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The role of CD14 and CSF1R in osteoarthritis and gastritis

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Abstract

Osteoarthritis (OA) is a non-inflammatory degenerative joint disease that mainly involves articular cartilage damage and involves the whole joint tissue. Gastritis is a common stomach disorder, typically referring to inflammation or lesions of the gastric mucosa. However, the relationship between CD14 and colony stimulating factor-1 receptor (CSF1R) and these 2 diseases is not yet clear. OA datasets GSE46750, GSE82107 and gastritis datasets GSE54043 profiles were downloaded from gene expression omnibus databases generated by GPL10558 and GPL570.The R package limma was used to screen differentially expressed genes (DEGs). Weighted gene co-expression network analysis was performed. The construction and analysis of protein–protein interaction network, functional enrichment analysis, gene set enrichment analysis and comparative toxicogenomics database analysis were performed. TargetScan was used to screen miRNAs regulating central DEGs. A total of 568 DEGs were identified. According to the gene ontology (GO) and biological processes analysis, they were mainly enriched in ATP metabolism negative regulation, toll-like receptor TLR1:TLR2 signaling pathway, and intracellular transport. The enrichment terms for OA and gastritis were similar to the GO and Kyoto encyclopedia of gene and genome enrichment terms of DEGs, mainly enriched in ATP metabolism negative regulation, secretion granules, transmembrane receptor protein kinase activity, cytokine–cytokine receptor interaction, Toll-like receptor signaling pathway, MAPK signaling pathway, and TGF-β signaling pathway. In the Metascape enrichment projects, GO enrichment projects showed functions related to cell–cell receptor interaction, cell secretion, and growth. Two core genes were identified through the construction and analysis of the protein–protein interaction network. The core genes (CD14 and CSF1R) exhibited high expression in OA and gastritis samples and low expression in normal samples. Comparative toxicogenomics database analysis revealed associations between core genes (CD14 and CSF1R) and diseases such as OA, osteoporosis, gastritis, juvenile arthritis, diarrhea, and inflammation. CD14 and CSF1R are highly expressed in OA and gastritis, making them potential therapeutic targets for both diseases.

Abbreviations: CSF1 = colony stimulating factor 1, CSF1R = colony stimulating factor-1 receptor, CTD = comparative toxicogenomics database, DEGs = differentially expressed genes, GO = gene ontology, GSEA = gene set enrichment analysis, KEGG = Kyoto encyclopedia of gene and genome, LBP = lipopolysaccharide binding protein, OA = osteoarthritis, PPI = protein–protein interaction, STRING = search tool for the retrieval of interacting genes, TLR = toll-like receptor.

Keywords: CD14, CSF1R, gastritis, molecular targets, osteoarthritis

1. Introduction

Osteoarthritis (OA) is a chronic and painful form of arthritis, and its stands as the leading cause of disability among patients.[1] Studies indicate that hundreds of millions of people worldwide are afflicted by osteoarthritis, and its prevalence continues to rise due to factors like aging and obesity. The disability caused by OA has caused huge losses to the global economy.[2] Osteoarthritis is a progressive chronic disease, characterized by its primary symptom of joint pain. This pain is often experienced at rest and may worsen after periods of inactivity but improve with moderate activity. However, excessive activity can exacerbate the pain. Another common symptom is joint stiffness, which frequently occurs upon waking in the morning or after maintaining a certain position for an extended period during the day.[3,4] The treatment of osteoarthritis typically involves a step-by-step approach aimed at effectively relieving pain. Surgical intervention may be necessary

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in advanced stages. Osteoarthritis commonly affects the knee and hand joints, as well as the cervical and lumbar vertebrae. Additionally, with aging, some smaller joints may undergo degeneration, leading to the proliferation of facet joints and contributing to the development of osteoarthritis.[5,6] Although OA is often referred to as a joint disease of cartilage injury and loss, OA is a more diverse disease with complex pathogenesis that affects all tissues in the joint.[7] The pathogenesis of OA depends to a large extent on the imbalance between pro-and anti-inflammatory mediators, leading to low-grade inflammation, cartilage degradation, bone remodeling and synovial hyperplasia.[8]

Gastritis is a common stomach disorder, typically characterized by inflammation or lesions of the gastric mucosa. It is a prevalent condition worldwide, affecting a large portion of the population. The incidence of gastritis varies among different regions and populations, but it is generally more common in developing countries.[9] Chronic gastritis is more frequently observed in the elderly, as the gastric mucosa becomes more vulnerable to damage with age. Gastritis primarily involves inflammation of the gastric mucosa and can be caused by various factors, including infections, medication misuse, alcohol abuse, autoimmune diseases, and more. It may manifest as inflammation, erosion, ulcers, and bleeding of the gastric mucosa, often accompanied by the infiltration of immune cells such as white blood cells.[10]

The etiology of gastritis is multifaceted, with causes including infections, medication abuse, alcohol consumption, autoimmune diseases, and others. Both diseases have complex and not fully understood pathogenesis. Studies suggest that genetic factors, chromosomal abnormalities, and gene fusions may be associated with the onset of both arthritis and gastritis. In-depth research into their molecular mechanisms can provide a better understanding of the underlying causes of these diseases and aid in the development of prevention and treatment strategies.[11,12]

CD14 is a surface antigen molecule in the human body, classified as a glycoprotein. It is typically found on the surface of monocytes, macrophages, and certain granulocytes. In immune cells, CD14's primary function is to recognize and bind to a structural molecule of bacteria called lipopolysaccharide, thereby initiating an immune inflammatory response.[13] Research suggests that abnormal activation of the immune system and inflammation may be involved in the pathological processes of osteoarthritis, with CD14 contributing to immune system dysregulation and exacerbating the condition.[14] In cases of gastritis, especially in the presence of bacterial infections like Helicobacter pylori, CD14 may play a role in prompting immune cells to respond to the infection.[15]

CSF1R, a receptor tyrosine kinase, plays a vital role in the human body, primarily responsible for receiving and transmitting signals of colony stimulating factor 1 (CSF1), which regulates the development, differentiation, and function of monocytes, such as macrophages. These immune cells play a crucial role in the inflammatory process, as they can secrete inflammatory mediators such as cytokines and chemokines. These factors affect conditions like osteoarthritis and gastritis. CSF1R typically plays a role in the differentiation and activation of immune cells, potentially influencing the immune and inflammatory processes of diseases.[16]

In recent years, various studies have begun to explore the molecular mechanisms behind osteoarthritis and gastritis. Xie[17] found that the risk of osteoarthritis is associated with polymorphisms in adipokine-related genes. Different genes play different roles in various diseases, and the exact molecular mechanisms of CD14 and CSF1R in these 2 diseases remain unclear.

