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Analysis of Differentially Expressed Genes in Osteonecrosis of Femoral Head, Osteoarthritis, and Rheumatoid Arthritis by Integrated Microarray Analysis

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// Abstract

Background

Osteonecrosis of femoral head (ONFH), osteoarthritis (OA) and rheumatoid arthritis (RA) are common diseases of hip joint, which will damage the joint to varying degrees, and will affect the mobility and quality of life of patients in severe cases. A better understanding of the expression of articular cartilage degeneration genes seems to be very important for further understanding the molecular mechanism of the joint action of the three diseases.

Objective

the purpose of this study was to explore the pathogenesis of cartilage injury in three diseases by analyzing the data sets of multiple gene expression groups and synthesizing the differentially expressed genes (DEGs) of ONFH, OA and RA.

Methods

the gene expression datasets of ONFH, OA and RA were obtained from Gene Expression Omnibus. Through the comprehensive analysis of multiple gene expression data sets, the common differentially expressed genes and specific DEGs in these diseases were found. Gene ontology (GO) analysis, KEGG pathway and protein-protein interaction analysis were used to investigate the functions of the altered proteins and biological pathways.

Results

A total of 59 common differentially expressed genes were obtained by GSE74089 and GSE55235 data sets, including 44 up-regulated genes and 15 down-regulated genes. GO and KEGG pathway enrichment analysis showed that DEGs concentrated on extracellular structure organization, extracellular matrix organization, fibrillar collagen trimer, platelet-derived growth factor binding, Relaxin signaling pathway, Protein digestion and absorption. Some hub genes with high interactions such as COL1A2, MMP1, VEGFC, SPP1, etc. Independent GEO dataset verification results show that these genes are consistent with the experimental results.

Conclusion

In this study, bioinformatics methods were used to identify the common differential genes of ONFH, OA and RA, and to analyze the occurrence and development of cartilage degeneration or osteogenic diseases induced by them. To provide molecular basis for follow-up experiments and clinical efficacy.

1 Introduction

Osteonecrosis of femoral head (ONFH), osteoarthritis (OA) and rheumatoid arthritis (RA) are all disability diseases caused by a variety of common causes of the hip joint, and Total hip arthroplasty (THA) is needed in severe cases. They affect the lives of over 240 million people around the world and seriously threatens human health[1]. They are multifactorial diseases, which are related to genetic factors, environmental factors, and their interactions[2−4].

Persistent recurrent inflammation of synovitis in these three diseases lead to rapid destruction of cartilage and bone which could result in joint dysfunction, chronic disability, poor life quality and reduced life expectancy. About 65-70% of advanced ONFH patients require total hip arthroplasty[5, 6]. Although ONFH, OA and RA share multiple common symptoms, the synovial pathological manifestations of the three diseases are not the same, the molecular mechanism is not very clear, and there is a lack of effective prevention and early treatment[7−10].

Compared with individual gene expression profiles, integrated analysis of these gene expression profile data in different platforms will contribute for exploring mechanism of RA and OA with larger sample size, more accurately. This study intends to extract the microarray data of ONFH, OA and RA from GEO database (National Center of Biotechnology Information NCBI, for differential gene expression profile analysis, find the biological functions and signal pathways of differential expression genes, explore the pathogenesis from the molecular level to provide theoretical basis for later experimental research.

2 Methods

2.1 Gene Expression Omnibus data set selection

The Gene Expression Omnibus (GEO, http://www.ncbi. nlm.nih.gov/geo) is the largest database of high-throughput gene expression data. To explore the changes of expression profiling and reveal biological processes in cartilage of patients with ONFH, RA and OA, eligible microarray data sets were downloaded from GEO database. The inclusion criteria of microarray data sets were as follows: (1) data sets should be the expression profile of genome-wide messenger RNA transcriptome data; (2) data sets consisted of expression profiles in synovium of patients with RA, OA, and normal controls; (3) data sets were standardized or raw data sets. Data sets with drug stimulation or transfection were excluded. R software (version 3.4.0; https://www.r-project.org/) and Bioconductor packages (http://www.bioconductor.org/) were used in the data analyses. The computer codes used in this study can be found in the Supplemental Files. The sva package that contains functions for removing batch effects and other unwanted variation in high-throughput experiments were used for normalizing data sets[11].

2.2 Identification of DEGs

The normalized data were intersected with gene symbol and reference information. And then the data were analyzed with the Limma package in the R to examine DEGs. Only the genes with P value≤0.05 and|log2 fold change (FC)| ≥ 1 were identified as DEGs. Differential expressed genes with statistical significance were identified through volcano plot filtering. Hierarchical clustering was performed using

Morpheus (https://software.broadinstitute.org/ morpheus/). The intersections of DEGs in different microarrays were visualized using Bioinformatics & Evolutionary Genomics(http://bioinformatics.psb.ugent.be/webtools/Venn/).

