated activation of the IL-6/JAK2/STAT3 signaling pathway is predominantly pro-inflammatory (76). Jiang M. et al (77) constructed a UC model in rats and reported anti-inflammatory protective effects via inhibition of the JAK2/STAT3 signaling pathway to reduce IL-1β, IL-6, and TNF-α expression. However, STAT3-β can promote the expression of certain anti-inflammatory genes while inhibiting the synthesis of inflammatory factors (76). Such predominant anti-inflammatory effects may be associated with IL-10-mediated activation of STAT3 (78). Li H. et al (79) ffound that targeting the activation of the IL-10/STAT3 axis could exert cardioprotective effects by modulating the inflammatory response, myocardial fibrosis, and apoptosis. In addition, activation of the IL-10/STAT3 signaling pathway promotes macrophage polarization to the M2 type (80). STAT3 and SPI1 are overexpressed in patients with ankylosing spondylitis and are closely associated with immune system disorders (81). Similarly, our study found that STAT3 and SPI1 were overexpressed in both AMI and UC patients, suggesting that SPI1/STAT3 may be an important pathway leading to AMI and UC; however, further experimental verification is warranted. Overactivation or inactivation of STAT3 can lead to human disease (82). Therefore, how to balance the activation of STAT3 should be further explored.

Integrin alpha-X (ITGAX) is a member of the integrin family and usually acts as a receptor for the extracellular matrix (83). ITGAX is considered a potential therapeutic site for various inflammatory and immune-related diseases, such as periodontitis, atherosclerosis, primary dry syndrome, and IgA nephropathy (84-86). Overexpression of ITGAX has been shown to activate the PI3k/Akt axis and promote angiogenesis in ovarian tumor tissues. However, no relevant animal experiments have been reported for ITGAX in AMI or UC.

The ICAM-1 is a transmembrane glycoprotein that is expressed at low basal levels in immune cells, endothelial cells and epithelial cells (87). ICAM-1 expression is induced by multiple inflammatory cytokines and

has tissue differences. ICAM-1 located in endothelial cells is mainly induced by TNFα or IL-1β, while in intestinal epithelial cells it is induced by IFNγ (88). Freitas IA. et al (89) demonstrated that circulating ICAM-1 level is positively associated with the risk of coronary artery disease and is a potential marker of cardiovascular disease. The ICAM-1 gene polymorphism is closely associated with the development of UC (90). ICAM-1 played a fundamental role in the neutrophil crossing of the endothelial cell layer (90). Yu J. et al(91) found that ICAM-1 accelerates atherosclerosis by promoting leukocyte infiltration. Moreover, Upregulation of ICAM-1 is associated with excessive activation of the RELA/NLRP3 axis and leads to dysfunction of the human umbilical vein endothelium by regulating inflammatory responses and oxidative stress (92). Similarly, the current study found that both RELA and ICAM-1 were stably upregulated in the disease group.

C-C motif chemokine ligand 1 (CCL1) belongs to the CC chemokine family and mediates the immigration of monocytes to regions of inflammation (93). Harpel PC. et al (94) suggested that CCL1 and its receptor CCR8 are closely associated with inflammation and atherosclerosis. CCL1 is upregulated in several immune diseases such as rheumatic heart disease, atopic dermatitis, and psoriasis (95, 96). CCR8 is activated by CCL1 and mediates the recruitment of T helper 2 cells to sites of inflammation (97). It is noteworthy that CCL1 has no significant chemotactic effect on neutrophils (98). Olsen RS. et al (97) demonstrated that elevated circulating CCL1 is strongly associated with prognosis and mortality in colorectal cancer. Currently, studies on CCL1 in AMI or UC are inadequate. In conclusion, our data showed that TNF, STAT3, ITGAX, ICAM1, and CCL1 are important targets for the treatment of patients with both UC and AMI.

Although previous studies have separately explored the hub genes associated with AMI and UC(99, 100). Most current animal studies are limited to a single disease, which is different from the actual clinical coexistence of multiple diseases. Moreover, few studies have explored the common molecular mechanism between them by advanced bioinformatics methods. Our study sought to elucidate the molecular mechanisms of AMI and UC, which may provide a novel insight into the clinical management of patients with these comorbidities. Reducing mortality and improving quality of life in AMI combined with UC by further standardizing clinical management strategies. However, this study has several limitations. First, only significantly differentially expressed genes we mainly analyzed between disease and normal tissues, ignoring certain genes with no significant changes in expression but played an important regulatory role. In addition, we need animal experiments to further reveal the causal relationship between these hub genes and the pathogenesis of the two diseases.

CONCLUSIONS

Overall, we used a bioinformatics approach to study patients with AMI combined with UC. We discovered many pathogenic mechanisms of AMI and UC shared possibly mediated by specified hub genes. Our research offered novel ideas to investigate the molecular mechanism of AMI combined with UC further.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

QS and QW developed a major research plan. CC and RC analyzed data, drew graphs and wrote manuscripts. CC helped collect data and references. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Sidhu RK. Association between Acute Myocardial Infarction and Periodontitis: A Review of the Literature. *J Int Acad Periodontol*. 2016;18:23-33.

2. Cai J-J, Jiang H. Application Potential of Probiotics in Acute Myocardial Infarction. *CVIA*. 2022;7.

3. Liu Y, Feng X, Yang J, et al. Prognostic Significance of HbA1c Level in Asian Patients with Prediabetes and Coronary Artery Disease. *CVIA*. 2022;6:147-60.

4. Gossage JR. Acute myocardial infarction. Reperfusion strategies. *Chest*. 1994;106:1851-66.

5. Soysal P, Arik F, Smith L, et al. Inflammation, Frailty and Cardiovascular Disease. *Adv Exp Med Biol*. 2020;1216:55-64.

6. Rout A, Tantry US, Novakovic M, et al. Targeted pharmacotherapy for ischemia reperfusion injury in acute myocardial infarction. *Expert Opin Pharmacother*. 2020;21:1851-65.

7. Li Y, Li Z, Liu J, et al. miR-190-5p Alleviates Myocardial Ischemia-Reperfusion Injury by

Targeting PHLPP1. *Dis Markers*. 2021;2021:8709298.

8. Du L, Ha C. Epidemiology and Pathogenesis of Ulcerative Colitis. *Gastroenterol Clin North Am*. 2020;49:643-54.

9. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. *Nat Rev Dis Primers*. 2020;6:74.

10. Li W, Zhao T, Wu D, et al. Colorectal Cancer in Ulcerative Colitis: Mechanisms, Surveillance and Chemoprevention. *Curr Oncol*. 2022;29:6091-114.

11. Gajendran M, Loganathan P, Jimenez G, et al. A comprehensive review and update on ulcerative colitis(). *Dis Mon*. 2019;65:100851.

12. Papadimitraki ED, Ahamed M, Bunce NH. Acute myocardial infarction complicating active ulcerative colitis: a case report. *Case Rep Cardiol*. 2011;2011:876896.

13. Nuñez P, García Mateo S, Quera R, et al. Inflammatory bowel disease and the risk of cardiovascular diseases. *Gastroenterol Hepatol*. 2021;44:236-42.

14. Osterman MT, Yang YX, Brensinger C, et al. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. *Clin Gastroenterol Hepatol*. 2011;9:875-80.

15. Choi YJ, Lee DH, Shin DW, et al. Patients with inflammatory bowel disease have an increased risk of myocardial infarction: a nationwide study. *Aliment Pharmacol Ther*. 2019;50:769-79.

16. Jucan AE, Gavrilescu O, Dranga M, et al. Ischemic Heart Disease in Patients with Inflammatory Bowel Disease: Risk Factors, Mechanisms and Prevention. *Life (Basel)*. 2022;12.

17. Jonsson AL, Bäckhed F. Role of gut microbiota in atherosclerosis. *Nat Rev Cardiol*. 2017;14:79-87.

18. Azimi T, Nasiri MJ, Chirani AS, et al. The role of bacteria in the inflammatory bowel disease development: a narrative review. *Apmis*. 2018;126:275-83.

