

Original Article

CD14 and CSF1R as developmental molecular targets for the induction of osteoarthritis

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Abstract: Objective: Osteoarthritis (OA) is a non-inflammatory degenerative joint disease that mainly involves articular cartilage damage and involves the whole joint tissue. However, the relationship between CD14 and CSF1R and osteoarthritis remains unclear. The aim of this study was to explore the important role of CD14 and CSF1R in osteoarthritis and provide a new direction for its prevention and treatment. Method: The osteoarthritis datasets GSE46750 and GSE82107 were downloaded from gene expression omnibus (GEO) database generated by GPL10558 and GPL570. R package limma was used to screen differentially expressed genes (DEGs). Weighted gene co-expression network analysis (WGCNA) was performed. The construction and analysis of a protein-protein interaction (PPI) network, functional enrichment analysis, gene set enrichment analysis (GSEA), and comparative toxicogenomics database (CTD) analysis were performed. TargetScan screened miRNAs that regulated central DEGs. Results: 687 DEGs were identified. According to gene ontology (GO), they were mainly concentrated in inflammatory response, IL-17 signaling pathway, rheumatoid arthritis, exercise, and regulation of response to external stimuli. The enrichment items are similar to the GO Kyoto Encyclopedia of Gene and Genome (KEGG) enrichment items of DEGs. These were mainly concentrated in exercise, inflammatory response, defense response, collagen containing extracellular matrix, and receptor regulator activity. In an enrichment project of Metascape, GO had inflammatory response, SARS-CoV-2 signal pathway network map, PIDIL8CXCR1 pathway, regulation of bone remodeling and endochondral ossification. 20 core genes were obtained by PPI network construction and analysis. Gene expression heat map showed that core genes (C1QC, CSF1R, CD14, TYROBP, HLA-DRA, C1QB, FCER1G, S100A9, HCLS1, WAS, BTK, TREM1) were highly expressed in osteoarthritis synovial tissues and were low in normal synovial tissues. CTD analysis showed that twelve genes (C1QC, CSF1R, CD14, TYROBP, HLA-DRA, C1QB, FCER1G, S100A9, HCLS1, WAS, BTK, TREM1) were found to be associated with inflammation, necrosis, gout, acute myeloid leukemia and thrombocytopenia. Conclusion: CD14 and CSF1R are highly expressed in osteoarthritis and may be therapeutic targets for osteoarthritis.

Keywords: CD14, CSF1R, molecular targets, osteoarthritis

Introduction

Osteoarthritis (OA) is a chronic painful disease and a major cause of disability in patients [1]. Hundreds of millions of people around the world suffer from osteoarthritis, and its incidence is rising with the increase in risk factors such as aging and obesity. The disability caused by OA causes huge losses to the global economy [2]. Patients with OA usually have many annoying complications, which affect quality of life, especially in the elderly. Osteoarthritis remains the most challenging arthritic disease

with a high disease burden and few effective treatments. Osteoarthritis is a progressive chronic disease, its main symptoms are joint pain, often pain at rest, the persistence of pain after rest, and long-lasting activity [3, 4]. The treatment of osteoarthritis often adopts step-by-step treatment to relieve pain effectively, and surgical treatment is needed at the end of the development. Osteoarthritis is easy to occur in the knee and hand joints, cervical vertebrae and lumbar vertebrae, and there are also some small joints degeneration with age, resulting in the proliferation of facet joints,

leading to the occurrence of osteoarthritis [5, 6]. Osteoarthritis is a joint disease that involves damage and loss of cartilage. It is also a complex and diverse disease affecting the tissues within the joint [7]. The pathogenesis of OA largely depends on imbalance between pro- and anti-inflammatory mediators, leading to inflammation, cartilage degeneration, and synovial hyperplasia [8].

The diagnostic criteria of osteoarthritis are usually based on some clinical physical characteristic combined with relevant imaging studies. Criteria for clinical characteristics: Joint stiffness, pain, swelling, joint inside the effusion, the presence of bone noise, bone hypertrophy, and joint deformity. Imaging diagnostic criteria: X-ray examination showed the presence of osteophytes at the edge of the joint, narrowing of the joint space, and disappearance of the joint space; Magnetic resonance imaging shows articular cartilage wear. Arthroscopic examination can find obvious hyperplasia and swelling of the synovial villi, and the articular cartilage may also be yellow and rough. Patients with osteoarthritis can be treated by drug therapy, physical therapy, or surgery, and the specific treatment should be formulated by the doctor according to the patient's condition. Most patients with osteoarthritis can return to normal work and life, and the prognosis is good. However, arthritis is caused by joint degeneration, due to severe cartilage degeneration. Although symptoms can be alleviated, the disease is not cured. Arthritis can occur repeatedly after overexertion or exposure to cold. Because of the complexity of its pathogenic mechanism, the pathogenesis of osteoarthritis is not clear. Therefore, it is particularly important to study the molecular mechanism of osteoarthritis.

As an important part of the development of life science, bioinformatics has been at the forefront of life science and technology research. In recent years, China's biotechnology has developed by leaps and bounds, and bioinformatic resources have also grown explosively. Through the analysis and reporting of genetic testing data, bioinformatics reveals the biologic significance represented by big data, which is a bridge connecting data and clinical practice [9, 10].

However, the relationship between CD14, CSF1R, and osteoarthritis is not clear. There-

fore, the paper intended to use bioinformatic technology to mine core genes between osteoarthritis and normal tissue, and carry out analysis. The public dataset was used to verify significant role of CD14 and CSF1R in osteoarthritis, followed by basic cell experiments.

Methods

Osteoarthritis synovial data set

The osteoarthritis synovial data set GSE46750 and GSE82107 profiles were downloaded from gene expression omnibus (GEO) generated by GPL10558 and GPL570. GSE46750 included 12 osteoarthritis synovium and 12 normal tissue samples. GSE82107 included 10 osteoarthritis synovium and 7 normal tissue samples.

Inclusion criteria: The disease is "osteoarthritis"; The tissue is from "synovial sample"; Entry type is "series"; Study type is "Expression profiling by array"; Organism is "Human".

Exclusion criteria: The expression data do not include the gene symbol; The organism is mice or rat or other animals.

Screening of differentially expressed genes (DEGs)

We used R software package limma (version 3.40.6) for difference analysis. We obtained the expression profile data sets of GSE46750 and GSE82107, used lmFit function for multiple linear regression, and further used eBayes function to adjust the standard error to a common value. We calculated the logarithmic ratio of regulated t statistics, regulated f statistics, and differential expressions. Finally, we obtained the significant differences of each gene and made a volcano plot to determine the DEGs.