2.3 Functional analysis

Gene Ontology (GO) is a major bioinformatics tool for annotating genes and analyzing their biological processes[12]. KEGG is a database resource for understanding high-level functions and biological systems from large-scale molecular datasets generated by high-throughput experimental technologies. The cluster Profiler package (https://bioconductor.org/packages/release/bioc/html/clusterProfiler.html) in Bioconductor was used to perform the GO and KEGG pathway analysis of the DEGs. $P < 0.05$ was considered statistically significant.

2.4 PPI network construction

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) was applied for predicting the PPI network and detecting the possible relationships (confidence score 0.150, maximum number of interactors = 0)[13, 14]. Furthermore, the differential allogeneic protein-protein interaction network model (PPI) was obtained by cytoscape, and the cytoHubba plug-in was used to calculate the top 20 genes respectively by using three different algorithms of Degree, Betweenness and closeness[15, 16]. Besides, the key genes are obtained by the intersection of the gene sets obtained by three different algorithms with the online analysis platform Draw Venn Diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/).

2.5 Verification of DEGs

Independent GEO databases was used to verify the accuracy of the screened gene data. According to the results of gene function research, all the differential genes selected in the gene chip experiment were brought into a separate sequencing database and compared with the ONFH, OA, RA, and normal control (NC) group to calculate the changes and differences of gene expression.

2.6 Statistical analysis

SPSS 26.0 was used to perform statistical analysis. The results are presented as mean ± standard deviation (mean ± SD). Data conforming to normal distribution were compared using Student t test, while those with non-normally distributed were tested using Mann-Whitney u test. $P < 0.05$ indicates statistical significance.

3 Results

3.1 Gene expression data sets of ONFH, OA and RA

Two expression data sets of ONFH, OA, RA, and normal controls were obtained with accession number of GSE74089 and GSE55235[17, 18]. The dataset GSE74089 was produced by GPL13497 Agilent 026652 Whole Human Genome Microarray 4x44K v2. The dataset GSE55235 was produced by GPL96 Affymetrix

Human Genome U133A Array (Agilent Technologies, Santa Clara, CA). The dataset GSE74089 contained data of hip cartilage with femoral head from 8 samples, including 4 NC, 4 ONFH samples. The dataset GSE55235 is including data of synovial tissues from 10 RA and 10 OA samples (Table 1). There are two other databases used for validation in the Table 1.

Table 1. Four datasets used for gene expression profiles analysis

GEO ID	Platform	Samples	Year	Country	Author	Use
GSE74089	GPL13497	ONFH :normal= 4:4	2016	China	Ruiyu L	Research
GSE55235	GPL96	RA:OA:normal= 10:10:10	2014	Germany	Kinne RW	Research
GSE123568	GPL15207	ONFH :normal= 30:10	2019	China	Zhang Y	Verification
GSE55457	GPL96	RA:OA:normal= 13:10:10	2014	Germany	Kinne RW	Verification
Date of visit: July 20, 2021; Species: Homo sapiens						

3.2 Identification of differentially expressed genes

The DEGs were investigated in ONFH, OA, RA, and NC in GSE74089 and GSE55235. All the results are based on the corrected $P < 0.05$ and $|\log2 FC$ (fold change) $| \geq 1$ as the standard. Compared with normal controls, 3742 (2782 upregulated and 960 downregulated DEGs) were identified in ONFH. Compared with normal controls, 340 DEGs (240 upregulated and 100 downregulated DEGs) were identified in OA. 650 DEGs (357 upregulated and 293 downregulated DEGs) were identified in RA. Only the genes with P value≤0.05 and|log2 fold change (FC)| ≥ 1 were identified as DEGs. The volcano plot of DEGs in each group was presented in Figure 1. The Venn diagrams showed the 59 overlap DEGs between DEGs of ONFH versus NC, OA versus NC and RA versus NC, consisting of 44 up-regulated genes and 15 down-regulated genes (Figure 2). The list of common DEGs is shown in Table 2.

Figure 2. Venn diagram of DEGs. Purple represented DEGs between ONFH and normal controls, green represented DEGs between RA and normal controls, red represented DEGs between OA and normal controls, and yellow-green in the middle represented DEGs between ONFH, OA and RA.A. up-regulated genes ;B. down-regulated genes.