Therefore, in this study, we aim to employ bioinformatics techniques to uncover core genes related to osteoarthritis, gastritis, and normal tissues, followed by enrichment analysis and pathway analysis. We will validate the significance of CD14 and CSF1R in osteoarthritis and gastritis using public datasets and conduct further experimental validation through cellular assays.

2. Methods

2.1. Osteoarthritis and gastritis datasets

In this study, the osteoarthritis datasets GSE46750 and GSE82107, and the gastritis dataset GSE54043 profiles were downloaded from the gene expression omnibus database (http://www.ncbi.nlm.nih.gov/geo/) generated from GPL10558 and GPL570. GSE46750 includes 12 osteoarthritis and 12 normal samples, GSE82107 includes 10 osteoarthritis and 7 normal samples, and GSE54043 includes 5 gastritis and 5 normal samples. These datasets were used to identify differentially expressed genes (DEGs) associated with osteoarthritis and gastritis.

2.2. Batch removal

To combine and batch-remove data from multiple datasets, we initially merged the osteoarthritis datasets GSE46750 and GSE82107 using the R package in Silico Merging [DOD:10.1186/1471-2105-13-335]. The merged matrix was then further processed using the remove Batch Effect function from the R package limma (version 3.42.2) to remove batch effects, resulting in a batch-effect-corrected matrix for subsequent analysis.

2.3. DEGs selection

We performed log2 transformation on the batch-corrected merged matrices of osteoarthritis datasets GSE46750 and GSE82107, and the gene expression matrix of gastritis dataset GSE54043. Using the lmFit function, multivariate linear regression was applied. Empirical Bayesian adjustments were made to estimate moderated t-statistics, moderated F-statistics, and log-odds of differential expression for each gene. This yielded significant differences for each gene, which were visualized in volcano plots. Subsequently, DEGs were obtained by taking the intersection of DEGs identified from osteoarthritis and gastritis datasets.

2.4. Functional enrichment analysis

Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) analyses were employed to assess gene function and biological pathways. DEGs were input into the KEGG REST API (https://www.kegg.jp/kegg/rest/keggapi.html) for the latest KEGG Pathway gene annotations. In addition, GO annotations from the org.Hs.eg.db package (version 3.1.0) were used. These annotations were used as background sets to map genes. ClusterProfiler (version 3.14.3) in R was used for enrichment analysis, with a minimum gene set size of 5 and a maximum gene set size of 5000. A P-value of <0.05 and a FDR of <0.25 were considered statistically significant.

Furthermore, Metascape database resources were used for gene list annotation and analysis, which were visualized and exported.

2.5. Gene set enrichment analysis (GSEA)

For GSEA, samples were divided into 2 groups based on disease status and normal controls. The c2.cp.kegg.v7.4.symbols.gmt gene set subset from the Molecular Signatures Database was downloaded. GSEA (version 3.0) software was used to evaluate relevant pathways and molecular mechanisms based on gene expression profiles and phenotype grouping. A minimum gene set size of 5, a maximum gene set size of 5000, 1000 permutations, and P-value < 0.05 with FDR < 0.25 were considered statistically significant. GO and KEGG analyses were also conducted.

2.6. Protein–protein interaction (PPI) network construction and analysis

The PPI network for DEGs was constructed using the search tool for the retrieval of interacting genes (STRING) database (http://string-db.org/). The Cytoscape software was utilized for visualization and prediction of hub genes from the STRING PPI network. The MCODE algorithm was applied to identify highly correlated modules, and 4 algorithms (MCC, MNC, EcCentricity, ClusteringCoefficient) were used to calculate the top ten genes, with intersections selected as core genes. The resulting core gene list was visualized.

2.7. Gene expression heatmaps

Heatmaps of core gene expression in osteoarthritis batch-corrected matrices and gastritis gene expression matrices were generated using the R package heatmap. High expression of core genes (CD14 and CSF1R) was observed in osteoarthritis and gastritis samples, while low expression was observed in normal samples.

2.8. Comparative toxicogenomics database (CTD) analysis

Hub gene lists were input into the CTD to identify diseases associated with core genes. Radar charts of gene expression differences for each gene were generated using Excel.

2.9. miRNA target prediction and functional annotation

The hub gene list was input into TargetScan (www.targetscan.org) to predict miRNAs related to core DEGs (CD14 and CSF1R).

3. Results

3.1. Analysis of DEGs

In this study, we identified DEGs in the osteoarthritis datasets GSE46750 and GSE82107 using a predefined cutoff value. In the end, we identified a total of 568 DEGs (Fig. 1A). Additionally, we identified DEGs in the gene expression matrix of the gastritis dataset GSE54043, resulting in a total of 1002 DEGs (Fig. 1B). Subsequently, we obtained a Venn diagram by intersecting the DEGs from osteoarthritis and gastritis datasets (Fig. 1C), and these overlapping DEGs were used for further analysis.

3.2. Functional enrichment analysis

3.2.1. DEGs. We conducted GO and KEGG pathway analyses on these DEGs. According to the GO analysis results, in biological processes, they were mainly enriched in ATP metabolism negative regulation, toll-like receptor TLR1:TLR2 signaling pathway, intracellular transport (Fig. 2A). In cellular components, they were mainly enriched in vesicles and secretory granules (Fig. 2B). In molecular functions, they were mainly concentrated in transmembrane receptor protein kinase activity, CCR6 chemokine receptor binding (Fig. 2C). In KEGG analysis, they were mainly enriched in cytokine-cytokine receptor interaction, MAPK signaling pathway, metabolic pathways, TGF-β signaling pathway, toll-like receptor signaling pathway, and regulation of inflammatory mediators on TRP channels (Fig. 2D).