Weighted gene co-expression network analysis (WGCNA)

We used expression profiles of GSE46750 and GSE82107 to calculate Median Absolute Deviation (MAD) of each gene. The good sample gene method of WGCNA in R package was used to remove outlier genes and samples to construct a scale-free co-expression network. The characteristic gene differences of the modules were calculated, the tangent lines were selected for module tree view, and some modules

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were merged. Modules with distances less than 0.25 were merged, and we obtained 28 co-expressed modules.

Construction and analysis of the protein-protein interaction (PPI) network

Protein-protein interaction networks are involved in various aspects of life processes such as biologic signaling, gene expression regulation, and cell cycle regulation.

The Search Tool to Retrieve Interacting Genes (STRING) is a search system for known and predicted PPIs. The STRING database also contains the results predicted using bioinformatics methods. The differential genes were input into the STRING database to construct a PPI network and predict the core genes. PPI network was visualized, and core genes were predicted by Cytoscape software. First, we imported the PPI network into the cytoscape, and then module with best correlation was found by MCODE, and genes with best correlation were calculated by MCC and MNC. Finally, a list of core genes was obtained after visualization.

Functional enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Gene and Genome (KEGG) are computational methods for evaluating function and biologic pathways of genetics. The list of differential genes screened by Wayne map was input into KEGG rest API to obtain latest KEGG Pathway gene annotation, which was used as the background. Gene set enrichment results were obtained using R package cluster Profiler.

Metascape (<http://metascape.org/>) is a powerful gene function annotation and analysis tool that can realize cognition of gene or protein function, and can be visually exported. We used Metascape to analyze functional enrichment of the above differential gene list and derive it.

Gene set enrichment analysis (GSEA)

GSEA is based on level-specific gene probes that evaluate data from microarrays and is a way to uncover genomic expression data through fundamental knowledge. Based on gene expression profiles and phenotype grouping, relevant pathways and molecular mechanisms were evaluated. The input for GSEA was

a gene expression matrix in which samples are divided into two groups: osteoarthritis and normal samples. All genes were sequenced and fold change was used to show the trend of gene expression between the two groups. The top of the sorted gene list can be regarded as up-regulated DEGs, and the bottom is down-regulated DEGs. GSEA analyzes whether all genes under a gene set are enriched at the top or bottom of this ranked list. If enriched at the top, this gene set (functional pathway) is an up-regulated trend, and conversely, if enriched at the bottom, this gene set (functional pathway) is a down-regulated trend. The minimum gene set was 5, and 500 was the maximum gene set, with 1000 resampling times. The whole genome was analyzed by GO and KEGG and developed by GSEA.

Gene expression heat map

The expression of core genes in GSE46750 and GSE82107 PPI networks was mapped using the R-packet heat map, to visualize a difference in core gene expression between osteoarthritis and normal samples.

CTD analysis

Comparative Toxicogenomics Database (CTD) was used to identify integrated chemical diseases, chemical genes, and gene-disease interactions to predict new associations and generate extended networks. The core genes were input into CTD, so as to find the diseases most related to the core gene, and Excel was used to draw a radar map of differential expression for each gene.

miRNA

TargetScan can predict and analyze the binding of miRNAs and their target genes as well as miRNA seed regions. TargetScan also introduces signal-to-noise ratio to evaluate the accuracy of the prediction results. Screening of miRNAs regulating central DEGs was performed using TargetScan in this study.

Results

Analysis of DEGs

According to set cutoff value and the de-batching merge matrix of GSE46750 and GSE82107, 687 DEGs were identified (**Figure 1A**).

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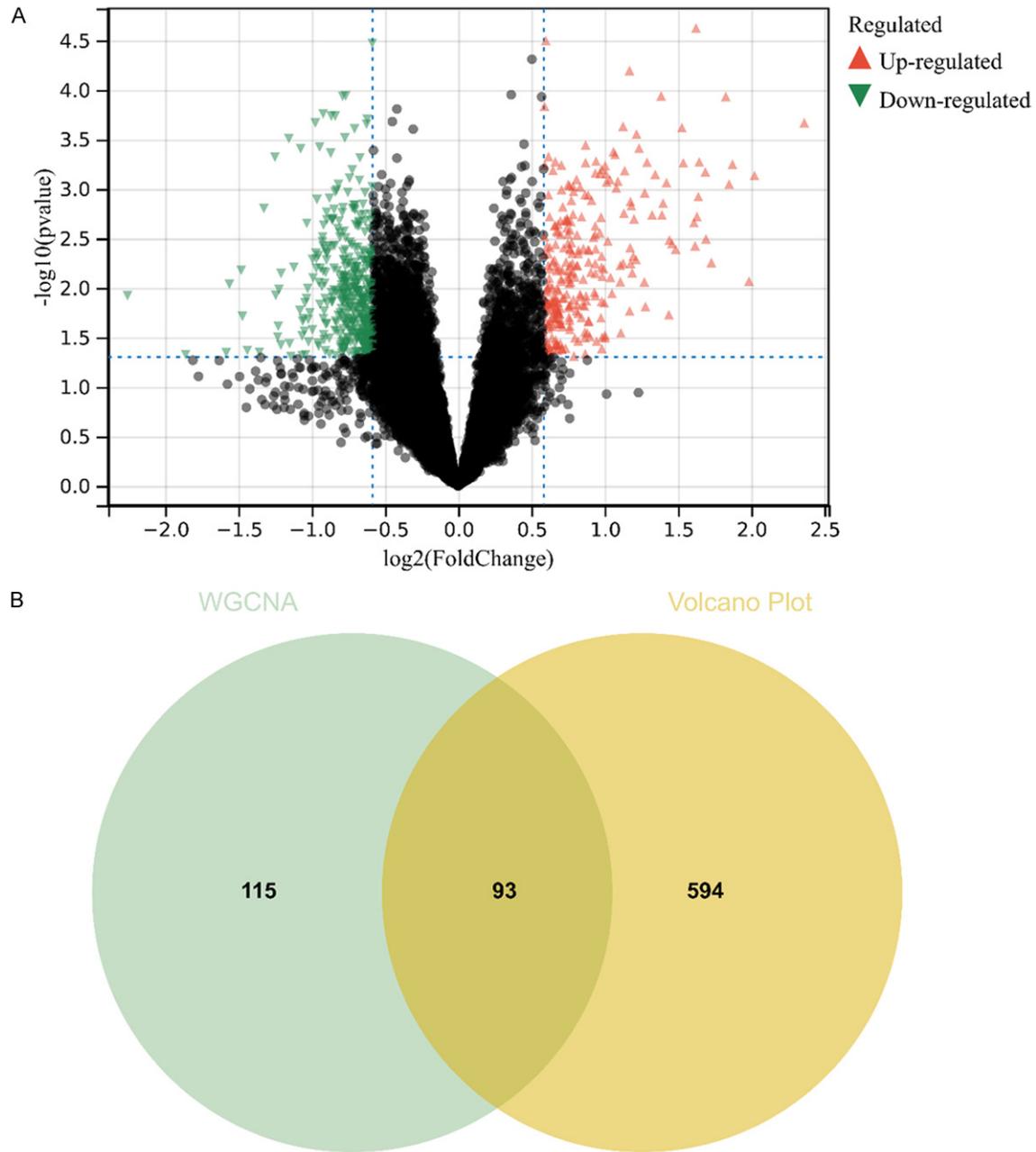