Table 2. List of common DEGs

Differential expression	Genes
up-regulated	ZFP30 VEGFC C1QTNF3 MXRA5 CEMIP SDC1 MMP1 CRIP1 C1ORF54 ANKH GASK1B DPYSL3 NREP LRRC15 PRSS23 COL5A2 PSPH JMJD4 MMP13 COL1A2 OSBPL3 COL5A1 OLFML2B TSPAN2 TNFSF12 LOXL1 COL3A1 FAP SPP1 ANTXR1 THY1 PLBD1 MARCKS DOCK4 RNASEL NAIP LRRC17 KCNN4 OGN SLC16A4 COL1A1 JAK2 ADCY7 GPR171
down-regulated	FMO2 CITED2 GJA4 NEUROG3 APOD CYP4B1 PLPP3 PPP1R15A MYOC TEAD3 DUSP4 PNPLA2 JUNB CCNL1 ADH1C

3.3 Enrichment analysis of DEGs

The online database DAVID (https://david.ncifcrf.gov/tools.jsp) was used to analyze the function and pathway enrichment of up-regulated and down-regulated common DEGs obtained from the intersection

of three data sets in the two chips, in order to further explore the potential pathogenesis of the disease.

GO functional enrichment analysis showed that the DEGs were mainly involved in Biological Process (extracellular structure organization, extracellular matrix organization, collagen fibril organization, neuron projection regeneration, collagen metabolic process), Cellular Component (fibrillar collagen trimer, banded collagen fibril, complex of collagen trimers, collagen trimer, collagen-containing extracellular matrix), and Molecular Function (platelet-derived growth factor binding, extracellular matrix structural constituent conferring tensile strength, extracellular matrix structural constituent, integrin binding, protease binding) (Fig. 3). KEGG pathway analysis revealed that the DEGs were mainly enriched in the Relaxin signaling pathway, Protein digestion and absorption, AGE-RAGE signaling pathway in diabetic complications, ECM-receptor interaction Platelet activation (Fig. 4).

3.4 Protein-protein interaction (PPI) network analysis

The selected differential genes are mapped to the STRING online analysis software, and the interaction network of proteins encoded by differential genes is obtained. The network consists of 59 nodes and 265 edges, as shown in figure 5.

Three different algorithms (MCC) in the Cytoscape software's cytoHubba plug-in were used to calculate top 15 upregulated key genes (Fig. 6, Table 3) and obtain the intersection. Hub genes for bone necrosis are as follows: COL1A2, COL1A1, COL3A1, COL5A1, COL5A2, MMP1, VEGFC, SPP1, THY1, SDC1, MMP13, FAP, LOXL1, OGN, LRRC15, MXRA5, ANTXR1, OLFML2B, MYOC, DPYSL3.

Table 3. List of common DEGs

Top 15 in network string_interactions ranked by MCC method		
Rank	Name	Score
1	COL1A2	5393042
2	COL1A1	5390754
3	COL3A1	5346048
3	COL5A1	5346048
5	COL5A2	5254602
6	MMP1	4941516
7	VEGFC	4515864
8	SPP1	4441843
9	THY1	4153681
10	SDC1	4112670
11	MMP13	4037214
12	FAP	1049064
13	LOXL1	822960
14	OGN	622848
15	LRRC15	488892

3.5 GEO validation of the hub genes

GSE123568 and GSE55457 were used to verify the identified DEGs[18]. The results showed that the expression trend of the gene of COL1A2, COL5A1, COL5A2, MMP1, VEGFC, SPP1, THY1, SDC1, MMP13, FAP, LOXL1, LRRC15, MXRA5, ANTXR1, OLFML2B, MYOC, DPYSL3in ONFH, OA and RA was consistent with the results of gene chip detection and bioinformatics analysis (adj P value < 0.05), but COL1A1, COL3A1, OGN, were not consistent with the experimental data (adj P value > 0.05) (Fig.7).

Fig.7 GEO validation of the hub genes. The X-axis represented the ONFH, OA, RA groups and the Y-axis represented the relative expression levels. ONFH, osteonecrosis of the femoral head; OA, osteoarthritis; RA, rheumatoid arthritis