3.2.2. GSEA. Furthermore, we conducted GSEA enrichment analysis on the entire genome to identify potential enrichments among non-DEGs and to validate the results of the DEGs. The intersection of enrichment terms from GSEA with the GO and KEGG enrichment terms of DEGs is shown in the figure. DEGs were primarily enriched in ATP metabolism negative regulation, secretion granules, transmembrane receptor protein kinase activity, cytokine-cytokine receptor interaction, Toll-like receptor signaling pathway, MAPK signaling pathway, and TGF-β signaling pathway (Fig. 3A–D). The enrichment results in the gene expression matrix of gastritis were similar to those of osteoarthritis (Fig. 3E–H).

3.3. Metascape enrichment analysis

In Metascape enrichment projects, the GO enrichment projects showed cell–cell receptor interaction, cell secretion, and growth (Fig. 4A). We also output the enrichment network colored by enrichment terms and *P*-values (Fig. 4B and C), visually representing the associations and confidence of each enrichment project.

3.4. Protein–protein interaction (PPI) network construction and analysis

The PPI network of DEGs was constructed using the STRING online database (Fig. 5A) and analyzed using Cytoscape software. Four algorithms were used to identify hub genes, and the union of these results yielded 2 core genes (CD14, CSF1R) (Fig. 5B–F).

3.5. Heatmaps of core gene expression

We visualized the expression levels of core genes in the batch-corrected matrix for osteoarthritis (Fig. 6A) and the gene expression matrix for gastritis (Fig. 6B) as heatmaps. We observed high expression of core genes (CD14, CSF1R) in osteoarthritis and gastritis samples, while they exhibited low expression in normal samples. Based on these results, we speculate that these core genes may play a regulatory role in osteoarthritis and gastritis.

3.6. CTD analysis

In this study, we input the hub gene list into the CTD website to search for diseases related to core genes, enhancing our understanding of the association between genes and diseases. Core genes (CD14, CSF1R) were found to be associated with osteoarthritis, osteoporosis, gastritis, juvenile arthritis, diarrhea, and inflammation (Fig. 6C).

3.7. Prediction and functional annotation of miRNAs associated with hub genes

In this study, we input the hub gene list into TargetScan to search for related miRNAs, enhancing our understanding of gene expression regulation (Table 1). We found that miRNAs related to the CSF1R gene were hsa-miR-34a-5p, hsa-miR-449b-5p, and hsa-miR-34c-5p.

4. Discussion

Osteoarthritis (OA) is the most common musculoskeletal disease and the leading cause of disability worldwide. Due to today's lifestyle, high obesity rates, and increased average life expectancy, its prevalence rate is on the rise. OA affects 240 million people globally, with an incidence of approximately 10% for men over the age of 60 and 18% for women.[18,19] It is highly prevalent around the world, resulting in a huge economic burden.[20,21] Traditionally, the treatment of osteoarthritis includes pain management and joint replacement for end-stage diseases.[22] This approach does not address the morbidity associated with early disease or the limitations of joint replacement

