

Differential Diagnosis of Osteoarthritis and Rheumatoid Arthritis by Bioinformatics Analysis

Qing Lin

Institute of Integrative Medicine,Fujian University of Traditional Chinese Medicine

Danhong Pan

Institute of Integrative Medicine, Fujian University of Traditional Chinese Medicine

Yanfeng Huang

Anhui University of Traditional Chinese Medicine

Wenyi Wang

School of Pharmacy, Fujian University of Traditional Chinese Medicine

Changlong Fu

Fujian Provincial Key Laboratory of Integrative Medicine on Geriatrics,Fujian University of Traditional Chinese Medicine

Xihai Li

Jiangsu Province Academy of Traditional Chinese Medicine

Jinxia Ye (✉ 53378330@qq.com)

Fujian University of Traditional Chinese Medicine <https://orcid.org/0000-0001-9369-8361>

Research article

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Abstract

Background: Osteoarthritis (OA) and rheumatoid arthritis (RA) is the most common joint disease. The aim of my current academic work is to identify important genes associated with OA and RA, clarify their underlying mechanisms, and define differences between OA and RA.

Methods: Gene expression profiles of GSE55235 were available from Gene Expression Omnibus database. Differentially expressed genes between 1) OA tissues and normal tissues, 2) RA tissues and normal tissues, were picked out by GEO2R tool, Venn diagram software, and Volcanic map. Next, we made use of the Database for Annotation, Visualization and Integrated Discovery to analyze Kyoto Encyclopedia of Gene and Genome pathway and gene ontology. The protein-protein interaction of these DEGs was visualized by Cytoscape with Search Tool for the Retrieval of Interacting Genes. Of entire PPI network analyzed by Molecular Complex Detection plug-in and obtain central nodes. Then the central nodes were re-analysis via DAVID. We next obtained the intersection of the analysis results of GSE55457 and GSE55235 to verify the results. Finally, potential biomarkers were evaluated by receiver operating characteristic.

Results: Twelve genes were found to be significantly enriched in the TNF signaling pathway in OA, and eleven genes were found to be significantly enriched in the Chemokine signaling pathway in RA. Receiver operating characteristic curve suggested that the detection of JUN in OA and CCL5, CXCL9, CXCL10, CXCL11, CXCL13 in RA exhibited a high diagnostic performance.

Conclusions: We have identified six significantly DEGs on the basis of integrated bioinformatical methods, which could be potential targets for differential diagnosis for OA and RA.

Background

Osteoarthritis (OA) and rheumatoid arthritis (RA) are common joint diseases in the world. Although they have different pathogenesis, they have similar etiology, similar clinical manifestations, and some of the same cellular and molecular bases [1-2]. RA is a multi-system chronic inflammatory disease, mainly characterized by persistent and symmetrical joint pain, swelling and morning stiffness. Basic pathological changes include synovial inflammation, RA pannus formation, articular cartilage, and bone destruction. Joint deformity and loss of function as a result of "swan neck" and "button hole" deformity in fingers of middle-late patients, joint stiffness, and joint subluxation has made this disease gradually become one of the leading causes of loss of human labor and disability [3-5]. According to epidemiological statistics, RA affects 0.5-1% of the global adult population [6], while OA, as a common joint disease, may cause symptomatic OA in about 10% of the global population over the age of 60 [7]. The prevalence of OA is significantly higher in women than in men, and the incidence tends to be younger [8]. OA is characterized by joint pain, stiffness, and swelling caused by synovitis, reduction of articular cartilage tissue, thickening of subchondral bone, and formation of osteophytes [9]. Synovial membrane can not only secrete synovial fluid to reduce the friction on the joint surface, but also can provide the necessary nutrients for the articular cartilage, which is conducive to maintaining the stability and flexibility of the joint. However, when the synovium is stimulated by trauma, infection and strain, it can cause synovitis and secrete inflammatory mediators, cause degradation of cartilage matrix, and accelerate the pathological process of OA. At present, the etiology of OA is not yet clear. According to existing research, the occurrence of OA is related to age, gender, family history, obesity, trauma, increased joint load and other factors [10].