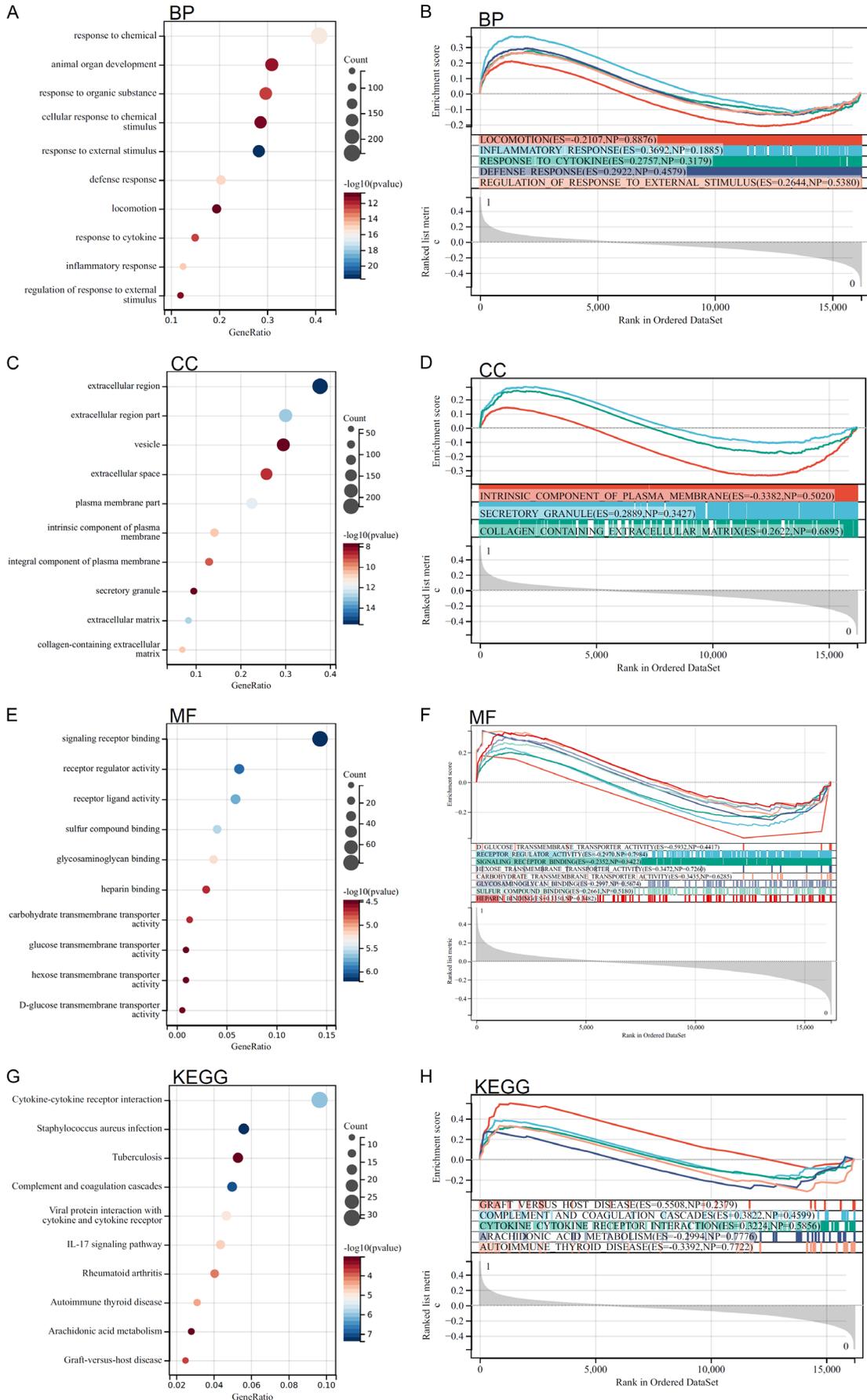
Figure 1. Analysis of differentially expressed genes (DEGs). A. A total of 687 DEGs. B. Drawing of the Venn diagram, taking the intersection through the differential genes screened by weighted gene co-expression network analysis (WGCNA) and DEGs.

Functional enrichment analysis

DEGs: We analyzed these differentially expressed genes by GO and KEGG. According to GO, they were mainly concentrated in inflammatory response, IL-17 signaling pathway, rheumatoid arthritis, exercise, and regulation of response to external stimuli (**Figure 2A, 2C, 2E, 2G**).

GSEA: GSEA was performed to search for possible enrichment items among non-differentially expressed genes, and results of DEGs were verified. The intersection of enrichment and GO KEGG enrichment of DEGs was mainly concentrated in exercise, inflammatory response, defense response, collagen containing extracellular matrix, and receptor regulator activity (**Figure 2B, 2D, 2F, 2H**).

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Figure 2. Functional enrichment analysis. A, C, E, G. DEGs. B, D, F, H. Gene set enrichment analysis (GSEA).

Metascape enrichment analysis

In the enrichment project of Metascape, GO had inflammatory response, SARS-CoV-2 signal pathway network map, PIDIL8CXCR1 pathway, regulation of bone remodeling, and endochondral ossification (**Figure 3A**), and an enrichment network colored by enrichment term and *p*-value (**Figures 3B, 3C, 4**).

WGCNA

The network topology is analyzed and soft threshold power of WGCNA is set to 9 (**Figure 5A, 5B**). The hierarchical clustering tree of all genes was constructed, which generated 28 meaningful modules (**Figure 5C**). Then we analyzed the interaction between these modules (**Figure 5D**). The module phenotypic correlation heat map (**Figure 5E**) and the GS-MM correlation scatter map of related hub genes were generated (**Figure 5F-H**). A Wayne diagram was drawn for the differentially genes screened by WGCNA and DEGs, and the intersection was taken (**Figure 1B**).

Protein-protein interaction (PPI) network

The PPI network was constructed using STRING and analyzed by Cytoscape (**Figure 6A**). The MCC algorithm was used to identify hub genes (**Figure 6B**), 20 core genes (TYROBP, CSF1R, FCER1G, CD14, CCR1, C1QB, CD163, C1QC, LY86, TREM1, S100A9, HLA-DRA, C1orf162, ADAP2, MS4A7, AQP9, BTK, HCLS1, LYN, WAS) were obtained.