4. Discussion

ONFH, OA and RA of the hip are common diseases of the hip. Joint replacement is needed in severe cases, which not only increases the economic burden of patients, but also reduces the living standard and exercise ability. The common pathological features of ONFH include decreased blood supply of hip joint, cartilage degeneration, collapse of femoral head and accumulation of microfractures without continuous remodeling[19, 20]. ONFH often leads to damage of local microcirculation of femoral head, stress of endoplasmic reticulum of osteoblasts and apoptosis of osteoblasts, as well as imbalance

between adipogenesis and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSC) due to long-term and heavy use of glucocorticoids. Osteonecrosis leads to the collapse of the femoral head and damage of the hip joint. In the middle and late stage, OFFH is often associated with severe intra-articular cartilage and synovial lesions, accompanied by obvious pain and insufficiency and other complications[21, 22]. OA is a chronic disease characterized by cartilage degeneration, synovial hyperplasia, osteophyte formation and subchondral osteosclerosis. Its typical signs and symptoms include joint swelling, pain, stiffness, deformity, resulting in dysfunction and limitation of activity[23-25]. RA is a chronic autoimmune disease characterized by persistent synovitis, systemic inflammation, and the production of autoantibodies, which can lead to the destruction of cartilage and bone[26].

Many studies have sequenced the necrotic areas and found DEGs to find out the law of the occurrence and development of the disease[27-29]. However, through arthroscopic examination, we found that there were pathological changes of articular cartilage in the early and middle stages of osteonecrosis of the femoral head. And previous studies have confirmed that hip arthroscopic debridement and drilling decompression can significantly improve the pain symptoms of patients with osteonecrosis of the femoral head and prolong the survival time of osteonecrosis of the femoral head. Hip arthroscopic surgery for OA and RA can also reduce pain and improve joint function. Histological changes of articular cartilage, including chondrocyte loss, surface fibrillation and subchondral bone thickening, may lead to differences in gene expression in articular cartilage.

Whether these lesions and osteonecrosis occur at the same time or one after another, whether there is a relationship between its pathogenesis and the destruction of cartilage by common cartilage lesions (OA, RA) needs to be explored from the genetic level[24]. In this study, the research group based on the GEO database fully mining these three diseases related to big data, integration, through bioinformatics analysis to find the common factors of hip cartilage injury, to provide a new perspective for future data mining research methods. DEGs can cause changes in cell function, participate in the regulation of cell gene expression through a variety of ways, and play an important role in a variety of pathophysiological processes. A total of 44 up-regulated genes and 15 down-regulated genes were screened. GO enrichment analysis showed that these differential genes were mainly involved extracellular matrix organization; collagen catabolic process; blood vessel development; collagen fibril organization; osteoblast differentiation; skeletal system development; positive regulation of cell migration; medallion binding; integrin binding; platelet-derived growth factor binding. Extracellular matrix provides a living environment for many cells in the body and affects the activity of many important cells in the body. The extracellular matrix of cartilage is synthesized by chondrocytes, and its synthesis and decomposition balance maintain cartilage homeostasis. It is mainly composed of proteoglycan, collagen, water, minerals, and fibrin, which is the basis of the biomechanical properties of articular cartilage. Provide shear stress and compressive stress for joint movement. The metabolism of cartilage extracellular matrix plays an important role in osteoarthritis. The synovium and extracellular matrix of cartilage in the hip joint were degraded, at the same time, the development of blood vessels and blood components and the ability of osteogenic differentiation decreased, which led to the further degeneration of cartilage.

These results indicate that the expression of cartilage and extracellular matrix-related genes is up-regulated and induces the repair process of degenerated cartilage, which may be caused by many factors such as cartilage hypoxia, ischemia, metabolic disorder, and insufficient angiogenesis. At the same time, the up-regulation of antigen processing related genes indicates that the immune response of degenerated cartilage is weakened, which may be the activation of cartilage protection. The differential expression of these genes may be due to the response of cartilage to hypoxia, ischemia, and metabolic regulation, but it failed to change the gradual degeneration process of cartilage.

KEGG pathway analysis focuses on PI3K-Akt signaling pathway; ECM-receptor interaction; Focal adhesion; Protein digestion and absorption; Platelet activation. These signal transduction pathways can regulate cell function from many angles. The activation of PI3K-Akt signaling pathway plays an important role in maintaining cell proliferation and reducing the rate of apoptosis. The activation of PI3K-Akt signaling pathway is very important for the osteogenic differentiation of bone marrow mesenchymal stem cells. When cells are exposed to hypoxia, the expression of hypoxia inducible factor-1α (HIF-1α) is up-regulated, and the transcription of downstream vascular endothelial growth factor (VEGF) is accelerated, which increases vascular permeability and mediates vascular endothelial neovascularization[30]. Focal adhesion is an important structure in the cytoskeleton, it may be involved in the regulation of cell growth in the early stage of osteonecrosis. Cells rely on the special structure of "Focal adhesion" to maintain its normal shape and function. Protein digestion and absorption is related to the destruction of bone balance and the collapse of articular cartilage in the later stage of avascular necrosis of the femoral head[31]. Relaxin signaling pathway has multiple effects, including vasodilation, anti-fibrosis, and angiogenesis.