The differential diagnosis of RA and OA is challenging because the progression of the diseases usually precedes clinical manifestations, in addition, symptoms of OA and RA also have overlap in advanced cases of the disease. Therefore, finding out the differentially expressed genes of OA and RA is helpful for the accurate diagnosis, accurate treatment and prognosis of the patients. While some genes and diagnostic markers have been identified in both RA and OA, they are insufficient to fully understand the mechanisms underlying the initiation and progression of these common joint disease [11,12].

In recent years, high-throughput platform-based microarrays have been widely used in the molecular diagnosis, classification and prognosis assessment of diseases [13]. This is an important method for high-throughput study of disease gene expression profiles, which can detect a large amount of genetic information in a short period of time. As research proceeds, large amounts of genetic information are uploaded to public databases. Most of the data has not been used effectively due to differences in research purpose and tissue specificity [14]. Therefore, on the basis of previous research results, using bioinformatics technology to re-select and analyze the gene chip data can make up for these deficiencies.

In this study, we first selected the GSE55235 from Gene Expression Omnibus (GEO). Second, we applied the GEO2R online tool, Venn diagram software and Volcanic map, to obtain the commonly differentially expressed genes (DEGs). Third, a database for annotation, visualization, and synthesis of discoveries (DAVID) was used to analyze these DEGs, including molecular function (MF), cellular component (CC), biological processes (BP), and the Kyoto encyclopedia of genes and genomes (KEGG) pathway. Fourth, we established a protein-protein interaction (PPI) network and then applied cellular molecular complex detection(MCODE) for additional DEG analysis to identify some core genes. We then reanalyzed the KEGG pathway enrichment of these genes. To further prove the reliability of the above results, GSE55457 from the same platform as GSE55235 is used for verification. GSE55235 also has OA tissue, RA tissue and normal tissue. Finally, potential biomarkers were evaluated by receiver operating characteristic. In conclusion, our bioinformatics study provides biomarkers that may be effective targets for the differential diagnosis of OA and RA patients.

Methods

Microarray data information

NCBI-GEO is regarded as a free public database of microarray gene profile and we obtained the gene expression profile of GSE55235 and GSE55457 in normal tissue, OA tissue and RA tissue from the different tissue samples. Microarray data of GSE55235 and GSE55457 were all on account of GPL96 Platforms ([HG-U133A] Affymetrix Human Genome U133A Array). GSE55235 consists of synovial tissue of 10 healthy joints, 10 OA joints and 10 RA joints. GSE55457 consists of synovial tissue of 10 healthy joints, 10 OA joints and 10 RA joints.

Data processing of DEGs

DEGs between OA and normal tissues, RA and normal tissues were identified via GEO2R online tools [15] with $|logFC| > 2$ and adjust P value < 0.05 . Then, the raw data in TXT format was checked in Venn software online to detect commonly DEGs. A DEG with $logFC < 0$ was considered a down-regulated gene, while a DEG with $logFC > 0$ was considered an up-regulated gene.

Gene ontology and pathway enrichment analysis

Gene ontology analysis (GO) is a common method of defining genes and their RNA or protein products to determine the unique biological properties of high-throughput transcriptome or genomic data [16]. KEGG is a collection of databases dealing with genomes, diseases, biological pathways, drugs, and chemical materials [17]. DAVID is an online bioinformatics tool that aims to identify the function of a large number of genes or proteins. We used DAVID to visualize DEG enrichment in BP, MF and CC pathways [18]. ($P < 0.05$).

PPI network and module analysis

PPI information was evaluated by an online tool, STRING (Search Tool for the Retrieval of Interacting Genes) [19]. Then, the STRING app in Cytoscape [20] was applied to examine the potential correlation between these DEGs (maximum number of interactors=0 and confidence score ≥ 0.4). In addition, the MCODE app in Cytoscape was used to check modules of the PPI network (degree cutoff=2, max. Depth=100, k-core=2, and node score cutoff=0.2).