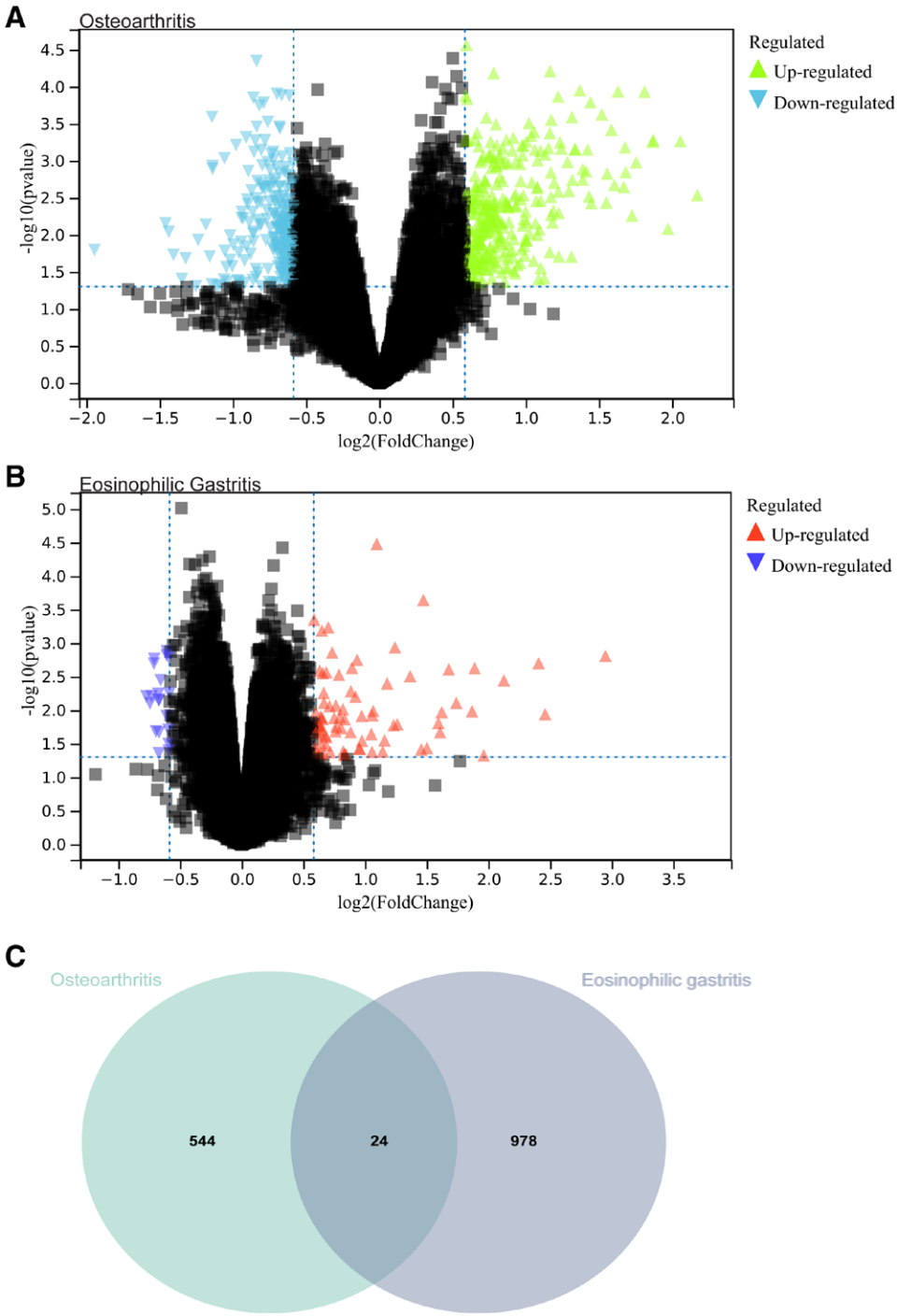

Figure 1. Analysis of differentially expressed genes. (A) A total of 568 DEGs. (B) The gene expression matrix of gastritis dataset GSE54043 identified differentially expressed genes, and 1002 DEGs were obtained. (C) The intersection of the differential genes of osteoarthritis and gastritis obtained the Venn diagram. DEGs = differentially expressed genes.

surgery, including possible adverse outcomes and the minimum life span of the prosthesis.

Gastritis can lead to inflammation and damage to the stomach's mucous membrane, affecting the normal functioning of the stomach, including the digestion and absorption of food. This can result in gastrointestinal discomfort, nausea, vomiting, diarrhea, and other digestive system issues. Since gastritis can impact the acidity and secretion of enzymes in the stomach, patients may experience problems with nutrient absorption, leading to weight loss, anemia, and other nutrition-related health problems. If chronic gastritis is not promptly treated, it may increase the risk of complications such as gastric cancer, which can pose a significant threat to the patient's life and health.[23]

In-depth research into the molecular mechanisms of both osteoarthritis and gastritis is crucial for finding targeted treatment approaches. Research results indicate that 2 molecules, CD14 and CSF1R, are highly expressed and associated with a poor prognosis. Therefore, CD14 and CSF1R are potential future targets for research and treatment of acute conditions, providing valuable clues for the development of new targeted drugs.

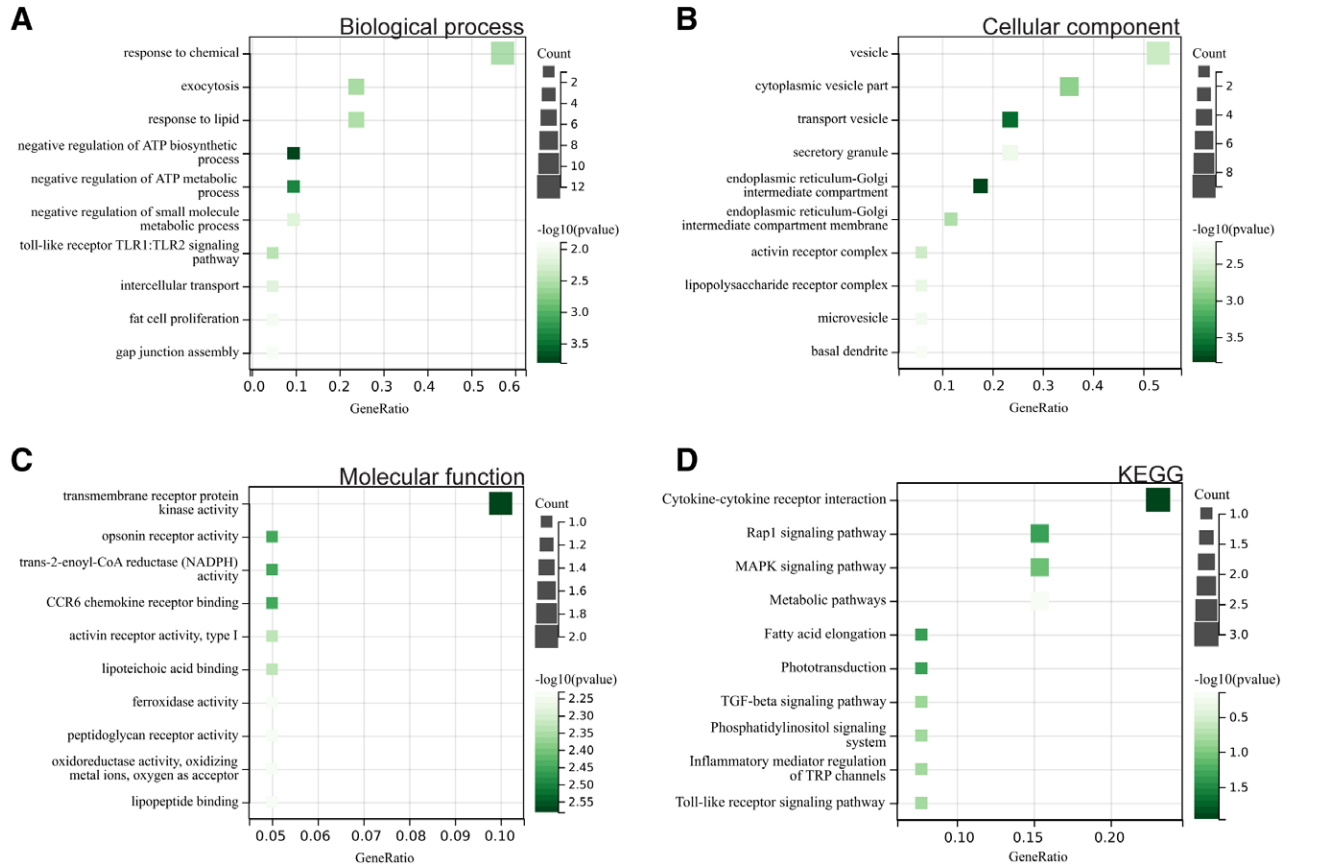

Figure 2. Functional enrichment analysis. (A–D) Functional enrichment analysis of DEGs.