Gene expression heat map

The difference in expression of core genes was determined between osteoarthritis synovium and normal tissue samples (**Figure 7**). It was found that core genes (C1QC, CSF1R, CD14, TYROBP, HLA-DRA, C1QB, FCER1G, S100A9, HCLS1, WAS, BTK, TREM1) were highly expressed in osteoarthritis synovial tissues and were low in normal synovial tissues.

CTD analysis

Core genes was entered into CTD to find diseases related to core genes. Twelve genes (C1QC, CSF1R, CD14, TYROBP, HLA-DRA,

C1QB, FCER1G, S100A9, HCLS1, WAS, BTK, TREM1) were found to be associated with inflammation, necrosis, gout, acute myeloid leukemia, and thrombocytopenia (**Figure 8**).

miRNA prediction and functional annotation related to hub genes

The hub genes were entered into Targetsacan to search for relevant miRNA (**Table 1**). The results showed that the related miRNA of CSF1R gene is related to hsa-miR-449b-5p, hsa-miR-34c-5p, and hsa-miR-34a-5p; HLA-DRA genes. miRNA is related to hsa-miR-325-3p scape FCER1G gene. miRNA is related to hsa-miR-325-3p scape TREM1 gene. miRNA is related to hsa-miR-542-3p.

Discussion

Osteoarthritis (OA) is a joint disease caused by inflammation and cartilage breakage. OA affects 240 million people worldwide, with an incidence of about 10% for men over the age of 60 and 18% for women [11, 12]. When there is a change in weather, cold, fatigue, can cause joint acid distention discomfort, and induce joint pain. In addition to the common joint related symptoms, patients sometimes present with other accompanying symptoms. OA is highly prevalent around the world, resulting in a huge economic burden [13, 14]. Traditionally, treatment of osteoarthritis includes pain management and joint replacement for end-stage disease [15]. Individualized and graded treatment is carried out according to the actual situation of patients. In-depth exploration of molecular mechanisms of osteoarthritis is very important for study of targeted drugs. The main result of the study was high expression of CD14 and CSF1R in osteoarthritis. The higher the expression of CD14 and CSF1R, the worse the prognosis.

CD14 can affect the inflammatory activity of OA. Due to the secretion of inflammatory cytokines, the immune cells of OA synovium are increased. Monocytes play a key role in OA synovitis through their own phagocytic activity and secretion of inflammatory mediators [16, 17]. Excessive migration and abnormal activation of monocytes may lead to cartilage

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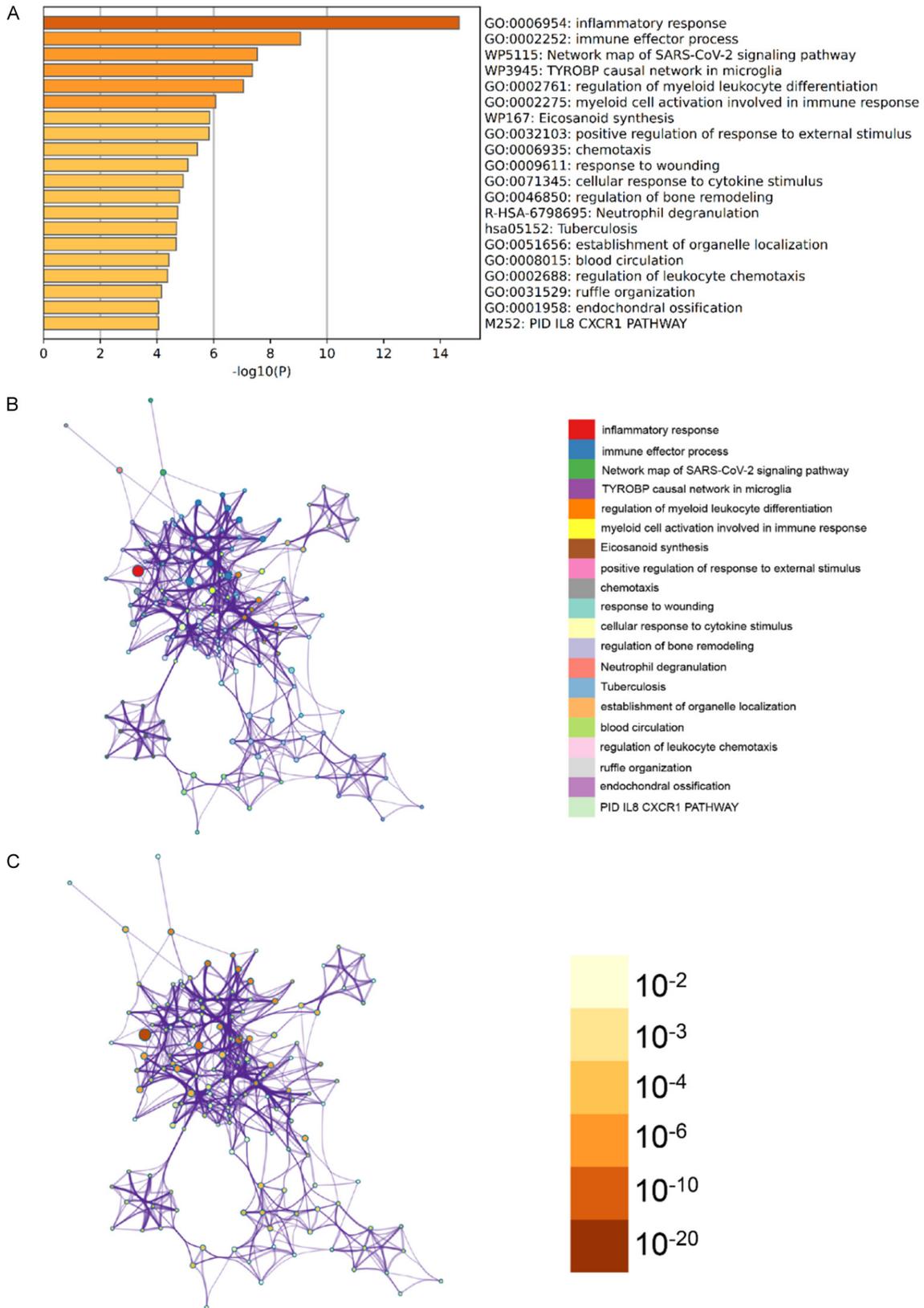


Figure 3. Metascape enrichment analysis. A. Gene Ontology (GO) has inflammatory response, SARS-CoV-2 signal pathway network map, PIDIL8CXCR1 pathway, regulation of bone remodeling, and endochondral ossification. B. Enrichment network colored by enrichment terms. C. The PPI network of P value.