Identification of candidate genes

We used GSE55457 to further prove the reliability of the above candidate genes by extracting the intersection of GSE55235 and GSE55457 core genes. Finally, potential biomarkers were evaluated by receiver operating characteristic curve (ROC) with R software (v3.4.0; <http://bioconductor.org/biocLite.R>). The results were visualized and the area under the ROC curve (AUC) of the core gene was calculated. AUC > 0.5 indicates this gene has good diagnostic value.

Results

Identification of DEGs

There were 10 normal tissues, 10 OA tissues and 10 RA tissues in our present study. From GEO2R online tools, we extracted 321 and 538 DEGs from OA and RA, respectively (Fig. 1). A total of 162 DEGs in common were detected, including 73 down-regulated genes ($logFC < 0$) and 89 up-regulated genes ($logFC > 0$) (Table. 1, Fig. 2)

Figure.1 Volcanic map of all genes.

Note: Red dots indicate up-regulated genes, blue dots indicate down-regulated genes and gray dots indicate genes that are not regulated. . a. OA. b. RA.

Table.1 Differentially expressed genes.

DEGs	Genes Name
Up-regulated	CCDC102B///IGKV1OR2-108///IGHV3-23///IGHV4-31///IGHM///IGHG3///IGHG1///IGHD///IGHA1///IGH//CRIP1///ADAM12///IGHV4-31///IGHM///IGHG4///IGHG3///IGHG1///IGHD///IGHA2///IGHA1///IGHD///CCL5///IGHM///RTN1///LILRB2//CECR//GPR65///HLA-DPA1///IGLJ3///TRAF3IP3///IGLJ3///IGLV1-44///CKAP2///IGLV@///IGLC1///FAP//SORL1//ABCC3///HLA-DMB///NREP//OSBPL3///IGHV3-23///IGHV4-31///IGHM///IGHG4///IGHG3///IGHG1///IGHD///IGHA2///IGHA1///IGH FAM198B ARHGAP25 RAC2 COL1A1 WNT5A CSF2RA//CALML4//IGKC//CLEC4A//TNFSF11//IGK//IKZF1///ATM///IGLJ3///IGLV@///IGLC1//NCF1C//NCF1B//NCF1///SDC1///TLR7//TRBC1///LST1//LRRC15//POU2AF1///TPPP3///BTN3A1///LOC100509457//HLA-DQA2//HLA-DQA1//IGLJ3///CKAP2//MXRA5//DOCK10//GAP43//IGHV3-23//IGHV4-31//IGHM//IGHG1//IGHA1///XIST//CX3CR1//LOC101060835//HLA-DQB1//LOC102725526//IGHV4-31//IGHM//IGHG3//IGHG2//IGHG1//IGHA2//IGHA1//IGH//RRM2//TRIM14//NDC80//IGLC1//CD52//TOP2A//IGHM//IGHG1//IGHA2//IGHA1//IGH//IGHV4-31//IGHM//IGHG3//IGHG2//IGHG1//IGHD//IGHA2//IGHA1//IGH//CYAT1//IGLV1-44//IGLC1//EPHB2//AIF1//IGK//IGKC//COL1A2//IGHG1//APLNR//IGLL3P//CIITA//MMP1//MIR8071-2//MIR8071-1//IGHV4-31//IGHM//IGHG2//IGHG1//GUSBP11//PLXNC1//TNFRSF25//JCHAIN//KCNQ1//IGLV1-44//HK3//UCP2//LOC100506718//FLRT2//PTPRC//NKGT
Down-regulated	FKBP5///EIF1///ELL2//NPAS2//RRAD//ARC//MIR6732//ZC3H12A//LAMA2//FOSL2//NR1D1//THRA//PTX3//TIMP4//CEBDP//PPP1R1//JUND//FNDCA4//ZFP36//BCL6//MIR1908//FADS1//VEGFA//APOD//APOLD1//C10orf10//ANGPTL7//LOC100129518//MYOC//MTSS1//ADH1B//MYC//CDKN1A//LDLR//JUN//SOCS3//NR4A2//DUOX2//ZBTB16//SLC6A8//KLF9//ACADL//CCNL1//CHST7//PMAIP1//LAMA3//CYR61//NFIL3//MAFF//ADM//ADCY2//GADD45A//MT1M//FAM107A//AASS//CDH19//ATF3//PTGS2//DUSP1//HSPA1L//HSPA1B//HSPA1A//PIGA//CYP4B1//CXCL8//EGR1//FOSB//SLC19A2//GADD45B//FOXO3B//FOXO3//MAOA//HSPA1B//HSPA1A//SAA2-SAA4//SAA2//SAA1//MIR6883//PER1//NR4A1//KLF4//TFPI