CD14 can impact the inflammatory activity of OA by influencing the secretion of inflammatory cytokines and chemokines, leading to an increase in immune cells (T cells, B cells and monocytes and macrophages) within the OA synovium. Among these immune cells, monocytes play a pivotal role in OA synovitis due to their phagocytic activity and the secretion of inflammatory mediators.[24,25] Synovial mononuclear cells, when present in the synovial fluid, contribute to inflammatory edema, synovial intimal cell thickening, and chondrocyte apoptosis. Excessive migration and abnormal activation of monocytes may lead to cartilage destruction and arthritis.[26]Monocyte crosstalk and fibroblast-like synoviocytes can affect joint inflammation through synovial fluid, and fibroblast-like synoviocytes stimulated by CD14 secretes some cytokines, which leads to the deterioration of OA progress. It was found that the number of CD14 monocytes in recurrent synovial fluid was significantly higher than that in initial synovial fluid. The short time of recurrence is related to the high proportion of CD14 monocytes in SFMC. Although the reason for the increase of population in synovial fluid is not clear, CD14 monocytes and CD14 may play a vital role in OA inflammation.[27] In a study by Daghestani et al, sCD14 in synovial fluid was strongly correlated with joint space stenosis and the severity of OA pain. Activation of Toll-like receptor (TLR) signal on monocytes induces production of proinflammatory cytokines/ chemokines and transmission of pain signals.[28,29] 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.[30] 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 the 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.[31] The review of the literature is consistent with our results. 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 an important role in the occurrence and development of osteoarthritis.

The bacterium most closely associated with gastritis is *Helicobacter pylori*.[32] *Helicobacter pylori* gastritis is an infectious disease, and almost all infected individuals develop some degree of chronic gastritis. It can establish persistent colonization by manipulating the host's immune response, leading to mucosal damage and inflammation. During Helicobacter pylori infection, CD14 can mediate the immune response by recognizing specific bacterial molecules such as lipopolysaccharides. When CD14 interacts with these molecules, it can activate immune cells, triggering an inflammatory response to combat the infection. Elevated expression of CD14 has a significant impact and results in poor prognosis. Based on the literature analysis and our research findings, we speculate that CD14 may play a crucial role in the development and progression of both osteoarthritis and gastritis.

CSF1R, also known as FMS kinase, is expressed in bone marrow lineage cells consisting of monocytes, macrophages, and osteoclasts.[33] When overstimulated by its ligand CSF1, it plays a crucial role in promoting inflammation, cancer and bone disease. CSF1 is recognized as a cytokine that influences monocyte/ macrophage differentiation and inflammation. CSF1 binds to CSF1R, inducing homodimerization of CSF1R and subsequently activating receptor signal transduction and tyrosine phosphorylation of CSF1R. This activation triggers