19. Muhlestein JB. Bacterial infections and atherosclerosis. *J Investig Med*. 1998;46:396-402.

20. Edgar R, Domrachev M, Lash AE. Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res*. 2002;30:207-10.

21. Muse ED, Kramer ER, Wang H, et al. A Whole Blood Molecular Signature for Acute Myocardial Infarction. *Sci Rep*. 2017;7:12268.

22. Kiliszek M, Burzynska B, Michalak M, et al. Altered gene expression pattern in peripheral blood mononuclear cells in patients with acute myocardial infarction. *PLoS One*. 2012;7:e50054.

23. Li K, Strauss R, Ouahed J, et al. Molecular Comparison of Adult and Pediatric Ulcerative Colitis Indicates Broad Similarity of Molecular Pathways in Disease Tissue. *J Pediatr Gastroenterol Nutr*. 2018;67:45-52.

24. Vanhove W, Peeters PM, Staelens D, et al. Strong Upregulation of AIM2 and IFI16 Inflammasomes in the Mucosa of Patients with Active Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2015;21:2673-82.

25. Davis S, Meltzer PS. GEOquery: a bridge between the Gene Expression Omnibus (GEO) and BioConductor. *Bioinformatics*. 2007;23:1846-7.

26. Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for

RNA-sequencing and microarray studies. *Nucleic Acids Res*. 2015;43:e47.

27. Klaus, Galensa. ggplot2: elegant graphics for data analysis (2nd ed.). *Computing Reviews*. 2017.

28. Liu J, Li J, Li H, et al. A comprehensive analysis of candidate genes and pathways in pancreatic cancer. *Tumour Biol*. 2015;36:1849-57.

29. Huang J, Liu L, Qin L, et al. Weighted Gene Coexpression Network Analysis Uncovers Critical Genes and Pathways for Multiple Brain Regions in Parkinson's Disease. *Biomed Res Int*. 2021;2021:6616434.

30. Chen H, Boutros PC. VennDiagram: a package for the generation of highly-customizable Venn and Euler diagrams in R. *BMC Bioinformatics*. 2011;12:35.

31. Harris MA, Clark J, Ireland A, et al. The Gene Ontology (GO) database and informatics resource. *Nucleic Acids Res*. 2004;32:D258-61.

32. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. 2000;28:27-30.

33. Wu T, Hu E, Xu S, et al. clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *Innovation (Camb)*. 2021;2:100141.

34. Szklarczyk D, Gable AL, Nastou KC, et al. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Res*. 2021;49:D605-d12.

35. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res*. 2003;13:2498-504.

36. Chin CH, Chen SH, Wu HH, et al. cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC Syst Biol*. 2014;8 Suppl 4:S11.

37. Mostafavi S, Ray D, Warde-Farley D, et al. GeneMANIA: a real-time multiple association network integration algorithm for predicting gene function. *Genome Biol*. 2008;9 Suppl 1:S4.

38. Han H, Shim H, Shin D, et al. TRRUST: a reference database of human transcriptional regulatory interactions. *Sci Rep*. 2015;5:11432.

39. Falk E, Nakano M, Bentzon JF, et al. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34:719-28.

40. Olivera PA, Zuily S, Kotze PG, et al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2021;18:857-73.

41. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. *PLoS One*. 2013;8:e56944.

42. Ha C, Magowan S, Accortt NA, et al. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol*. 2009;104:1445-51.

43. Sinh P, Tabibian JH, Biyani PS, et al. Inflammatory Bowel Disease Does Not Impact Mortality but Increases Length of Hospitalization in Patients with Acute Myocardial Infarction. *Dig Dis Sci*. 2021;66:4169-77.

44. Matoba K. Monitoring Leukocyte Migration During Atherosclerosis In Vivo. *Methods Mol Biol*. 2022;2419:475-9.

45. Bonaventura A, Montecucco F, Dallegri F, et al. Novel findings in neutrophil biology and their impact on cardiovascular disease. *Cardiovasc Res*. 2019;115:1266-85.

46. Xu S, Kamato D, Little PJ, et al. Targeting epigenetics and non-coding RNAs in atherosclerosis: from mechanisms to therapeutics. *Pharmacol Ther*. 2019;196:15-43.

47. Veny M, Fernández-Clotet A, Panés J. Controlling leukocyte trafficking in IBD. *Pharmacol Res*. 2020;159:105050.

48. Wang H, Reddy ST, Fogelman AM. The role of gut-derived oxidized lipids and bacterial lipopolysaccharide in systemic inflammation and atherosclerosis. *Curr Opin Lipidol*. 2022;33:277-82.

49. Akadam-Teker AB, Teker E, Daglar-Aday A, et al. Interactive effects of interferon-gamma functional single nucleotid polymorphism (+874 T/A) with cardiovascular risk factors in coronary heart disease and early myocardial infarction risk. *Mol Biol Rep*. 2020;47:8397-405.

50. Giannini D, Antonucci M, Petrelli F, et al. One year in review 2020: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol*. 2020;38:387-97.

51. Lee JK, Kim H, Hong JB, et al. Association of acute myocardial infarction with seropositive rheumatoid arthritis in Korea: A nationwide longitudinal cohort study. *J Clin Neurosci*. 2020;78:97-101.

52. Meisinger C, Freuer D. Rheumatoid arthritis and inflammatory bowel disease: A bidirectional two-sample Mendelian randomization study. *Semin Arthritis Rheum*. 2022;55:151992.

53. Hariharan A, Hakeem AR, Radhakrishnan S, et al. The Role and Therapeutic Potential

of NF-kappa-B Pathway in Severe COVID-19 Patients. *Inflammopharmacology*. 2021;29:91-100.

54. Akhavanpoor M, Akhavanpoor H, Gleissner CA, et al. The Two Faces of Interleukin-17A in Atherosclerosis. *Curr Drug Targets*. 2017;18:863-73.

55. Fitzgerald KA, Kagan JC. Toll-like Receptors and the Control of Immunity. *Cell*. 2020;180:1044-66.

56. Jaén RI, Val-Blasco A, Prieto P, et al. Innate Immune Receptors, Key Actors in Cardiovascular Diseases. *JACC Basic Transl Sci*. 2020;5:735-49.

57. Behzadi P, García-Perdomo HA, Karpiński TM. Toll-Like Receptors: General Molecular and Structural Biology. *J Immunol Res*. 2021;2021:9914854.

58. Xiang C, Li H, Tang W. Targeting CSF-1R represents an effective strategy in modulating inflammatory diseases. *Pharmacol Res*. 2022;187:106566.

59. van Loo G, Bertrand MJM. Death by TNF: a road to inflammation. *Nat Rev Immunol*. 2022:1-15.

60. Luo X, Zhao C, Wang S, et al. TNF-α is a Novel Biomarker for Predicting Plaque Rupture in Patients with ST-Segment Elevation Myocardial Infarction. *J Inflamm Res*. 2022;15:1889-98.

61. Vulliemoz M, Brand S, Juillerat P, et al. TNF-Alpha Blockers in Inflammatory Bowel Diseases: Practical Recommendations and a User's Guide: An Update. *Digestion*. 2020;101 Suppl 1:16-26.

62. Gissler MC, Stachon P, Wolf D, et al. The Role of Tumor Necrosis Factor Associated Factors (TRAFs) in Vascular Inflammation and Atherosclerosis. *Front Cardiovasc Med*.

2022;9:826630.

63. Aggarwal BB, Shishodia S, Takada Y, et al. TNF blockade: an inflammatory issue. *Ernst Schering Res Found Workshop*. 2006:161-86.

64. Liu Z, Huang S. Upregulation of SPI1 during myocardial infarction aggravates cardiac tissue injury and disease progression through activation of the TLR4/NFκB axis. *Am J Transl Res*. 2022;14:2709-27.

65. Zhang L, Zhang T, Yang Z, et al. Expression of nuclear factor kappa B in ovine maternal inguinal lymph nodes during early pregnancy. *BMC Vet Res*. 2022;18:266.

66. Jin SY, Luo JY, Li XM, et al. NFKB1 gene rs28362491 polymorphism is associated with the susceptibility of acute coronary syndrome. *Biosci Rep*. 2019;39.

67. Chen YE, Xu SJ, Lu YY, et al. Asperuloside suppressing oxidative stress and inflammation in DSS-induced chronic colitis and RAW 264.7 macrophages via Nrf2/HO-1 and NF-κB pathways. *Chem Biol Interact*. 2021;344:109512.