In this study, it was found that in the PPI network constructed by differentially expressed genes, in addition to COL1A1, COL1A2,COL3A1,COL5A1,COL5A2, which is the main component of cartilage, eight up-regulated hub gene of MMP1, MMP13,VEGF-C,SPP1,THY1,SDC1 and LOXL1,OGN may be involved in the occurrence and development of cartilage degeneration in three diseases.COL1A1 encodes the pre-α1 chain of type I collagen, which is abundant in bone. COL1A1 mutation is one of the main causes of osteogenesis imperfecta. COL3A1 encodes the pre-α1 chain of type Ⅲ collagen, which is widely expressed in vascular system. COL5A1 and COL5A2 encode α chain and β chain of V collagen, which are secondary components of connective tissue and may be related to joint relaxation and osteoarthritis. Matrix metalloproteinases (MMPs) are the main mediators of extra-cellular matrix (ECM) degradation. Tissue metalloproteinases family is considered to play a key role in the destruction of cartilage and bone. VEGF-C is a vascular endothelial growth factor C, which has immunocyte chemotaxis and cytokine activity, and is rich in growth factor receptor binding and growth factor activity, which is related to the degradation of cartilage matrix and the destruction of synovium. VEGF promotes angiogenesis by stimulating mitosis and inducing endothelial cell migration. It can enhance and maintain the permeability of capillaries, which is not only conducive to the formation of neovascularization in the form of budding, but also conducive to the transport of nutrients and the spread of inflammation. MMP-1 and MMP13 can promote the proteoglycan in cartilage matrix to cleave highly and finally form the destruction of articular cartilage.

Interstitial collagen [illegible], [illegible], [illegible], which are the components of extracellular matrix, can be cleaved by MMP1 and MMP13. Among these proteases, MMP13 acts as the central node of cartilage degradation network and plays a combined role mainly through the degradation of extracellular matrix and cartilage in the early stage of osteoarthritis. SPP1 encodes phosphoprotein-1, which is produced by osteoblasts, chondrocytes, synoviocytes, T cells and other tissues and cells. Studies have shown that SPP1 is involved in the molecular mechanism of osteoarthritis and is an important factor leading to osteoarthritis. SPP1 induces the proliferation of synovial cells and the release of inflammatory factors, which plays an important role in the degradation of articular cartilage. SPP1 contributes to osteoclast-mediated bone resorption and joint inflammatory responses in the mouse model of rheumatoid arthritis. THY1 mediates cartilage degeneration by immunity. SDC1 is a transmembrane (type I) heparan sulfate proteoglycan, which is a member of the Syndecan proteoglycan family. Sdc1 is expressed in hepatocytes, epithelial cells, and the endothelium, where it interacts with various chemokines and cytokines to regulate differentiation, migration and proliferation. The syndecans mediate cell binding, cell signaling, and cytoskeletal organization. The syndecan-1 protein functions as an integral membrane protein and participates in cell proliferation, cell migration and cell-matrix interactions via its receptor for extracellular matrix proteins. OGN affects the formation of bone and blood vessels through metabolic pathway. Some studies have shown that OGN is involved in the process of osteocyte apoptosis in ONFH, which is a signal of osteoclast recruitment and increases bone mass loss 7. According to the analysis of the results of this study, OA and RA are also involved in OGN, which may induce bone composition destruction by similar pathways and mechanisms. The results of enrichment analysis of these key gene biological processes show that they are mainly involved in the composition and metabolism of extracellular matrix. The results once again suggest that these key genes may damage articular cartilage by regulating extracellular matrix metabolism.

Based on the above information analysis, in the initial stage of ONFH, reduced angiogenesis, insufficient blood supply, hypoxia, metabolic disorders, leading to local osteonecrosis, apoptosis, osteoclast-mediated bone resorption[20, 32, 33]. Then the osteoblast-mediated repair response begins[34, 35]. However, the imbalance between bone remodeling and resorption destruction leads to structural damage and collapse of the subchondral bone of the femoral head. The cartilage tissue of the collapsed femoral head eventually degenerated and softened due to the decrease of nutritional support of subchondral bone. At the same time, the collapse of the femoral head leads to the unevenness of the articular surface and the increase of wear leads to the acceleration of osteoarthritis. RA is a chronic autoimmune joint disease, which can progress to osteonecrosis of the femoral head[36]. If induced by hormones or steroids, the incidence of osteonecrosis will increase significantly. Rheumatoid arthritis may also be caused by a single immune mechanism of cartilage metabolism disorder, the formation of deficiency and thinning, decreased joint fluid secretion, joint space stenosis, secondary hip osteoarthritis. Therefore, the three diseases may interact with each other in some mechanisms, and the same clinical phenotype may be similar genes and pathway mechanisms.