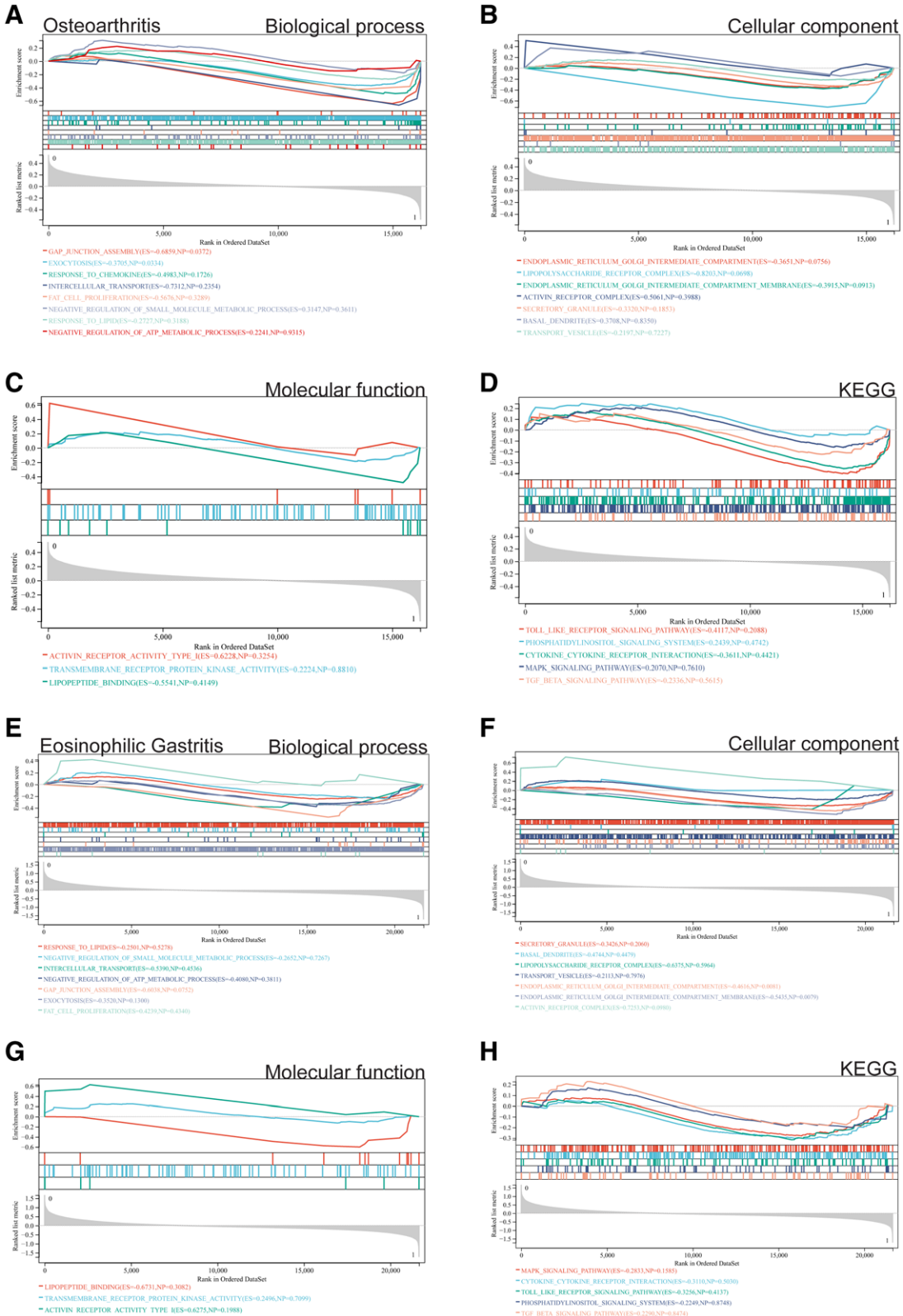

Figure 3. GSEA. (A–D)The intersection of gene expression matrix enrichment entries of osteoarthritis and GO KEGG enrichment entries of differentially expressed genes. (E–H) The intersection of gene expression matrix enrichment items of gastritis and GO KEGG enrichment items of differentially expressed genes. GO = gene ontology, GSEA = gene set enrichment analysis. KEGG = Kyoto encyclopedia of gene and genome.

downstream signaling pathways, including the phosphatidylinositol 3 kinase/ phosphorylated AKT (PI3K/pAKT) pathway, which regulates cell survival. The differentiation, proliferation, and survival of several cell types, such as macrophages, depend on CSF1R-mediated signal transduction.[34,35] CSF1R/c-FMS is overexpressed in many cancers and tumor-associated macrophages, making it a promising drug target for cancer and inflammatory diseases treatment.[36] Pexidartinib, an oral

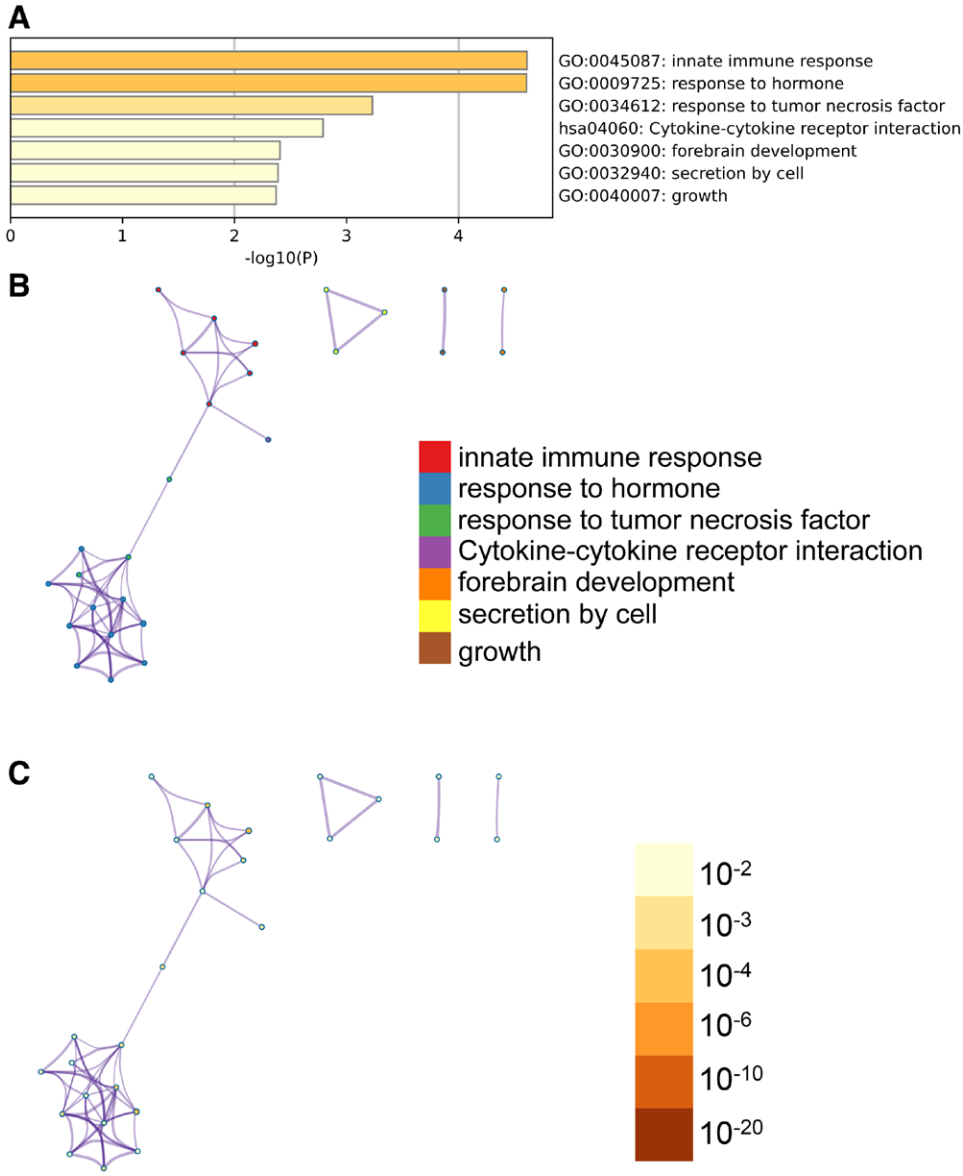

Figure 4. Metascape enrichment analysis. (A) Cytokine–cytokine receptor interaction, cell secretion, and growth were seen in the GO enrichment project. (B) The enrichment network colored by enrichment term. (C) The enrichment network colored by *P* value. GO = gene ontology.

bioavailable and effective CSF1R inhibitor, is among the most commonly used drugs in clinical practice.[37] Studies have shown that pexidartinib can slow tumor growth by reducing immunosuppression and angiogenesis, resulting in a decrease in TAM and an increase in CD4 and CD8T lymphocytes within the tumor. These findings provide a basic principle for the study of CSF1R inhibition in many other cancers. Takehiro Ota et al analyzed the possible correlation between the expression levels of CSF1, CSF1R and RANKL and the clinical course of PVNS, indicating that there was a significant correlation between the high expression of CSF1 and the incidence of osteochondral changes, while the patients with high expression of CSF1R tended to have a higher local recurrence rate of knee joint PVNS.[38] In the study of Samuel Garcia, it has been proved that specific antibodies to CSF1R can prevent CSF1 and IL-34 from binding to their receptors, reduce the severity of CIA and the production of inflammatory mediators in RA synovial explants.[39] 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 an important role in the occurrence and development of osteoarthritis.