68. Wang J, Yuan J, Cai Y, et al. [Effects of electroacupuncture on inflammatory response of cardiac muscle tissue in mice with acute myocardial ischemia]. *Zhongguo Zhen Jiu*. 2018;38:5133-8.

69. Liu J, Gao H, Li C, et al. Expression and regulatory characteristics of peripheral blood immune cells in primary Sjögren's syndrome patients using single-cell transcriptomic. *iScience*. 2022;25:105509.

70. Wang JM, Ko CY, Chen LC, et al. Functional role of NF-IL6beta and its sumoylation and acetylation modifications in promoter activation of cyclooxygenase 2 gene. *Nucleic Acids Res*. 2006;34:217-31.

71. Wang Q, Ozer HG, Wang B, et al. A hierarchical and collaborative BRD4/CEBPD partnership governs vascular smooth muscle cell inflammation. *Mol Ther Methods Clin Dev*. 2021;21:54-66.

72. Rustenhoven J, Scotter EL, Jansson D, et al. An anti-inflammatory role for C/EBPδ in human brain pericytes. *Sci Rep*. 2015;5:12132.

73. Balamurugan K, Sterneck E. The many faces of C/EBPδ and their relevance for inflammation and cancer. *Int J Biol Sci*. 2013;9:917-33.

74. Lee H, Jeong AJ, Ye SK. Highlighted STAT3 as a potential drug target for cancer therapy. *BMB Rep*. 2019;52:415-23.

75. Lim CP, Fu XY. Multiple roles of STAT3 in cardiovascular inflammatory responses. *Prog Mol Biol Transl Sci*. 2012;106:63-73.

76. Chen Q, Lv J, Yang W, et al. Targeted inhibition of STAT3 as a potential treatment strategy for atherosclerosis. *Theranostics*. 2019;9:6424-42.

77. Jiang M, Zhong G, Zhu Y, et al. Retardant effect of dihydroartemisinin on ulcerative colitis in a JAK2/STAT3-dependent manner. *Acta Biochim Biophys Sin (Shanghai)*. 2021;53:1113-23.

78. Schmetterer KG, Pickl WF. The IL-10/STAT3 axis: Contributions to immune tolerance by thymus and peripherally derived regulatory T-cells. *Eur J Immunol*. 2017;47:1256-65.

79. Li H, Gong ZJ, He Y, et al. YQWY Decoction Improves Myocardial Remodeling via Activating the IL-10/Stat3 Signaling Pathway. *Evid Based Complement Alternat Med*. 2020;2020:7532892.

80. Pang QM, Yang R, Zhang M, et al. Peripheral Blood-Derived Mesenchymal Stem Cells

Modulate Macrophage Plasticity through the IL-10/STAT3 Pathway. *Stem Cells Int*. 2022;2022:5181241.

81. Liang T, Chen J, Xu G, et al. STAT3 and SPI1, may lead to the immune system dysregulation and heterotopic ossification in ankylosing spondylitis. *BMC Immunol*. 2022;23:3.

82. Hillmer EJ, Zhang H, Li HS, et al. STAT3 signaling in immunity. *Cytokine Growth Factor Rev*. 2016;31:1-15.

83. Wang J, Yang L, Liang F, et al. Integrin alpha x stimulates cancer angiogenesis through PI3K/Akt signaling-mediated VEGFR2/VEGF-A overexpression in blood vessel endothelial cells. *J Cell Biochem*. 2019;120:1807-18.

84. Zeng Y, Cao S, Chen M. Integrated analysis and exploration of potential shared gene signatures between carotid atherosclerosis and periodontitis. *BMC Med Genomics*. 2022;15:227.

85. Verstappen GM, Ice JA, Bootsma H, et al. Gene expression profiling of epithelium-associated FcRL4(+) B cells in primary Sjögren's syndrome reveals a pathogenic signature. *J Autoimmun*. 2020;109:102439.

86. Cox SN, Chiurlia S, Divella C, et al. Formalin-fixed paraffin-embedded renal biopsy tissues: an underexploited biospecimen resource for gene expression profiling in IgA nephropathy. *Sci Rep*. 2020;10:15164.

87. Mukhopadhyay S, Malik P, Arora SK, et al. Intercellular adhesion molecule-1 as a drug target in asthma and rhinitis. *Respirology*. 2014;19:508-13.

88. Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in

inflammation, injury resolution, and tumorigenesis. *J Leukoc Biol*. 2020;108:787-99.

89. Freitas IA, Lima NA, Silva GBD, Jr., et al. Novel biomarkers in the prognosis of patients with atherosclerotic coronary artery disease. *Rev Port Cardiol (Engl Ed)*. 2020;39:667-72.

90. Vainer B. Intercellular adhesion molecule-1 (ICAM-1) in ulcerative colitis: presence, visualization, and significance. *Inflamm Res*. 2005;54:313-27.

91. Yu J, Liu Y, Peng W, et al. Serum VCAM-1 and ICAM-1 measurement assists for MACE risk estimation in ST-segment elevation myocardial infarction patients. *J Clin Lab Anal*. 2022;36:e24685.

92. Hu R, Wang MQ, Ni SH, et al. Salidroside ameliorates endothelial inflammation and oxidative stress by regulating the AMPK/NF-κB/NLRP3 signaling pathway in AGEs-induced HUVECs. *Eur J Pharmacol*. 2020;867:172797.

93. Zhao Y, Bu H, Hong K, et al. Genetic polymorphisms of CCL1 rs2072069 G/A and TLR2 rs3804099 T/C in pulmonary or meningeal tuberculosis patients. *Int J Clin Exp Pathol*. 2015;8:12608-20.

94. Harpel PC, Haque NS. Chemokine receptor-8: potential role in atherogenesis. *Isr Med Assoc J*. 2002;4:1025-7.

95. Guilherme L, Kalil J. Rheumatic Heart Disease: Molecules Involved in Valve Tissue Inflammation Leading to the Autoimmune Process and Anti-S. pyogenes Vaccine. *Front Immunol*. 2013;4:352.

96. Kim HO, Cho SI, Chung BY, et al. Expression of CCL1 and CCL18 in atopic dermatitis and psoriasis. *Clin Exp Dermatol*. 2012;37:521-6.

97. Olsen RS, Nijm J, Andersson RE, et al. Circulating inflammatory factors associated with worse long-term prognosis in colorectal cancer. *World J Gastroenterol*. 2017;23:6212-9.

98. Miller MD, Krangel MS. The human cytokine I-309 is a monocyte chemoattractant. *Proc Natl Acad Sci U S A*. 1992;89:2950-4.

99. Xue J, Chen L, Cheng H, et al. The Identification and Validation of Hub Genes Associated with Acute Myocardial Infarction Using Weighted Gene Co-Expression Network Analysis. *J Cardiovasc Dev Dis*. 2022;9.

100. Xu M, Kong Y, Chen N, et al. Identification of Immune-Related Gene Signature and Prediction of CeRNA Network in Active Ulcerative Colitis. *Front Immunol*. 2022;13:855645.