Note: All 162 commonly differentially expressed genes (DEGs) were detected from profile datasets, including 89 up-regulated genes and 73 down-regulated genes.

Fig.2. The common DEGs between OA and normal tissues, RA and normal tissues.

Note: Different color meant different datasets. The common DEGs between OA and normal tissues, RA and normal tissues in GSE55235 were verified through Venn diagrams software(available online: <http://bioinformatics.psb.ugent.be/webtools/Venn/>). a 89 DEGs were up-regulated ($\log FC > 0$). b 73 DEGs were down-regulated ($\log FC < 0$).

DEGs gene ontology and KEGG pathway analysis

All DEGs of OA and RA were analyzed by DAVID software, and the GO analysis results were as follows 1) for BP, the DEGs of OA and RA were enriched in immune response and inflammatory response, OA DEGs were enriched in cellular response to fibroblast growth factor stimulus, while RA DEGs were enriched in response to cAMP. 2) for GO CC, DEGs of OA and RA were enriched in extracellular region and integral component of plasma membrane, OA DEGs were enriched in extracellular space, and RA DEGs were enriched in external side of plasma membrane. 3) for MF, they were both enriched in immunoglobulin receptor binding, OA DEGs were enriched in antigen binding, transcription factor activity, and RNA polymerase II core promoter proximal region sequence-specific binding, while RA DEGs were enriched in chemokine activity and immunoglobulin receptor binding (Fig. 3).

KEGG analysis results demonstrated that OA and RA DEGs both enriched in Rheumatoid arthritis, Osteoclast differentiation. OA DEGs were particularly enriched in TNF signaling pathway while RA DEGs were particularly enriched in Leishmaniasis ($P < 0.05$) (Fig. 4).

Fig. 3 . KEGG pathway analysis of DEGs in osteoarthritis and Rheumatoid arthritis

Note: The top 3 biological processes, cellular component and molecular function analysis in DEGs. a. OA. b. RA.

Fig. 4 KEGG pathway analysis of DEGs in osteoarthritis and Rheumatoid arthritis

Note: The dot size indicates the counts of genes and the redder the color, the richer the gene. a. OA. b. RA.

Protein–protein interaction network (PPI) and modular analysis

The DEGs of OA and the DEGs of RA were respectively imported into the DEG PPI network complex. OA contained 190 nodes and 882 edges, including 141 down-regulated and 180 up-regulated genes . RA contains 319 nodes and 2194 edges, including 199 down-regulated and 339 up-regulated genes (Fig. 5). Then we applied Cytotype MCODE for further analysis, and the results showed that there were 23 central nodes in OA DEGs and 17 central nodes in RA DEGs (figure. 6).

Fig. 5 Common DEGs PPI network

1. Note: Common DEGs PPI network constructed by STRING online database and Module analysis. The nodes meant proteins; the edges meant the interaction of proteins; blue circles meant down-regulated DEGs and red circles meant up-regulated DEGs.a. OA. b. RA.

Fig. 6 Module analysis of OA and RA

Note: Degree cutoff=2, node score cutoff=0.2, k-core= 2, and max. Depth= 100

1. b. RA.