Huang[40] found that SERPINB5 is significantly expressed in the epithelial cells of gastric high-grade intraepithelial neoplasia slices and the adjacent extracellular matrix. This expression is negatively correlated with the expression of CSF1R, which inhibits the production of related cytokines, such as TGF-β and IL-10. Activation of CSF1R can induce M1-type activation of macrophages, associated with pro-inflammatory responses. Furthermore, CSF1R may also influence the infiltration of inflammatory cells and histopathological changes in tissues. Liu[41] demonstrated in their research that the mRNA encoding the colony stimulating factor-1 receptor (CSF1R) is a direct target of miR-34a. In colorectal tumors, the loss of miR-34a confers resistance to 5-FU mediated by Csf1r, suggesting that targeting Csf1r might effectively treat defects in the p53/miR-34a pathway, a detail relevant to intestinal cells given their proximity and communication with the stomach.

The literature reviews mentioned above align with our findings, where CSF1R is highly expressed in both osteoarthritis

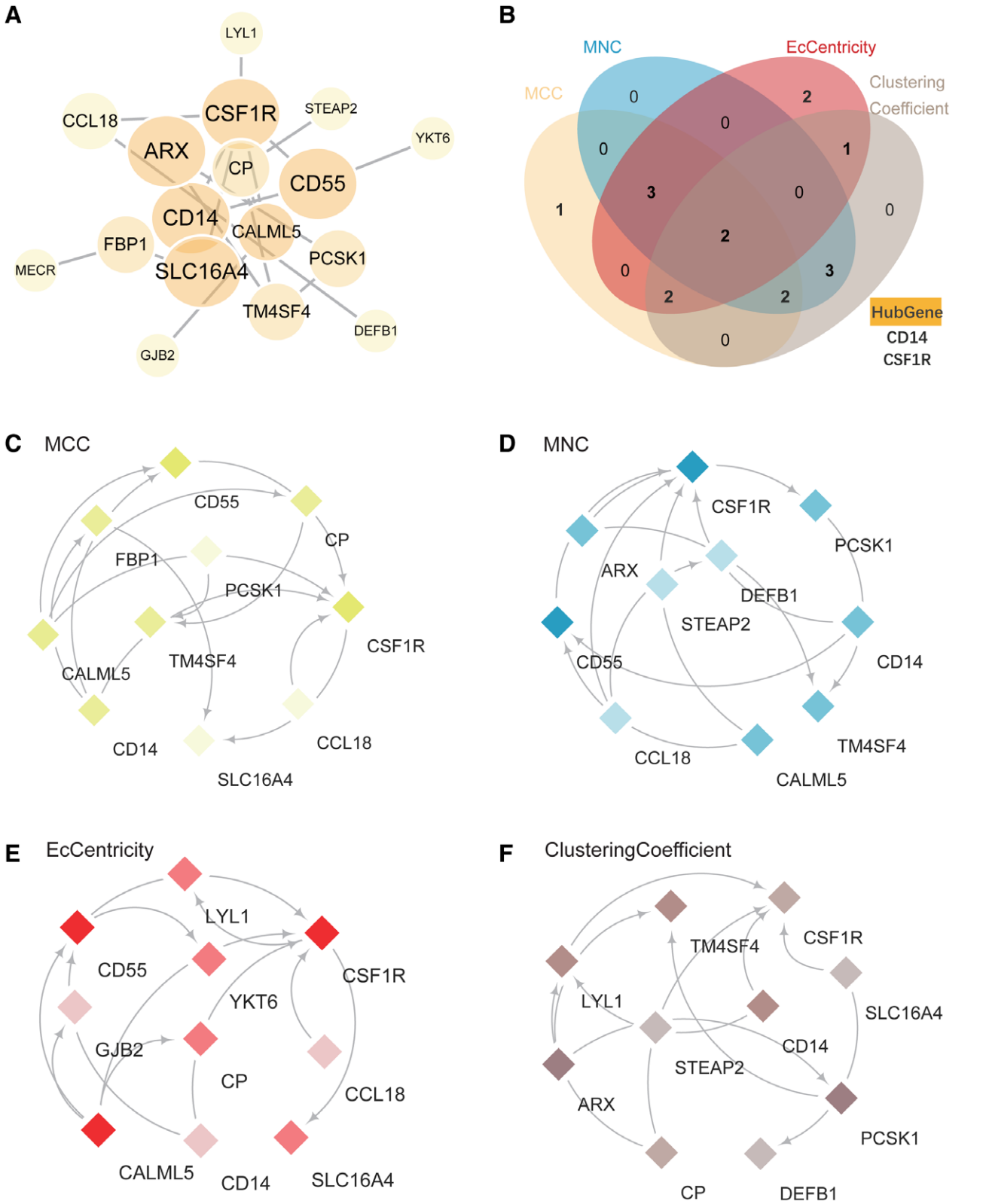

Figure 5. Construction and analysis of protein–protein interaction (PPI) network. (A) DEGs's PPI network. (B) Identification central gene. (C–F) Four algorithms (MCC, MNC, EcCentricity, ClusteringCoefficient) identified central genes. DEGs = differentially expressed genes.

and gastritis. Higher CSF1R expression is associated with poorer prognosis. Based on the analysis of the literature and our research results, we speculate that CSF1R may play a crucial role in the development and progression of both osteoarthritis and gastritis.