https://doi.org/10.55415/deep-2023-0035.v1

Figure

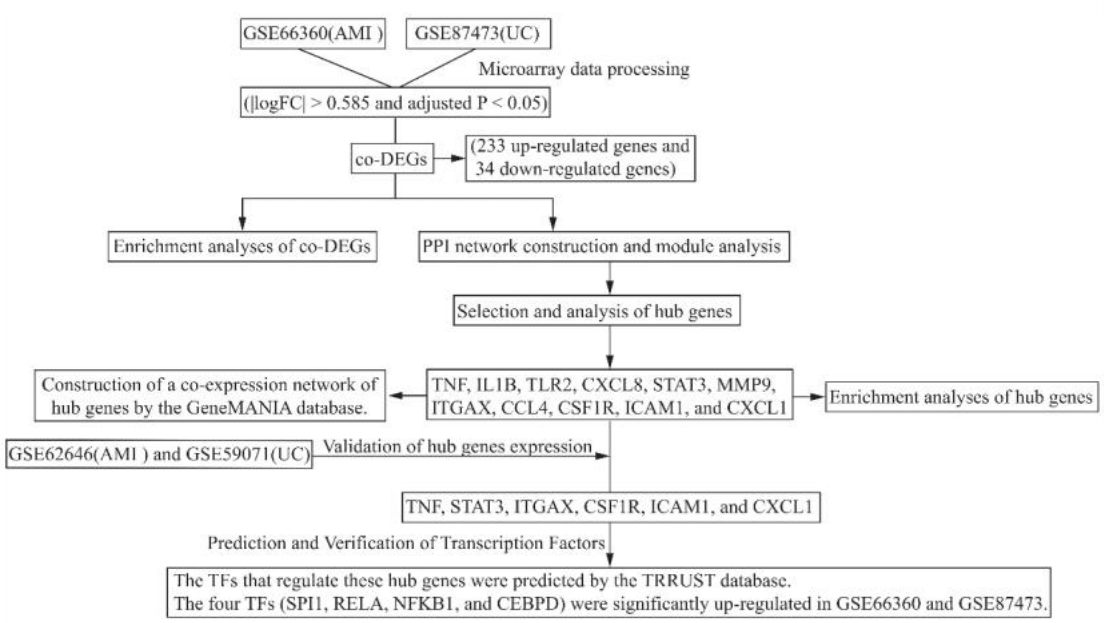

Figure 1 Schematic diagram of the study design and workflow.

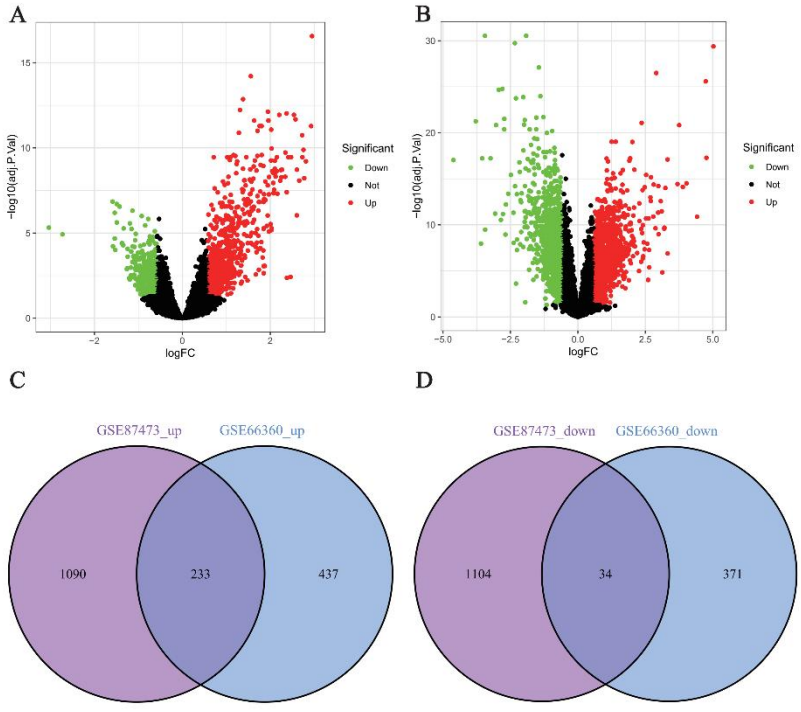

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Figure 2 Volcano diagram and Venn diagram. Volcano map of DEGs. **(A)** The volcano map of GSE66360. **(B)** The volcano map of GSE87473. Red indicates upregulated genes and green indicates downregulated genes. Venn diagram of **(C)** upregulated and **(D)** downregulated genes in GSE66360 and GSE87473 datasets.

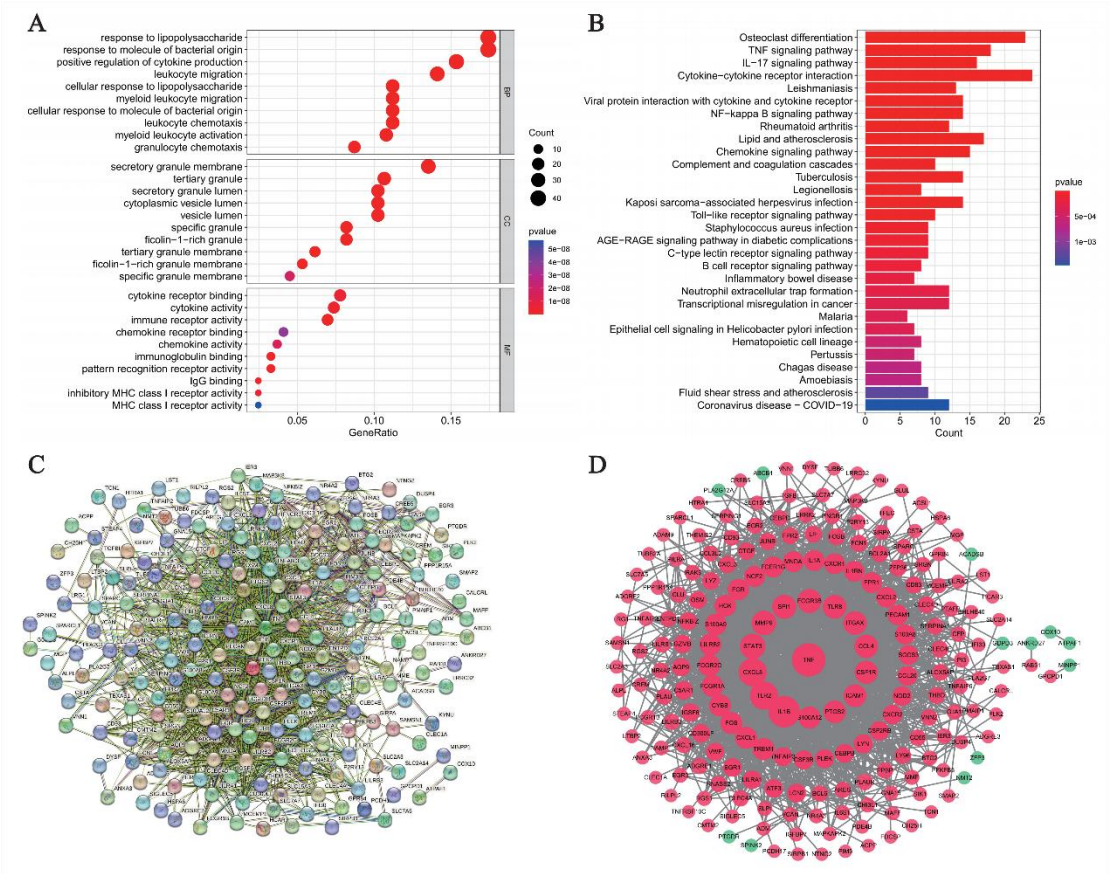

Figure 3 Functional enrichment and PPI network analyses of co-DEGs. **(A)** GO and **(B)** KEGG. **(C)** STRING. **(D)** Cytoscape. Red indicates upregulated genes and green indicates downregulated genes.