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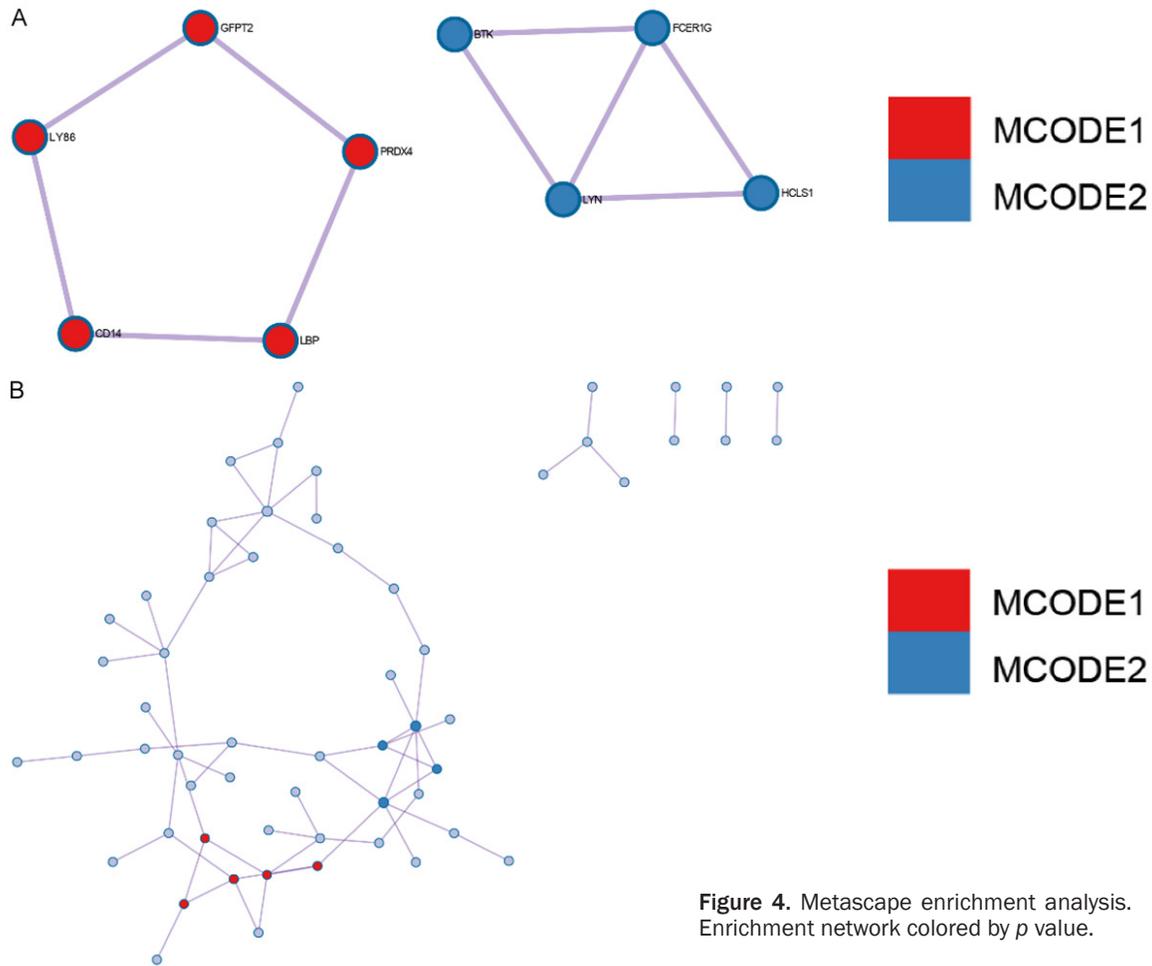


Figure 4. Metascape enrichment analysis. Enrichment network colored by p value.

destruction and arthritis [18]. Monocyte cross-talk and FLS can affect joint inflammation through synovial fluid, and FLS stimulated by CD14 secretes some cytokines, which leads to the deterioration of OA progression. It was found that the number of CD14 monocytes in recurrent synovial fluid was significantly higher than that in initial synovial fluid. Although the reason for the increased number in synovial fluid is unknown, CD14 monocytes and CD14 may play an important role in OA inflammation [19]. Daghestani et al showed that sCD14 in synovial fluid was strongly correlated with joint space stenosis and the severity of OA pain. Activation of toll-like receptor (TLR) signaling on monocytes induces proinflammatory cytokine/chemokine production and pain signal transmission [20]. A recent study has shown that the typical response of CD14CD16 monocytes to knee synovial-derived mediators is a key target for overcoming the onset and progression of osteoarthritis [21]. TLR pathway

plays an important role in OA inflammation. The TLR signaling pathway consists of several components, such as lipopolysaccharide binding protein (LBP) and CD14. Yun Qingyuan et al. proved that TLR helper molecules LBP and CD14 play an important role in deterioration of OA cartilage destruction after trauma induced by low-grade inflammation. LBP and CD14 may regulate metastatic inflammation and/or inflammation in the pathogenesis of OA [22]. A review of the literature is consistent with the results that CD14 is highly expressed in osteoarthritis. The higher the CD14, the worse the prognosis. Based on the above literature analysis and our research results, we speculate that CD14 may play a role in the occurrence and development of osteoarthritis.

Colony stimulating factor-1 receptor (CSF-1R) is expressed in bone marrow lineage cells composed of monocytes, macrophages and osteoclasts [23]. When overstimulated by its ligand