After all, bioinformatics analysis is only a summary of previous research data, and there is still a gap between bioinformatics analysis and gene expression in the real world, so it is necessary to carry out further experimental verification. for example, samples are obtained for immunohistochemical analysis or study of gene expression at the cellular level.

5. Conclusion

This study found common differential genes in three ONFH, OA, RA diseases through two data sets, and analyzed the occurrence and development of cartilage degeneration or osteogenic disorders that may be induced by them. In this paper, bioinformatics methods were used to screen the intersection of different disease databases to find the common phenotype of different diseases, to provide molecular basis for follow-up experiments and clinical efficacy. In addition, there are some shortcomings, the article only from the synovium samples, relatively limited, through bioinformatics mining biomarkers and effective targets need to be further verified by experiments.

Abbreviations

Analysis of DEGs in ONFH, OA, and RA by integrated microarray analysis

Declarations

Ethical review approval and consent to participate in the study

Not applicable.

Consent for publication

All participants agreed to submit the data involved in the literature to the journal.

Availability of data and materials.

All data generated or analyzed during this study are included in this published article.

Competing interests.

The authors declare that they have no competing interests, and all authors should confirm its accuracy.

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Author contribution statement

Zhao Gang conducted data analysis and completed the paper writing; Liu Yujie and Li Zhongli put forward research ideas; Li Chunbao directed the writing of the thesis. All authors read and approved the final manuscript.