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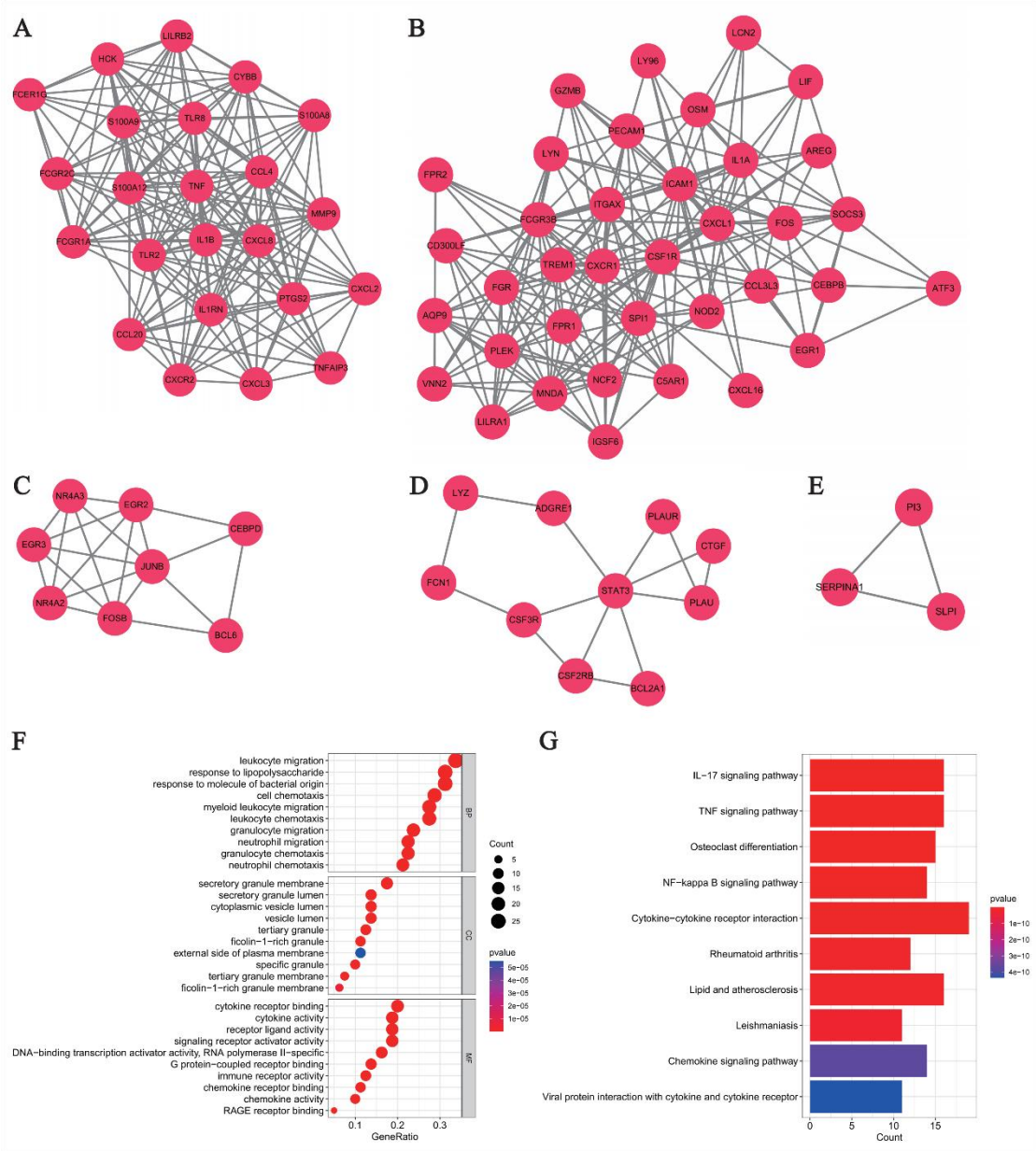

Figure 4 Significant gene module and enrichment analysis of the modular genes. **(A-E)** Five significant gene clustering modules. Functional enrichment analyses of the modular genes. **(F)** GO and **(G)** KEGG.

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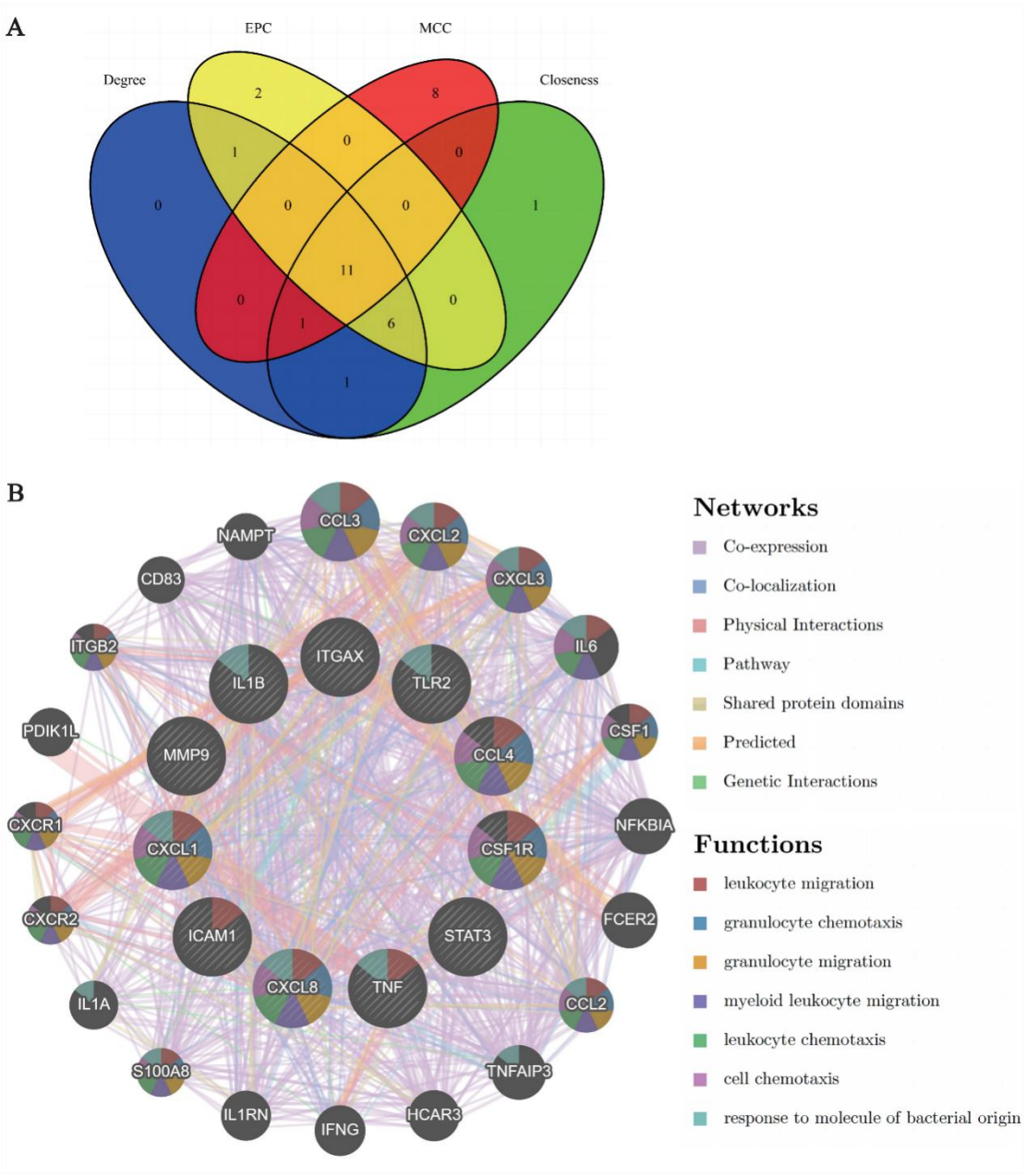

Figure 5 Venn diagram and co-expression network of hub genes. **(A)** The Venn diagram showed that four algorithms have screened out 11 overlapping hub genes. **(B)** Co-expression network of hub genes.