Although this paper has carried out rigorous bioinformatics analysis, there are still some shortcomings. In this study, no animal experiments of gene overexpression or knockout were carried out to further verify its function. Therefore, in the future research, we should make an in-depth exploration in this aspect.

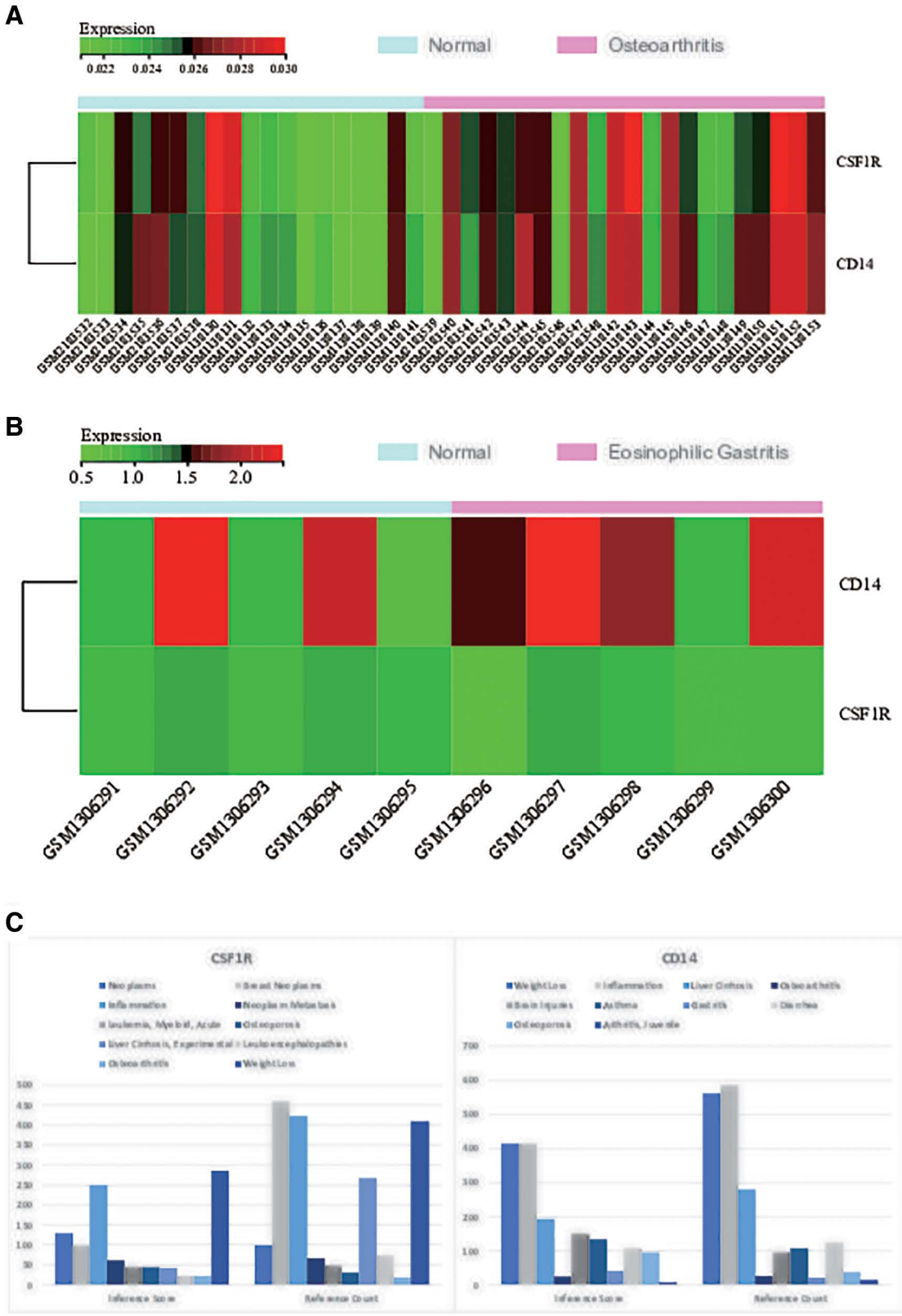

Figure 6. (A) The difference in the expression of core genes between osteoarthritis synovium and normal tissue samples. (B) Differences in core gene expression between gastritis and normal tissue samples. (C) CTD analysis showed that core genes (CD14, CSF1R) were associated with osteoarthritis, osteoporosis, gastritis, juvenile arthritis, diarrhea, and inflammation. CTD = comparative toxicogenomics database.

5. Conclusion

In summary, CD14 and CSF1R are highly expressed in patients with osteoarthritis and gastritis, and they may play a significant role in the development of these conditions through mechanisms involving inflammation and regulation of immune cells. CD14 and CSF1R can serve as molecular targets for early diagnosis and precision treatment of osteoarthritis and

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	MIRNA		
1	*CSF1R*	hsa-miR-34a-5p	hsa-miR-449b-5p	hsa-miR-34c-5p
2	*CD14*	None		

gastritis, providing a foundation for research into the molecular mechanisms of these 2 diseases.

Author contributions

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Formal analysis: Shiyang Hou, Chunbo Kang.
Investigation: Meiliang Zheng, Jie Zhang.
Methodology: Zheng Li, Yingfa Feng, Jie Zhang, Shiyang Hou, Chunbo Kang.
Resources: Shiyang Hou, Chunbo Kang.
Software: Zheng Li, Jie Zhang, Shiyang Hou, Chunbo Kang.
Supervision: Meiliang Zheng, Yingfa Feng.
Validation: Zheng Li, Yingfa Feng, Shiyang Hou, Chunbo Kang.
Visualization: Shiyang Hou, Chunbo Kang.
Writing – review & editing: Meiliang Zheng.
Writing – original draft: Yingfa Feng, Jie Zhang, Shiyang Hou, Chunbo Kang.

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