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Figures

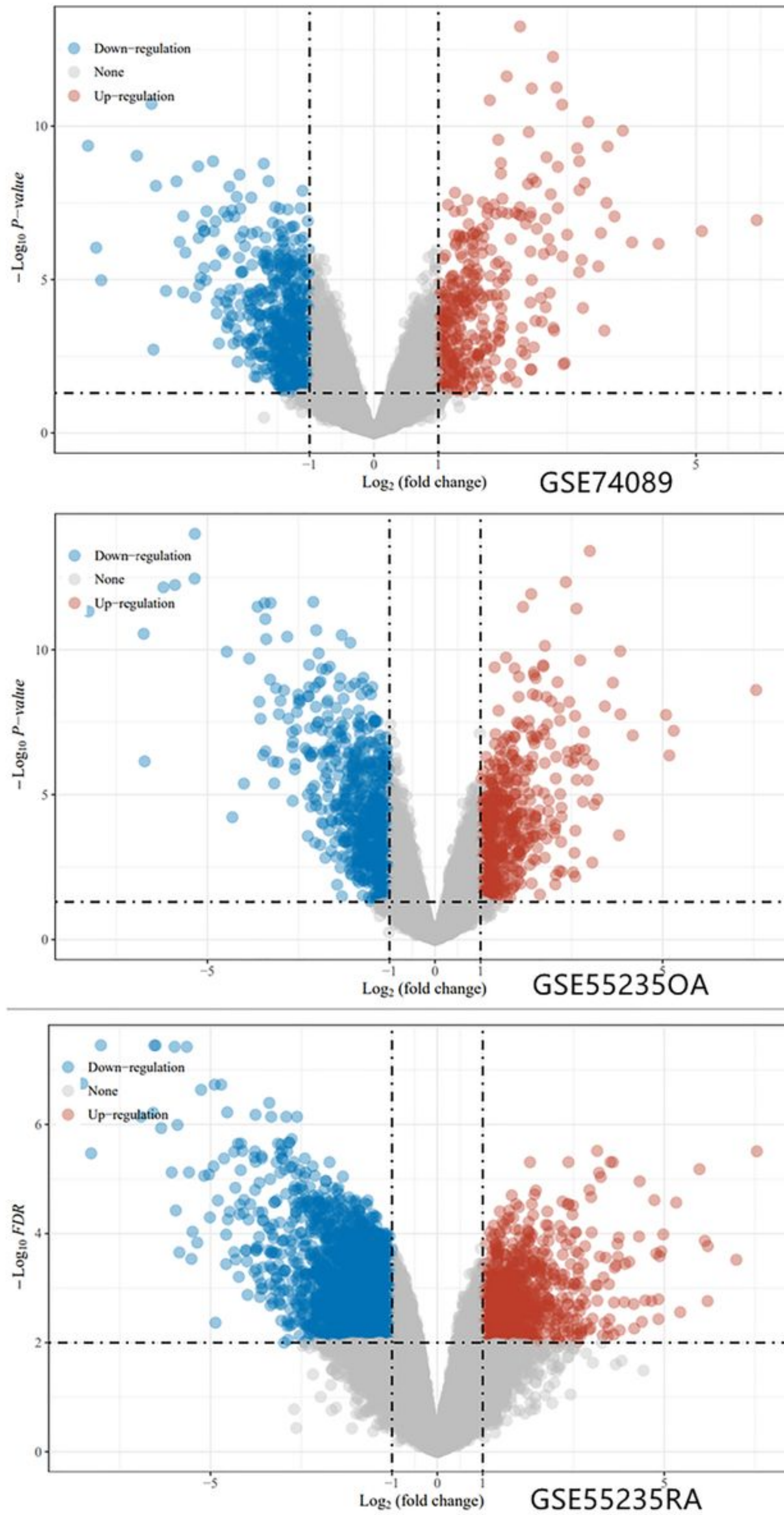

Figure 1

Volcano plot of DEGs in each group

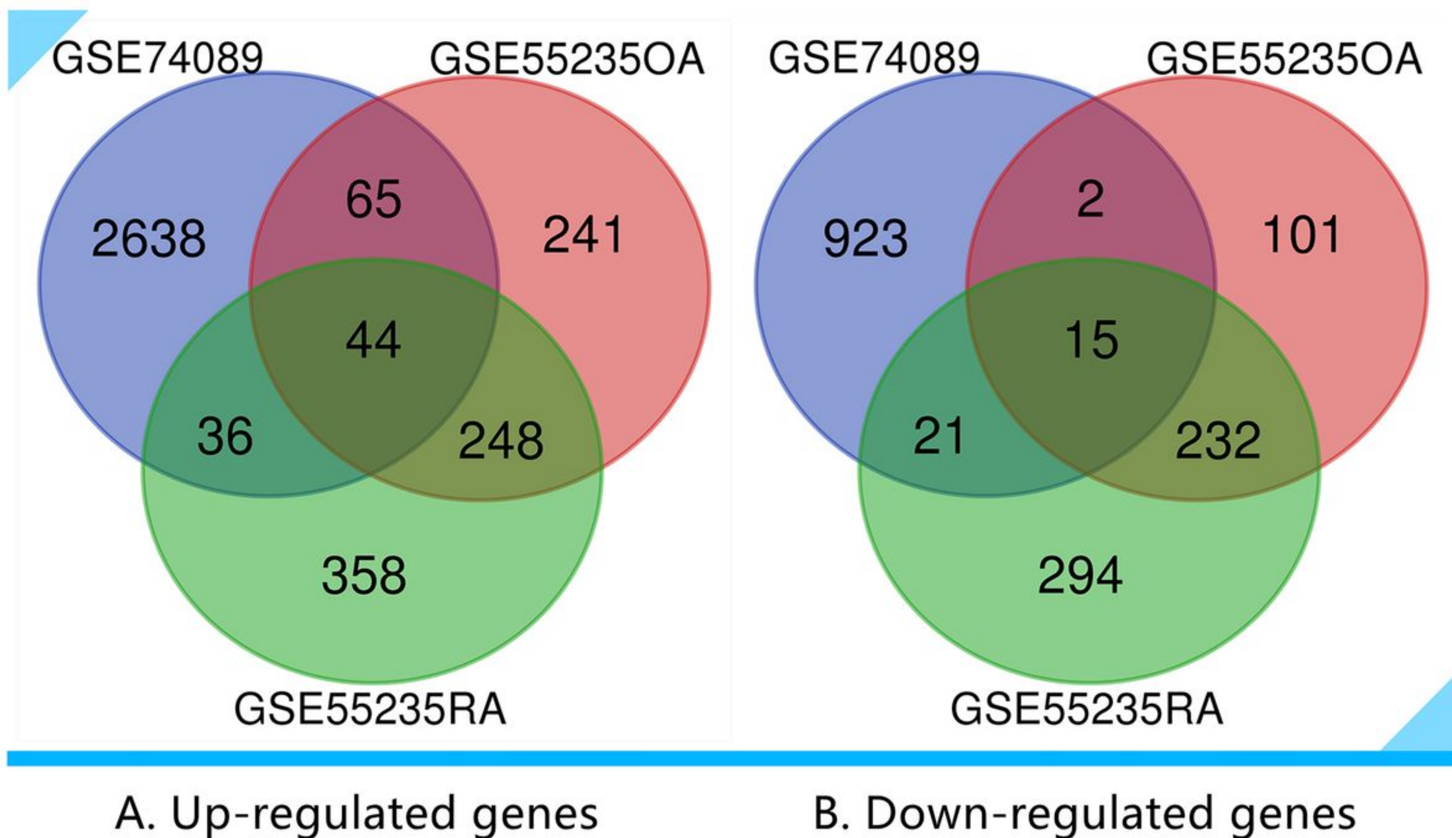

Figure 2

Venn diagram of DEGs. Purple represented DEGs between ONFH and normal controls, green represented DEGs between RA and normal controls, red represented DEGs between OA and normal controls, and yellow-green in the middle represented DEGs between ONFH, OA and RA.A. up-regulated genes ;B. down-regulated genes.