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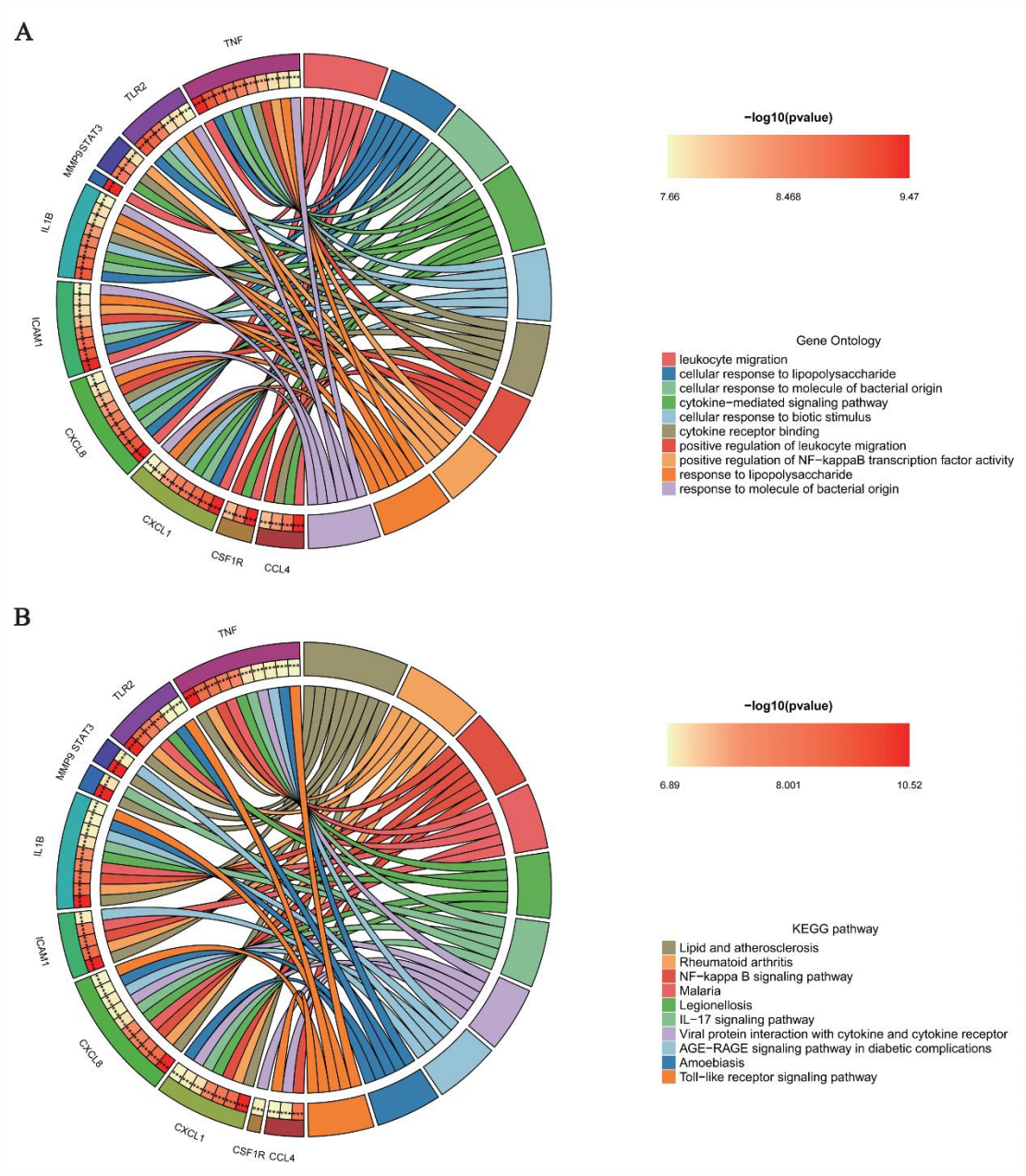

Figure 6 Functional enrichment analyses of hub genes. **(A)** GO and **(B)** KEGG. The left half-circle represents hub genes that are significantly enriched in different terms. Different colors on the right side represent different terms. *** $p<0.001$.

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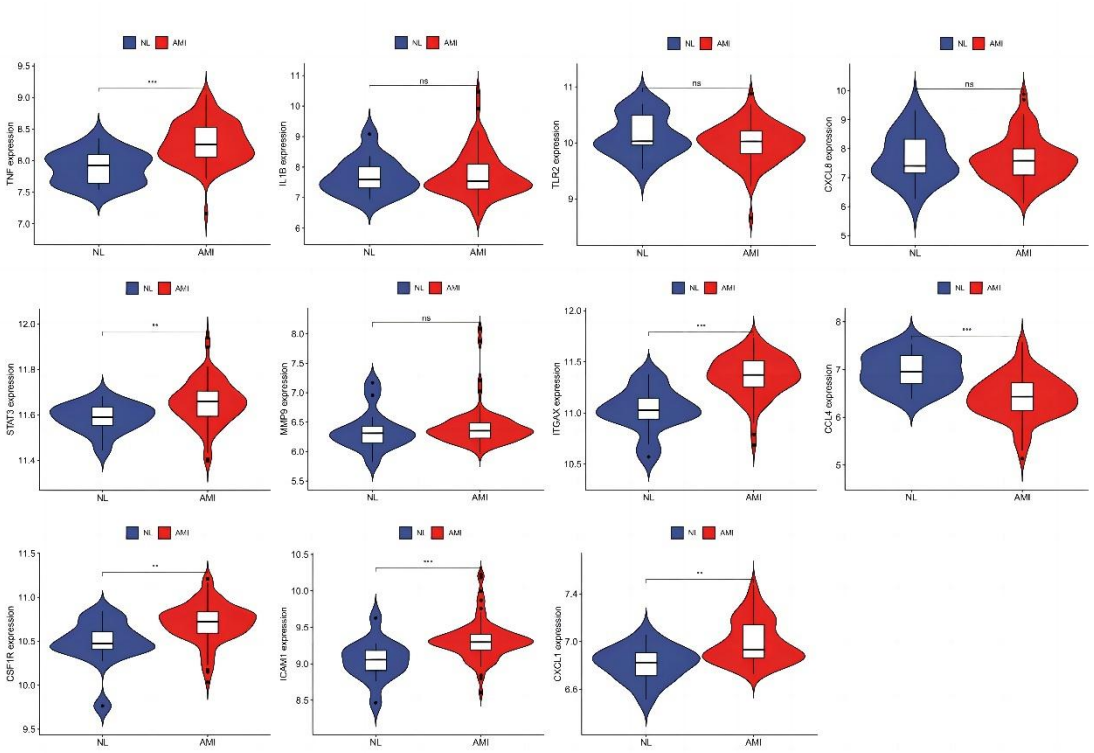

Figure 7 Expression of 11 hub genes in GSE62646. AMI, acute myocardial infarction; NL, normal. *p<0.05; ** p<0.05 and ≥0.001; *** p<0.001.

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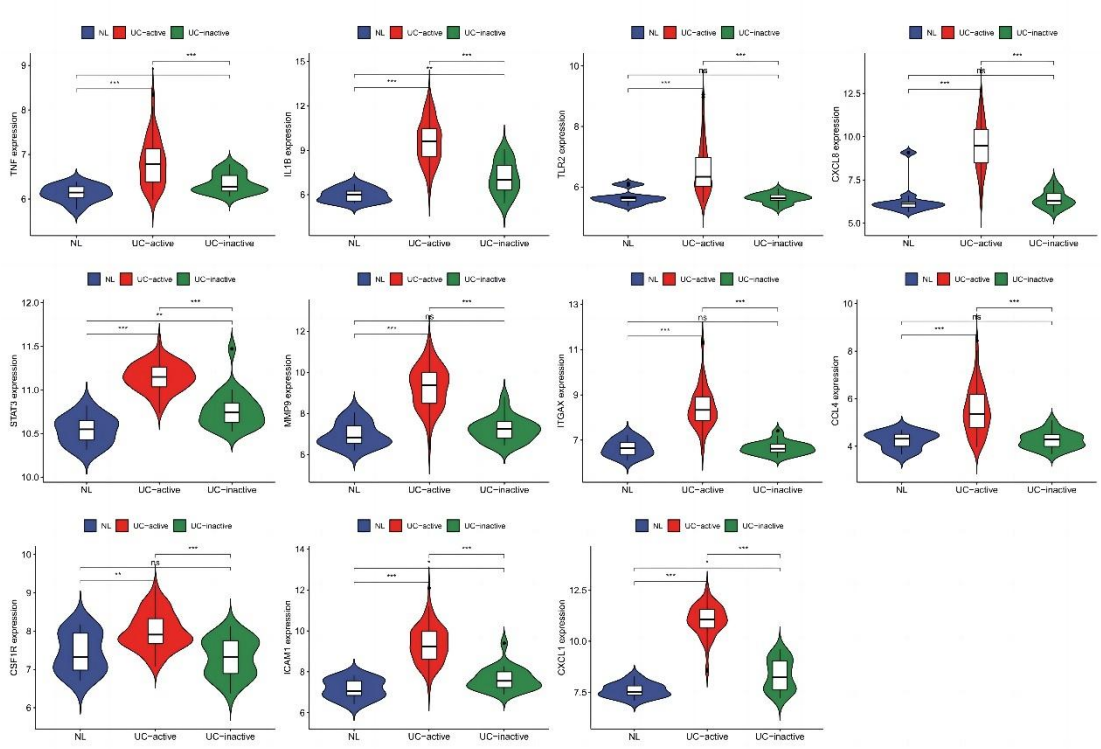

Figure 8 Expression of 11 hub genes in GSE59071. UC, ulcerative colitis; NL, normal. *p<0.05; ** p<0.05 and ≥0.001; *** p<0.001.