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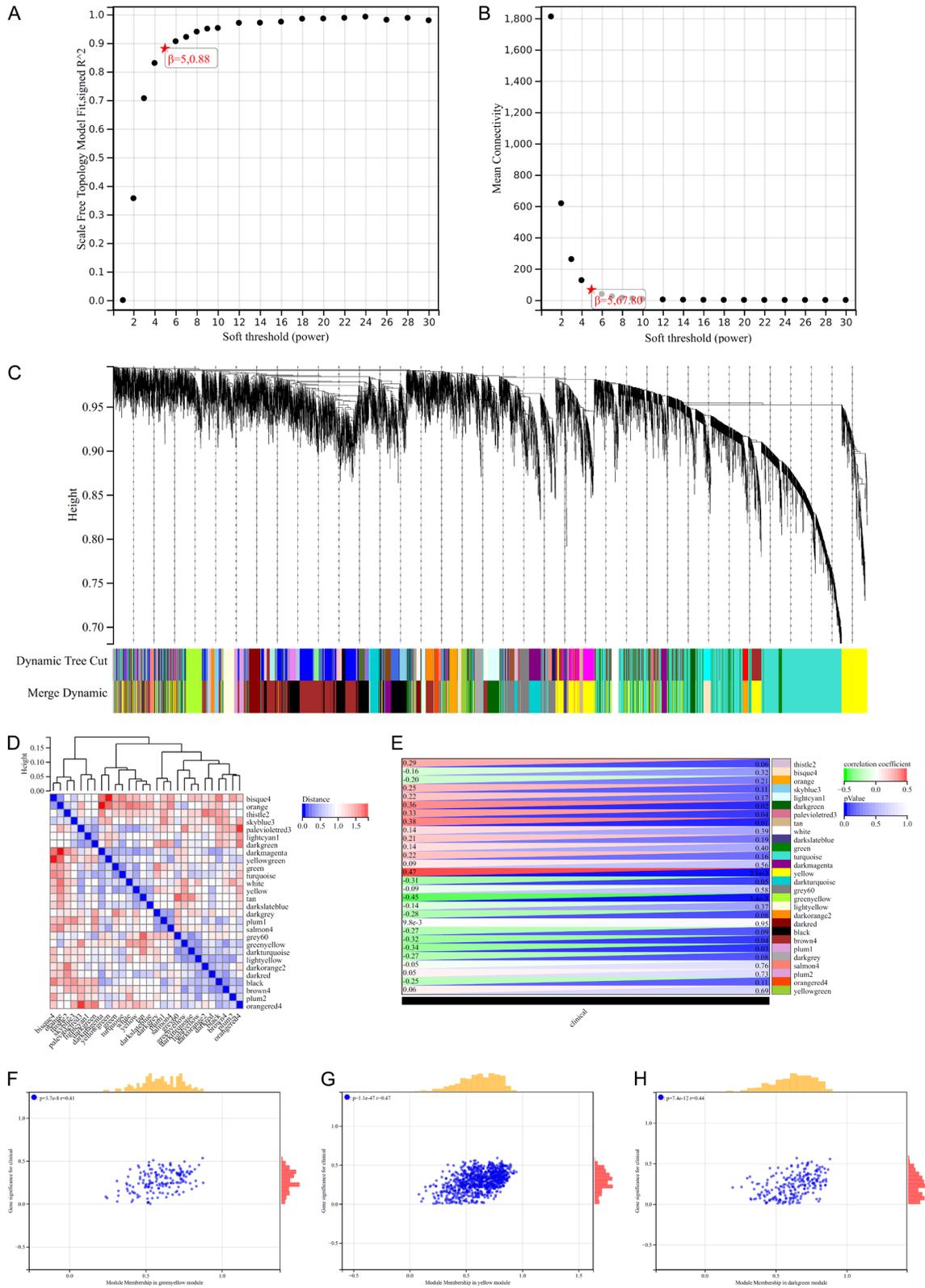


Figure 5. WGCNA. A. $\beta=5, 0.88$. B. $\beta=5, 67.80$. C. A hierarchical clustering tree of all genes was constructed, and 28 important modules were generated. D. The interaction between these modules. E. Module phenotypic correlation heat map. F. GS-MM correlation scatter map of related hub genes: $P=3.7e-8$, $r=0.41$. G. GS-MM correlation scatter map of related hub genes: $P=1.1e-47$, $r=0.47$. H. GS-MM correlation scatter map of related hub genes: $P=7.4e-12$, $r=0.44$.

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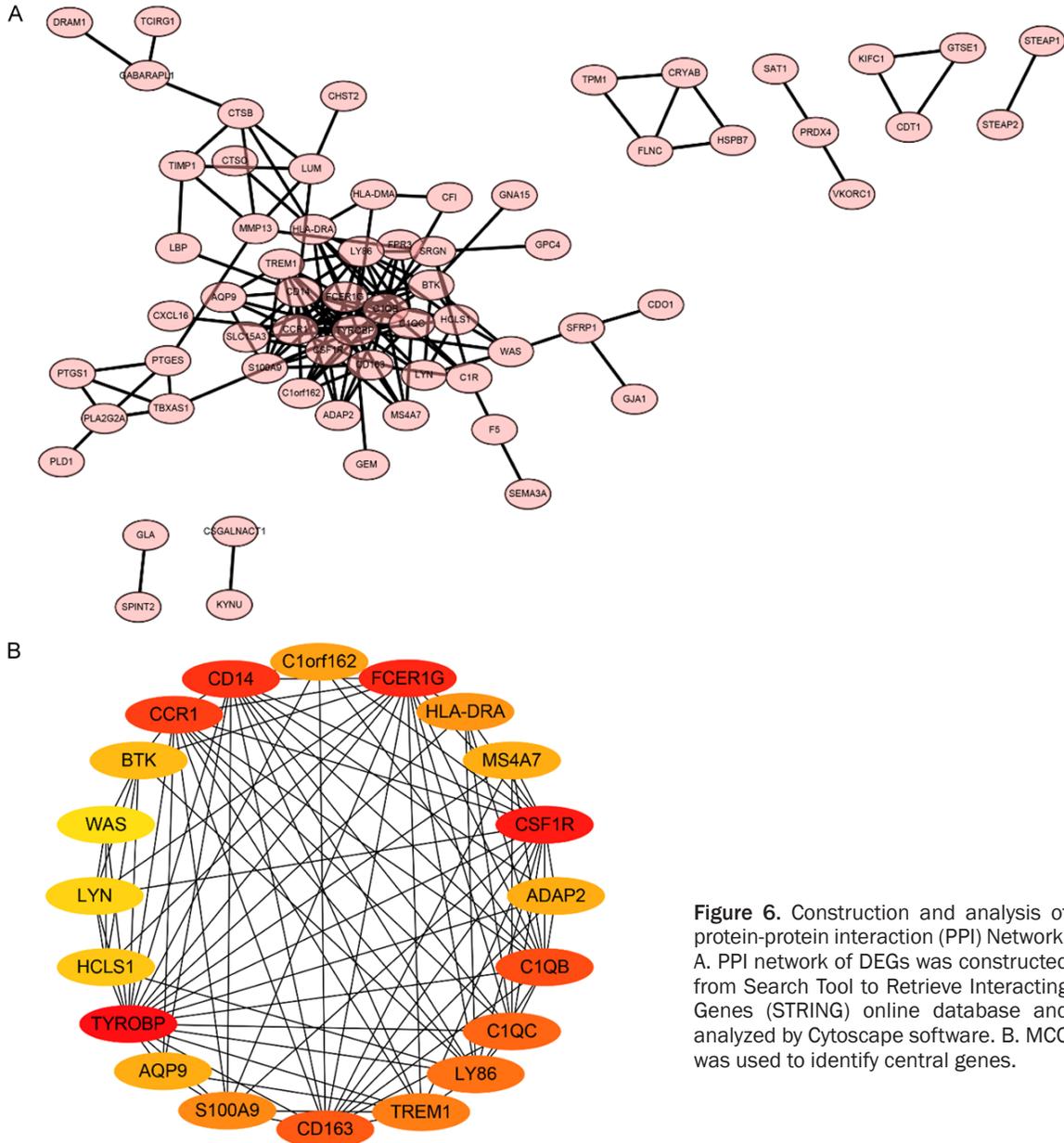