Re-analysis of selected genes via KEGG pathway enrichment

To understand the possible pathway of these selected DEGs, KEGG pathway enrichment was re-analyzed via DAVID ($P < 0.05$). Results showed that twelve genes (CCL5, CXCL1, CXCL2, CXCL3, IL-1 β , IL-6, NFKBIA, SOCS3, TNFAIP3, JUN, MMP9 and PTGS2) in osteoarthritis markedly enriched in the TNF signaling pathway ($P = 1.24E-11$, Table 2) and eleven genes (CCL5, CCR5, CXCL5, CXCL6, CXCL9, CXCL10, CXCL11, CXCL13, ADCY2, CX3CL1, CX3CR1) in rheumatoid arthritis markedly enriched in the Chemokine signaling pathway ($P = 4.39E-13$,Table 3).

Table 2 Re-analysis of 23 genes for osteoarthritis via KEGG pathway enrichment

Pathway ID	Name	Cout	%	P-value	Genes
bta04668	TNF signaling pathway	10	0.278473962684489	1.24E-11	IL6, PTGS2, SOCS3, MMP9, CXCL3, JUN, IL1B, NFKBIA, TNFAIP3, CCL5
bta05323	Rheumatoid arthritis	9	0.250626566	1.96E-10	IL6, TNFSF11, JUN, VEGFA, IL1B, CXCL8, CCL5, CXCL12, MMP1

Table 3 Re-analysis of 17 genes for rheumatoid arthritis via KEGG pathway enrichment.

Pathway ID	Name	Cout	%	P-value	Genes
hsa04062	Chemokine signaling pathway	11	0.533462658	4.39E-13	ADCY2, CXCL5, CCR5, CXCL13, CX3CR1, CXCL9, CXCL6, CX3CL1, CCL5, CXCL11, CXCL10
hsa04060	Cytokine-cytokine receptor interaction	10	0.484966052	3.08E-10	CXCL5, CCR5, CXCL13, CX3CR1, CXCL9, CXCL6, CX3CL1, CCL5, CXCL11, CXCL10

Verify genes with GSE55457 and evaluated by ROC

The reliability of the above results is further verified by GSE55457. Results showed that three genes markedly enriched (JUN, VEGFA, HGF) in osteoarthritis and five genes (CCL5, CXCL9, CXCL10, CXCL11, CXCL13) markedly enriched in rheumatoid arthritis. The results of extracting the intersection of GSE55235 and GSE55457 core genes showed as JUN, CCL5, CXCL9, CXCL10, CXCL11, CXCL13. ROC curves were constructed by R software to calculate the AUCs of JUN (99.0%), CCL5 (88.5%), CXCL9 (97.7%), CXCL10 (95.4%), CXCL11 (96.6%) and CXCL13 (96.5%) (Fig. 7).

Figure 7. Receiver operating characteristic curves.

Note: Receiver operating characteristic curves of the six genes in the core network using data from the GSE55457. Receiver operating characteristic curves of JUN, CCL5, CXCL9, CXCL10, CXCL11, CXCL13 are presented.

Discussion

To identify more useful biomarkers for the differential diagnosis of OA and RA, this study used bioinformatic methods on the basis of GSE55235 profile datasets. Using GEO2R and Venn software, we revealed a total of 162 changed DEGs in common, including 89 up-regulated and 73 down-regulated DEGs. Then, Gene Ontology and Pathway Enrichment Analysis using DAVID methods showed that 1) for BP, the difference is that OA DEGs are enriched in cellular response to fibroblast growth factor stimulus, while RA is enriched in response to cAMP. 2) for GO CC the difference is that OA DEGs are enriched in extracellular space, while RA DEGs are enriched in external side of plasma membrane. 3) for molecular function (MF), OA DEGs are enriched in antigen binding, transcription factor activity, and RNA polymerase II core promoter proximal region sequence-specific binding, while RA DEGs are enriched in chemokine activity and immunoglobulin receptor binding. For pathway analysis, OA was particularly enriched in TNF signaling pathway while RA was particularly enriched in Leishmaniasis ($P < 0.05$). Next, OA DEGs PPI network complex of 190 nodes and 882 edges was constructed via the STRINGonline database and Cytoscape software. Then, 23 vital genes were screened from the PPI network complex by Cytotype MCODE analysis. And RA DEGs PPI network complex of 319 nodes and 2194 edges was constructed and 17 vital genes were screened. There were 12 genes found to significantly enrich in the TNF signaling pathway in OA and eleven genes were found to significantly enrich in the Chemokine signaling pathway in RA via re-analysis of DAVID. In order to further prove the reliability of the above results, the GSE55457 was used for verification, and the intersection of the analysis results of GSE55457 and GSE55235 was obtained. Finally, potential biomarkers were evaluated by receiver operating characteristic analyses, which suggested that the detection of JUN in OA and CCL5, CXCL9, CXCL10, CXCL11 and CXCL13 in RA exhibited a high diagnostic performance.