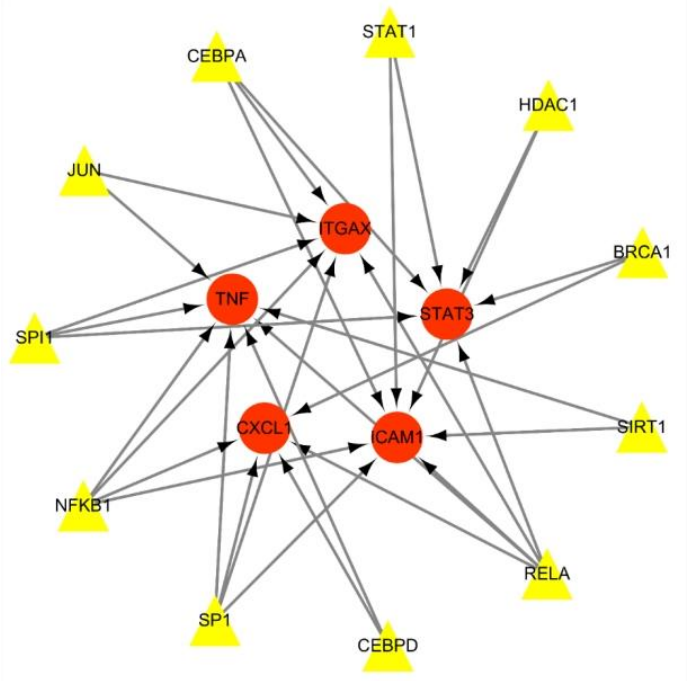

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Figure 9 Transcriptional regulatory network. Yellow represents transcription factors and red represents genes.

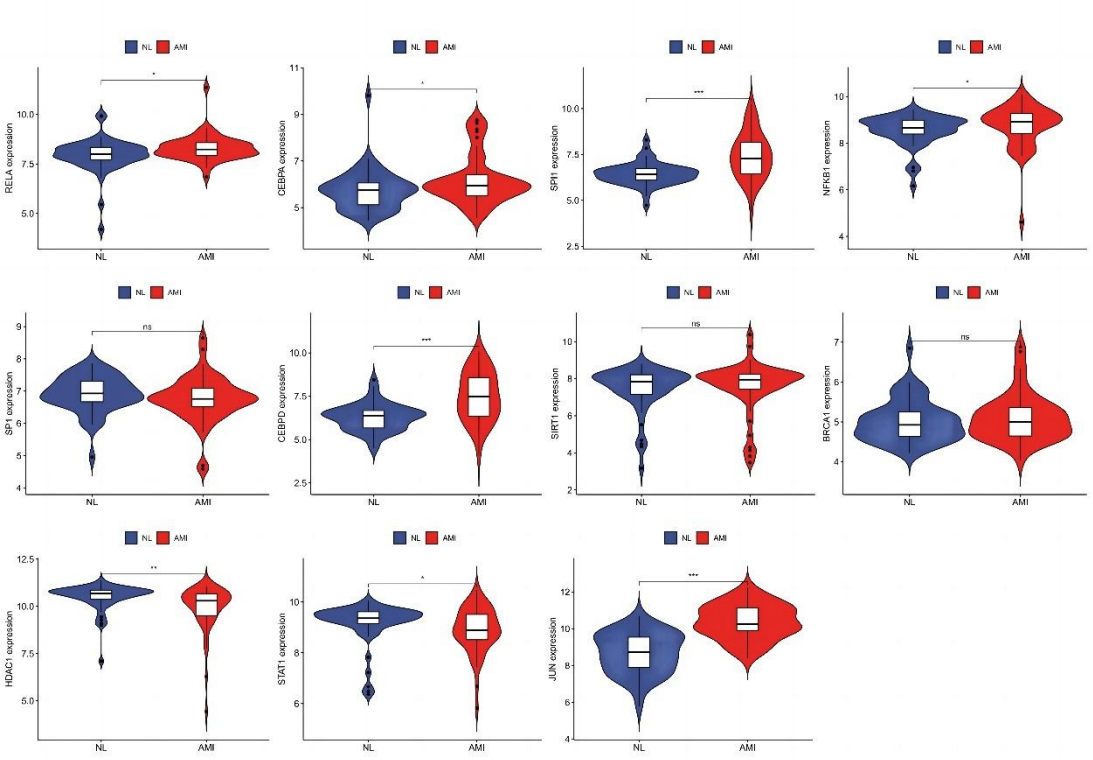

Figure 10 Expression of 11 TFs in GSE66360. AMI, acute myocardial infarction; NL, normal.

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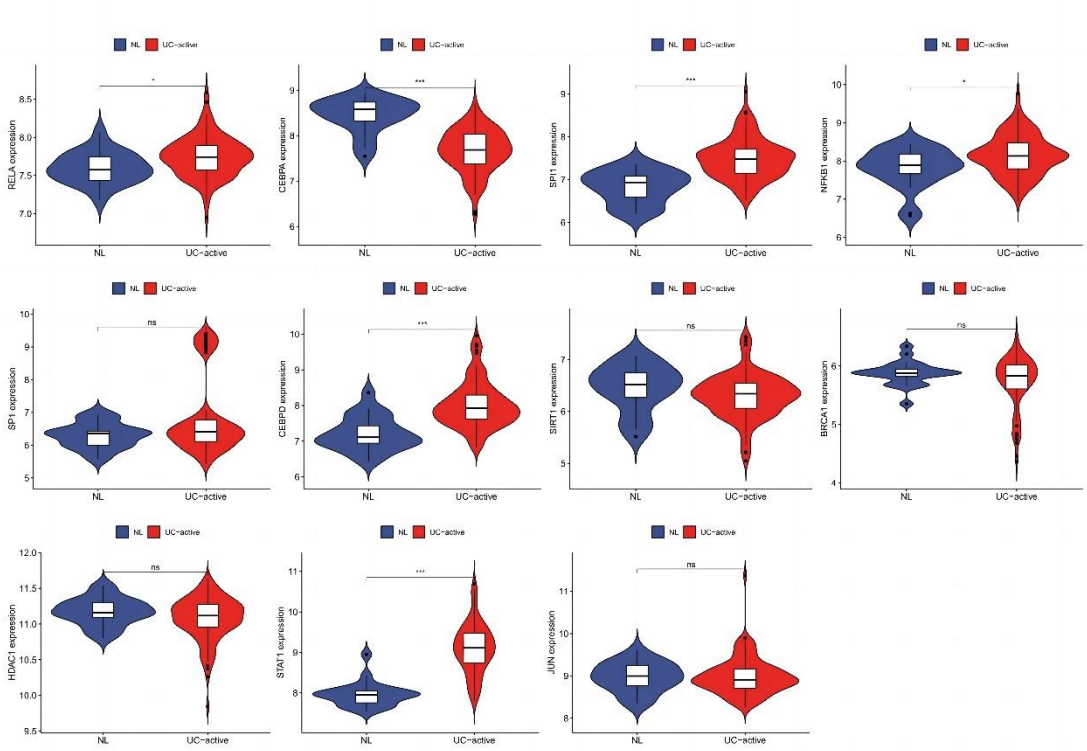

Figure 11 Expression of 11 TFs in GSE87473. UC, ulcerative colitis; NL, normal.

Table

Table 1 Top 30 enriched KEGG pathways.