Figure 6. Construction and analysis of protein-protein interaction (PPI) Network. A. PPI network of DEGs was constructed from Search Tool to Retrieve Interacting Genes (STRING) online database and analyzed by Cytoscape software. B. MCC was used to identify central genes.

colony stimulating factor 1 (CSF1), it plays a role in causing inflammation, cancer, and bone disease. CSF-1 binds to CSF-1R, induces homodimerization of CSF-1R, then activates receptor signal transduction and tyrosine phosphorylation of CSF-1R. Several cell types, such as macrophages, depend on CSF-1R-mediated signaling for differentiation, proliferation, and survival [24, 25]. CSF-1R/c-FMS is overexpressed in many cancers and tumor-associated macrophages and is used as a drug target for the treatment of cancer and inflammatory diseases [26]. Pexidartinib is an orally bioavailable

and effective CSF-1R inhibitor, and is one of the most commonly used drugs in the clinic [27]. These findings provide a basic principle for the study of CSF-1R inhibition in many other cancers. Takehiro Ota et al found a significant correlation between high CSF1 expression and the incidence of osteochondral changes, while patients with high CSF1R expression tended to have a higher local recurrence rate of PVNS29 in the knee [28]. In the study of Garcia, it was shown that specific antibodies to CSF1R could prevent CSF-1 and IL-34 from binding to their receptors, reducing production of inflammatory

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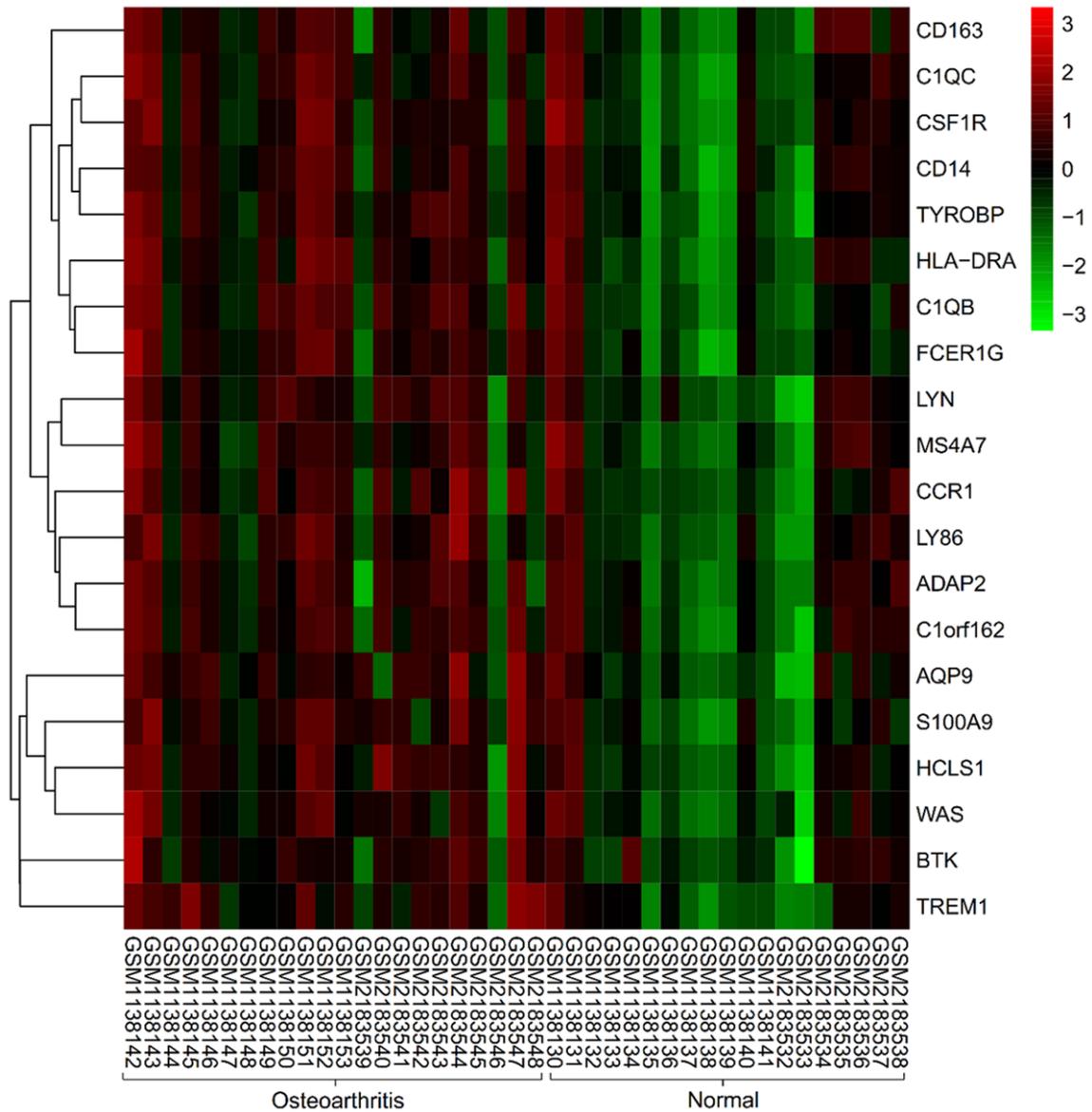


Figure 7. Gene expression heat map. Differences in the expression of core genes between osteoarthritis synovium and normal tissue samples.

mediators in synovial tissue [29]. The above literature review is consistent with our results. CSF1R is highly expressed in osteoarthritis. The higher the CSF1R, the worse the prognosis. Based on the above literature analysis and our research results, we speculate that CSF1R may play a role in occurrence and development of osteoarthritis.