JUN family members Jun B, c-Jun and Jun D constitute the transcriptional activation protein important subunits (AP-1; activator protein 1), widely involved in cell proliferation, differentiation, apoptosis, and the tumor formation process [21]. Typically, in families of protooncogenes, there is a class of genes that can be directly induced and activated by a second messenger, which we call IEGs, or immediate early genes. This group of genes is mainly related to the biochemical changes in the cell, but also related to the specific changes in the cell, or is one of the mediators, so it is sometimes called the third messenger [22]. C-Jun is an important member of the IEG family and an important indicator of subchondral bone remodeling. Immunohistochemical studies reveal that c-Jun proteins are upregulated in chondrocytes from the articular cartilage of OA patients [23]. Additionally, studies have shown that c-Jun regulates chondrocyte apoptosis during OA [24].

Chemokines (CK) are a class of chemotactic cytokines, which mediate the entry of inflammatory cells such as neutrophils and monocytes into the synovium where inflammation exists. According to the different positions of conserved cysteine residues, chemokines can be divided into four classes, namely CXC, CC, C and CX3C. In the process of mediating inflammation, CXC and CC chemokines play a particularly important role [25]. The results of bioinformatics analysis showed that CCL5, CXCL9, CXCL10, CXCL11 and CXCL13 had significant differences.

The serum level of CCL5 is increased in RA patients, and CCL5 is significantly correlated with the range of motion lesions in rheumatoid arthritis, such as joint swelling index, blood sedimentation, and c-reactive protein [26]. In contrast, the content of CCL5 in synovial fluid of OA patients did not significantly increase, even though there was a large number of inflammatory cells [26]. The level of CCL5 produced by synovial inflammatory cells in vitro was not significantly different from that of CCL5 produced by peripheral blood leukocytes. Current research suggests that when stimulated with a combination of IFN-gamma and TNF-alpha, synovial tissue cells and synovial fibroblast-cell lines (fourth or fifth passage) were able to secrete large amounts of CXCL9, CXCL10, CXCL11, and CXCL13 [27,28]. Beyond that, the expression levels of chemokines CCL5, CXCL9, and CXCL10 in RA synovial membrane were significantly higher than that of OA synovial membrane [29]. The CXCL13 level increase was associated with disease activity of RA. Serum CXCL13 can be used as a reference index to evaluate the severity of RA patients and is of high value in the diagnosis of RA [29].

Chemokines and chemokine receptors play an important role in the inflammatory process and are also widely involved in the occurrence of some inflammatory diseases. Therefore, the use of chemokines and chemokine receptors as differential diagnostic targets may provide new ideas and methods for the clinical diagnosis of OA and RA.

Conclusions

Taken above, our bioinformatics analysis study identified six genes (JUN, CCL5, CXCL9, CXCL10, CXCL11, and CXCL13) between OA and normal tissues, and RA and normal tissues on the base of microarray datasets. Results showed that these six genes could play key roles in the progression of OA or RA. Therefore, these genes are expected to be a new molecular target for the differential diagnosis of OA and RA. However, there are few reports on the comparative study of these 6 genes between OA and RA. Therefore, these predictions should be verified by a series of experiments in the future. Moreover, this work has important theoretical significance and broad application prospect for finding new drug targets and screening new drugs and clinical application in the treatment of OA and RA.