ID	Description	P-value	GeneID
hsa04380	Osteoclast differentiation	1.15E-16	*IL1B/SOCS3/LILRB2/FOS/FCGR2A/FOSB/JUNB/SIRI*
hsa04668	TNF signaling pathway	2.21E-12	*MAP3K8/IL1B/CCL20/SOCS3/CXCL2/ICAM1/FOS/JU*
hsa04657	IL-17 signaling pathway	1.60E-11	*IL1B/CCL20/S100A9/CXCL2/FOS/FOSB/MMP9/CXCI*
hsa04060	Cytokine-cytokine receptor interaction	1.15E-09	*IL1B/CCL20/IL1RN/CCL4/CXCL2/CCL3L3/IL6ST/CSI*
hsa05140	Leishmaniasis	1.56E-09	*IL1B/TLR2/FOS/FCGR2A/FCGR2C/IFNGR1/FCGR3E*
hsa04061	Viral protein interaction with cytokine and cytokine receptor	4.55E-09	*CCL20/CCL4/CXCL2/CCL3L3/IL6ST/CXCL1/CXCL8/*

hsa04064	NF-kappa B signaling pathway	7.67E-09	*IL1B/CCL4/CXCL2/ICAM1/BCL2A1/CXCL1/CXCL8/L*
hsa05323	Rheumatoid arthritis	1.53E-07	*IL1B/CCL20/TLR2/CXCL2/CCL3L3/ICAM1/FOS/CXC*
hsa05417	Lipid and atherosclerosis	5.60E-07	*IL1B/TLR2/CXCL2/CCL3L3/ICAM1/FOS/MMP9/STAT*
hsa04062	Chemokine signaling pathway	3.14E-06	*CCL20/CCL4/CXCL2/CCL3L3/CXCL16/STAT3/CXCL*
hsa04610	Complement and coagulation cascades	4.54E-06	*THBD/PLAUR/SERPINA1/CD55/C5AR1/ITGAX/VWF*
hsa05152	Tuberculosis	7.16E-06	*CLEC4E/IL1B/FCER1G/TLR2/FCGR2A/FCGR2C/ITG*
hsa05134	Legionellosis	1.03E-05	*IL1B/TLR2/CXCL2/CXCL1/CXCL8/CXCL3/HSPA6/TN*
hsa05167	Kaposi sarcoma-associated herpesvirus infection	1.69E-05	*ZFP36/CXCL2/ICAM1/IL6ST/FOS/MAPKAPK2/STAT*
hsa04620	Toll-like receptor signaling pathway	2.50E-05	*MAP3K8/IL1B/TLR2/CCL4/CCL3L3/FOS/CXCL8/LY9*
hsa05150	Staphylococcus aureus infection	7.84E-05	*C5AR1/ICAM1/FCGR2A/FCGR2C/FPR1/FPR2/PTAF*
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.000107926	*THBD/IL1B/ICAM1/STAT3/CXCL8/TNF/EGR1/IL1A/C*
hsa04625	C-type lectin receptor signaling pathway	0.000146178	*CLEC4E/IL1B/FCER1G/CLEC4D/MAPKAPK2/TNF/E*
hsa04662	B cell receptor signaling pathway	0.000149294	*LILRB2/FOS/LILRA2/LILRB1/LYN/LILRA3/LILRB3/LI*
hsa05321	Inflammatory bowel disease	0.000210338	*IL1B/TLR2/STAT3/IFNGR1/TNF/IL1A/NOD2*
hsa04613	Neutrophil extracellular trap formation	0.000245589	*TLR2/C5AR1/AQP9/FCGR2A/FPR1/FPR2/VWF/FCGI*
hsa05202	Transcriptional misregulation in cancer	0.000283882	*NFKBIZ/BCL6/NR4A3/BCL2A1/MMP9/CXCL8/PLAU*
hsa05144	Malaria	0.000332765	*IL1B/TLR2/ICAM1/CXCL8/PECAM1/TNF*
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	0.000334702	*CXCL2/CXCL1/CXCL8/LYN/CXCR1/CXCL3/CXCR2*
hsa04640	Hematopoietic cell lineage	0.000546951	*IL1B/CD55/CSF3R/MME/TNF/CSF1R/FCGR1A/IL1A*
hsa05133	Pertussis	0.000555306	*IL1B/FOS/CXCL8/LY96/TNF/SERPING1/IL1A*
hsa05142	Chagas disease	0.00066795	*IL1B/TLR2/CCL3L3/FOS/GNA15/CXCL8/IFNGR1/TN*
hsa05146	Amoebiasis	0.00066795	*IL1B/TLR2/CXCL2/GNA15/CXCL1/CXCL8/CXCL3/TN*

hsa05418	Fluid shear stress and atherosclerosis	0.001243797	*THBD/IL1B/ICAM1/FOS/MMP9/PECAM1/TNF/NCF2*
hsa05171	Coronavirus disease - COVID-19	0.001456841	*IL1B/TLR2/C5AR1/IL6ST/FOS/FCGR2A/STAT3/VWF/*

Table 2 Top 20 genes rank in cytoHubba.

Rank	Degree	Closeness	EPC	MCC
1	*TNF*	*TNF*	*IL1B*	*TLR2*
2	*IL1B*	*IL1B*	*TNF*	*TNF*
3	*TLR2*	*CXCL8*	*TLR2*	*IL1B*
4	*CXCL8*	*TLR2*	*CXCL8*	*CXCL8*
5	*STAT3*	*STAT3*	*CCL4*	*CCL4*
6	*MMP9*	*MMP9*	*STAT3*	*STAT3*
7	*SPI1*	*SPI1*	*ITGAX*	*ICAM1*
8	*FCGR3B*	*CCL4*	*TLR8*	*CXCL1*
9	*TLR8*	*FCGR3B*	*FCGR3B*	*CXCL2*
10	*ITGAX*	*TLR8*	*SPI1*	*IL1A*
11	*CCL4*	*ICAM1*	*MMP9*	*IL1RN*
12	*CSF1R*	*CSF1R*	*CSF1R*	*PTGS2*
13	*ICAM1*	*ITGAX*	*TREM1*	*CXCL3*
14	*PTGS2*	*PTGS2*	*CXCL1*	*MMP9*
15	*S100A12*	*CYBB*	*CYBB*	*CCL20*
16	*TREM1*	*CXCL1*	*S100A12*	*CXCR2*
17	*CYBB*	*FOS*	*ICAM1*	*TNFAIP3*
18	*FOS*	*S100A12*	*S100A9*	*SOCS3*
19	*CXCL1*	*TREM1*	*LILRB2*	*ITGAX*
20	*FCGR2C*	*FCGR1A*	*FCGR2C*	*CSF1R*

Table 3 Information on the 11 hub genes.

Entry	Gene Symbol	Description
P01375	*TNF*	Tumor necrosis factor
P01584	*IL1B*	Interleukin-1 beta
O60603	*TLR2*	Toll-like receptor 2
P10145	*CXCL8*	C-X-C motif chemokine 8
P40763	*STAT3*	Signal transducer and activator of transcription 3
P14780	*MMP9*	Matrix metalloproteinase-9
P20702	*ITGAX*	Integrin alpha-X
P13236	*CCL4*	C-C motif chemokine 4
P07333	*CSF1R*	Macrophage colony-stimulating factor 1 receptor
P05362	*ICAM1*	Intercellular adhesion molecule 1
P09341	*CXCL1*	C-X-C motif chemokine 1

Table 4 Key transcriptional factors of co-hub genes.

Key TF	Description	P-value	Genes
RELA	v-rel reticuloendotheliosis viral oncogene homolog A (avian)	5.91E-09	*ICAM1, STAT3, ITGAX, TNF, CXCL1*

CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	3.70E-07	*ICAM1, ITGAX, STAT3*
SPI1	spleen focus forming virus (SFFV) proviral integration oncogene spi1	6.71E-07	*STAT3, TNF, ITGAX*
NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	9.53E-07	*ITGAX, ICAM1, TNF, CXCL1*
SP1	Sp1 transcription factor	5.57E-06	*ICAM1, TNF, ITGAX, CXCL1*
CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	1.14E-05	*TNF, CXCL1*
SIRT1	Sirtuin 1	9.44E-05	*ICAM1, TNF*
BRCA1	Breast cancer 1, early onset	0.000133	*CXCL1, STAT3*
HDAC1	Histone deacetylase 1	0.000207	*STAT3, ICAM1*
STAT1	Signal transducer and activator of transcription 1, 91kDa	0.00029	*ICAM1, STAT3*
JUN	Jun proto-oncogene	0.00091	*ITGAX, TNF*