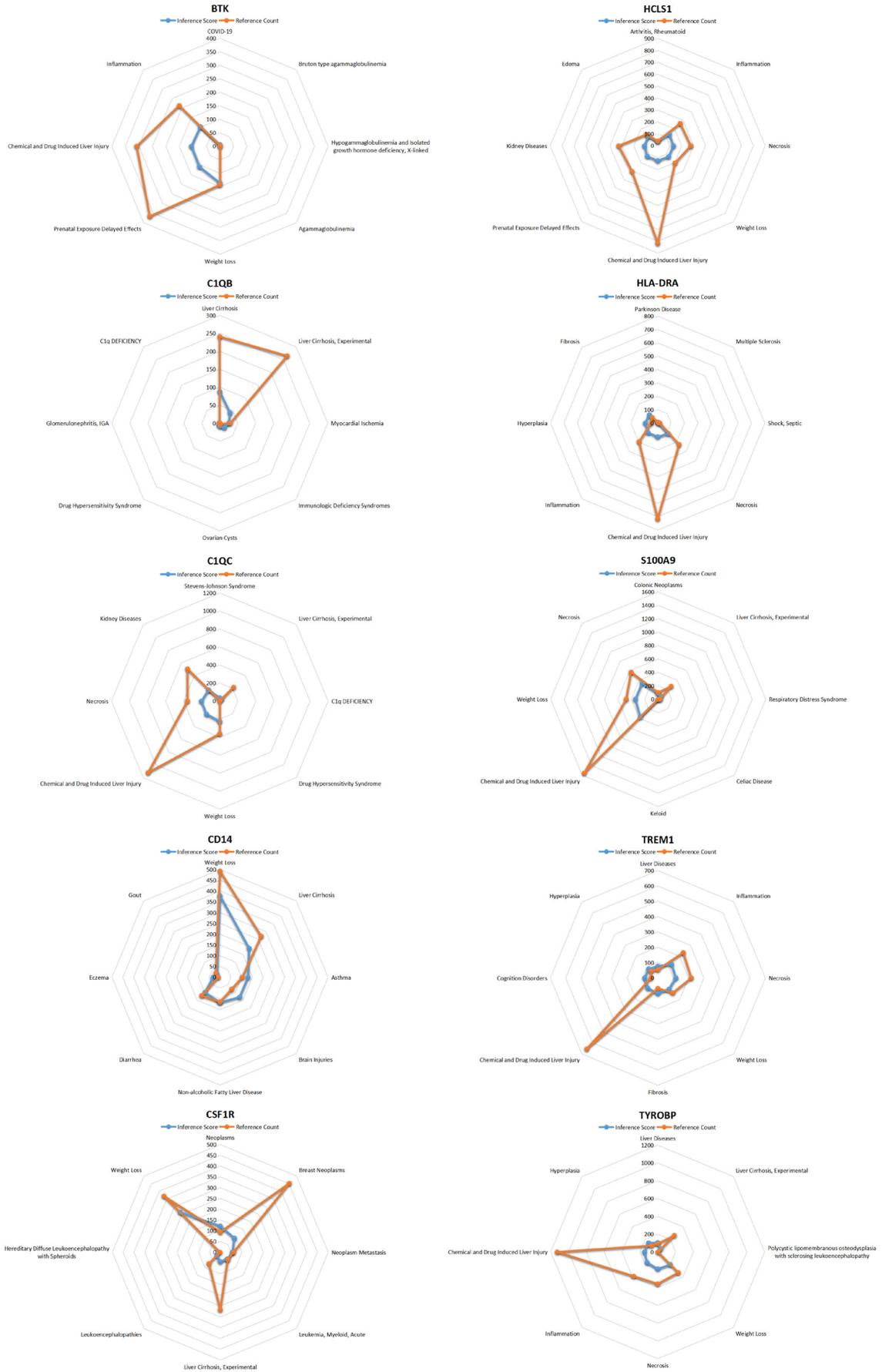
Although this paper has carried out rigorous bioinformatic analysis, there are some shortcomings. Animal experiments with overexpression or knockdown of the gene were not performed in this study to further verify its function.

Therefore, this aspect should be explored in depth in future studies.

Conclusion

CD14 and CSF1R are highly expressed in patients with osteoarthritis, and may play a significant role in development of osteoarthritis through inflammation and regulation of immune cells. Reducing the expression levels of CD14 and CSF1R is beneficial in the treatment of osteoarthritis. CD14 as a resident macrophage, is involved in the pathogenesis of autoimmune arthritis and maintains disease activity.

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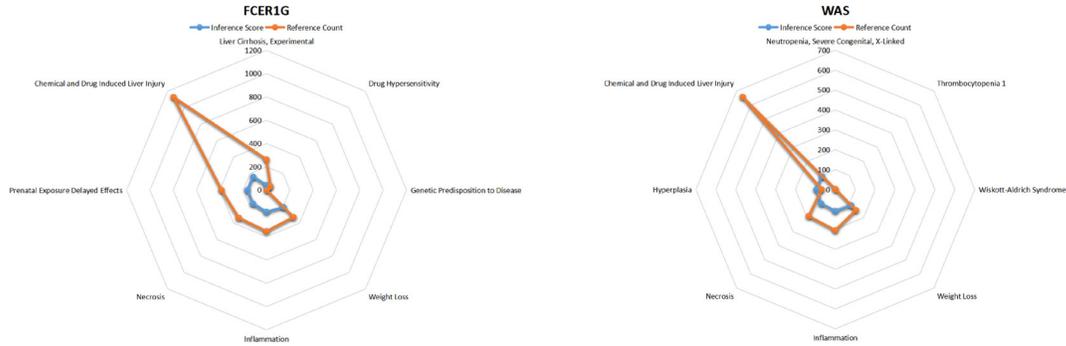


Figure 8. Comparative toxicogenomics database (CTD) analysis. 12 genes (C1QC, CSF1R, CD14, TYROBP, HLA-DRA, C1QB, FCER1G, S100A9, HCLS1, WAS, BTK, TREM1) were found to be associated with inflammation, necrosis, gout, acute myeloid leukemia, and thrombocytopenia.

Table 1. A summary of miRNAs that regulate hub genes

Gene	miRNA
1 CSF1R	hsa-miR-449b-5p hsa-miR-34c-5p hsa-miR-34a-5p
2 HLA-DRA	hsa-miR-325-3p
3 FCER1G	hsa-miR-325-3p
4 TREM1	hsa-miR-542-3p
5 C1QC	none
6 C1QB	none
7 CD14	none
8 S100A9	none
9 HCLS1	none
10 WAS	none
11 BTK	none
12 TYROBP	none

Reducing the expression level of CD14 can inhibit the production of inflammatory mediators and promote the increase in joint matrix. Colony-stimulating factor 1 receptor (CSF-1R) is the receptor for colony-stimulating factor 1 (CSF-1). Colony-stimulating factor-1 (CSF-1) is one of the most common proinflammatory cytokines, leading to various inflammatory diseases, and it has a significant role in the development and progression of osteoarthritis and other autoimmune diseases. Reducing the expression level of CSF-1R can inhibit the occurrence of bone and joint-related inflammation. CD14 and CSF1R can be used as the molecular targets of osteoarthritis, which provides a basis for the study of the pathogenesis of osteoarthritis.

Disclosure of conflict of interest

None.

Abbreviations

OA, Osteoarthritis; GEO, gene expression omnibus; DEGs, differential epigenetic genes; WGCNA, weighted gene co-expression network analysis; PPI, protein-protein interaction; GSEA, Gene set enrichment analysis; CTD, Comparative Toxicogenomics Database; STRING, Search Tool for the Retrieval of Interacting Genes; GO, gene ontology; KEGG, Kyoto Encyclopedia of Gene and Genome; MAD, Median Absolute Deviation; TLR, toll-like receptor; LBP, lipopolysaccharide binding protein; CSF-1R,

colony stimulating factor-1 receptor; CSF1, colony stimulating factor 1.

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