Abbreviations

abbreviations	Full Name
OA	Osteoarthritis
RA	rheumatoid arthritis
GEO	Gene Expression Omnibus
DEGs	differentially expressed genes
DAVID	Database for Annotation, Visualization and Integrated Discovery
KEGG	Kyoto Encyclopedia of Gene and Genome
GO	gene ontology
PPI	protein-protein interaction
STRING	Search Tool for the Retrieval of Interacting Genes
MCODE	Molecular Complex Detection
DEGs	differentially expressed genes
MF	molecular function
CC	cellular component
BP	biological processes
ROC	receiver operating characteristic curve
AUC	area under the ROC curve
AP-1	activator protein 1

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QL conceived and designed the study. WW, DP and YH collected the expression data and screened for the differentially expressed genes. CF analyzed and interpreted the data. QL wrote the manuscript. XL and JY reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Figures

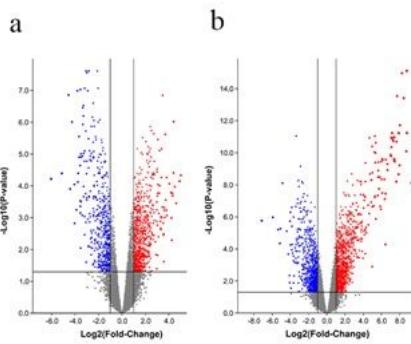


Figure 1

Volcanic map of all genes.

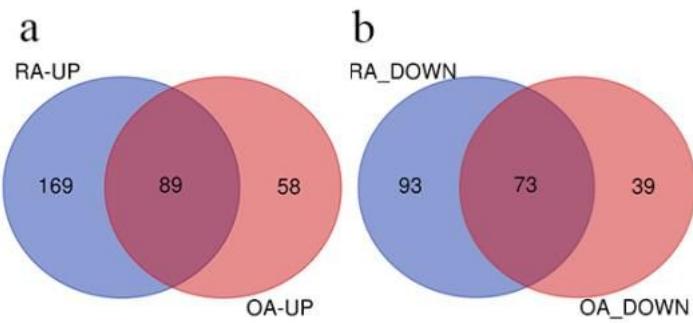
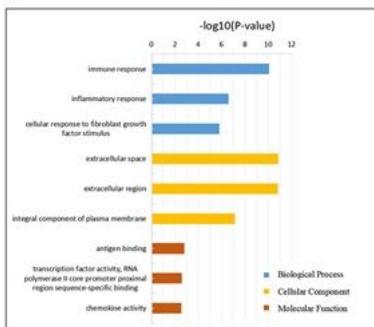


Figure 2

The common DEGs between OA and normal tissues, RA and normal tissues.

a



b

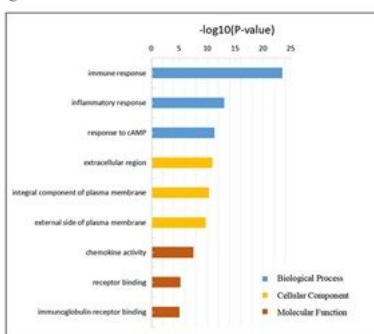
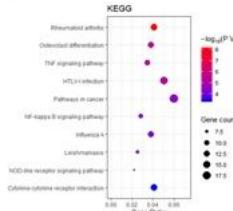


Figure 3

KEGG pathway analysis of DEGs in osteoarthritis and Rheumatoid arthritis Note: The top 3 biological processes, cellular component and molecular function

a



b

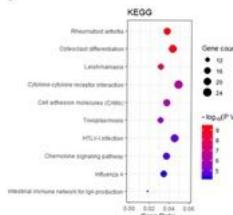


Figure 4

KEGG pathway analysis of DEGs in osteoarthritis and Rheumatoid arthritis Note: The dot size indicates the counts of genes and the redder the color, the richer the gene. a. OA. b. RA.

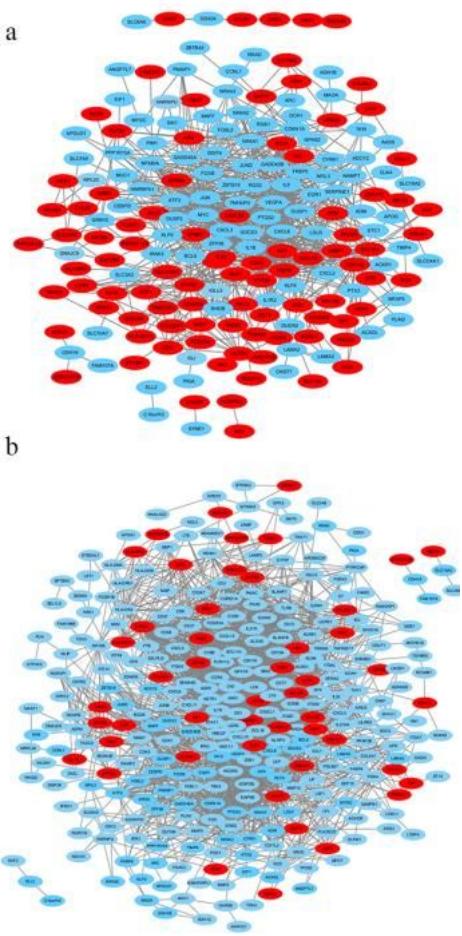


Figure 5

Common DEGs PPI network a. Note: Common DEGs PPI network constructed by STRING online database and Module analysis. The nodes meant proteins; the edges meant the interaction of proteins; blue circles meant down-regulated DEGs and red circles meant up-regulated DEGs.a. OA. b. RA.

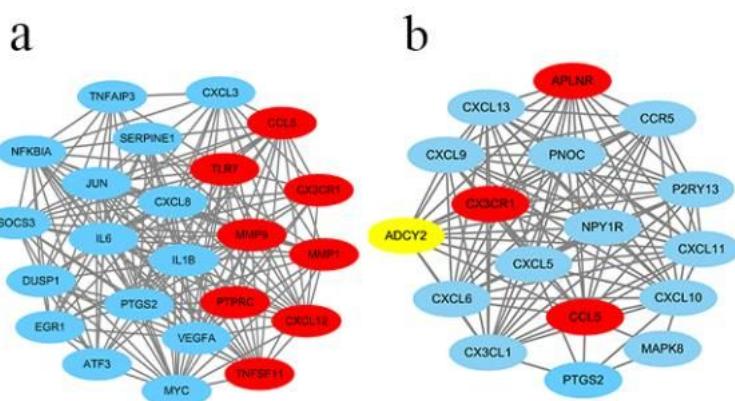


Figure 6

Module analysis of OA and RA Note: Degree cutoff=2, node score cutoff=0.2, k-core= 2, and max. Depth= 100 b. OA. b. RA.

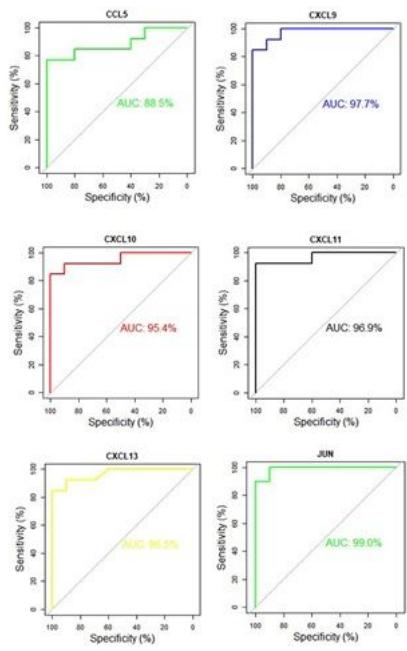


Figure 7

Receiver operating characteristic curves. Note: Receiver operating characteristic curves of the six genes in the core network using data from the GSE55457. Receiver operating characteristic curves of JUN, CCL5, CXCL9, CXCL10, CXCL11, CXCL13 are presented.