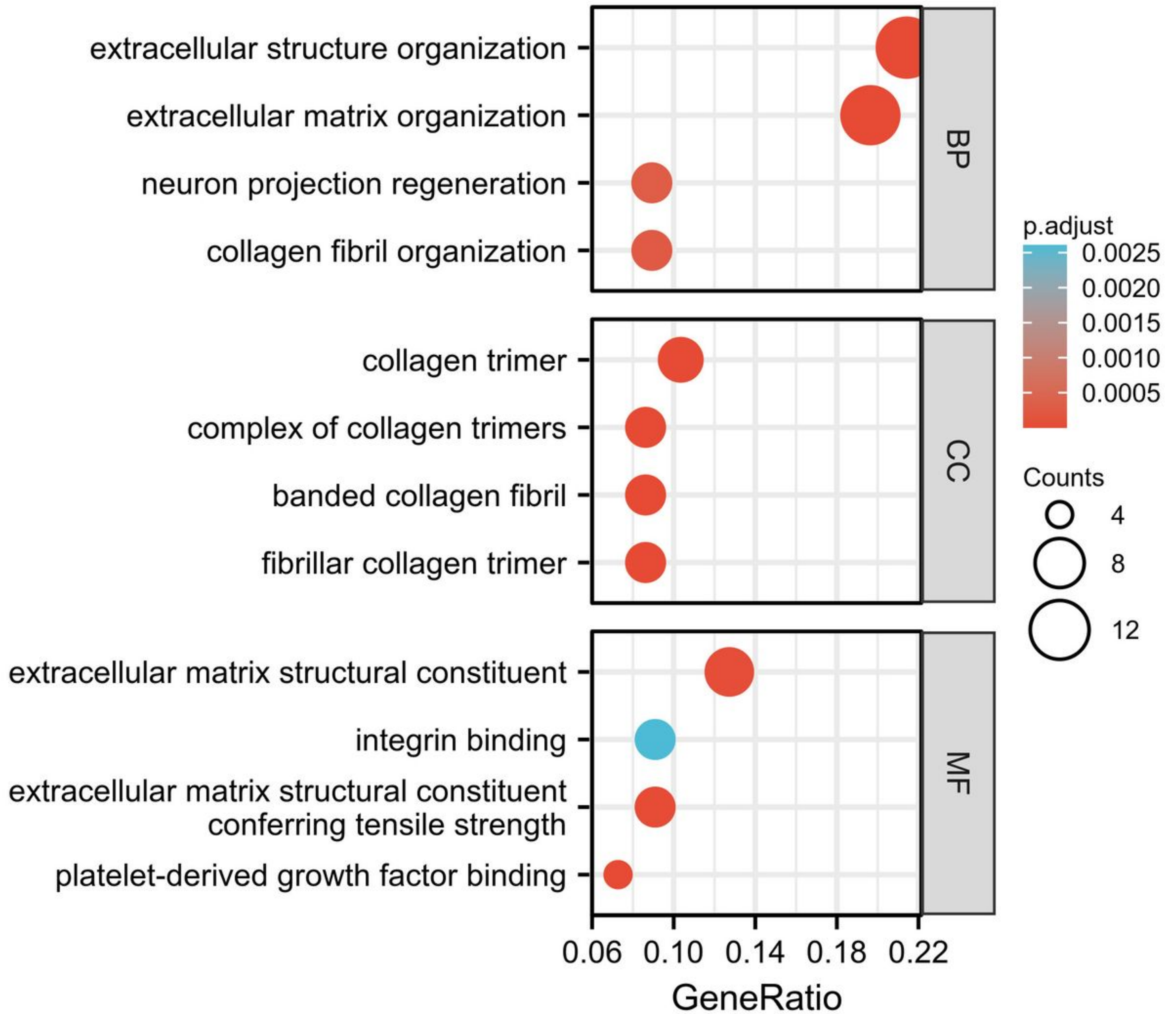

Figure 3

The significant terms identified by GO enrichment analysis for the DEGs (p<0.05)

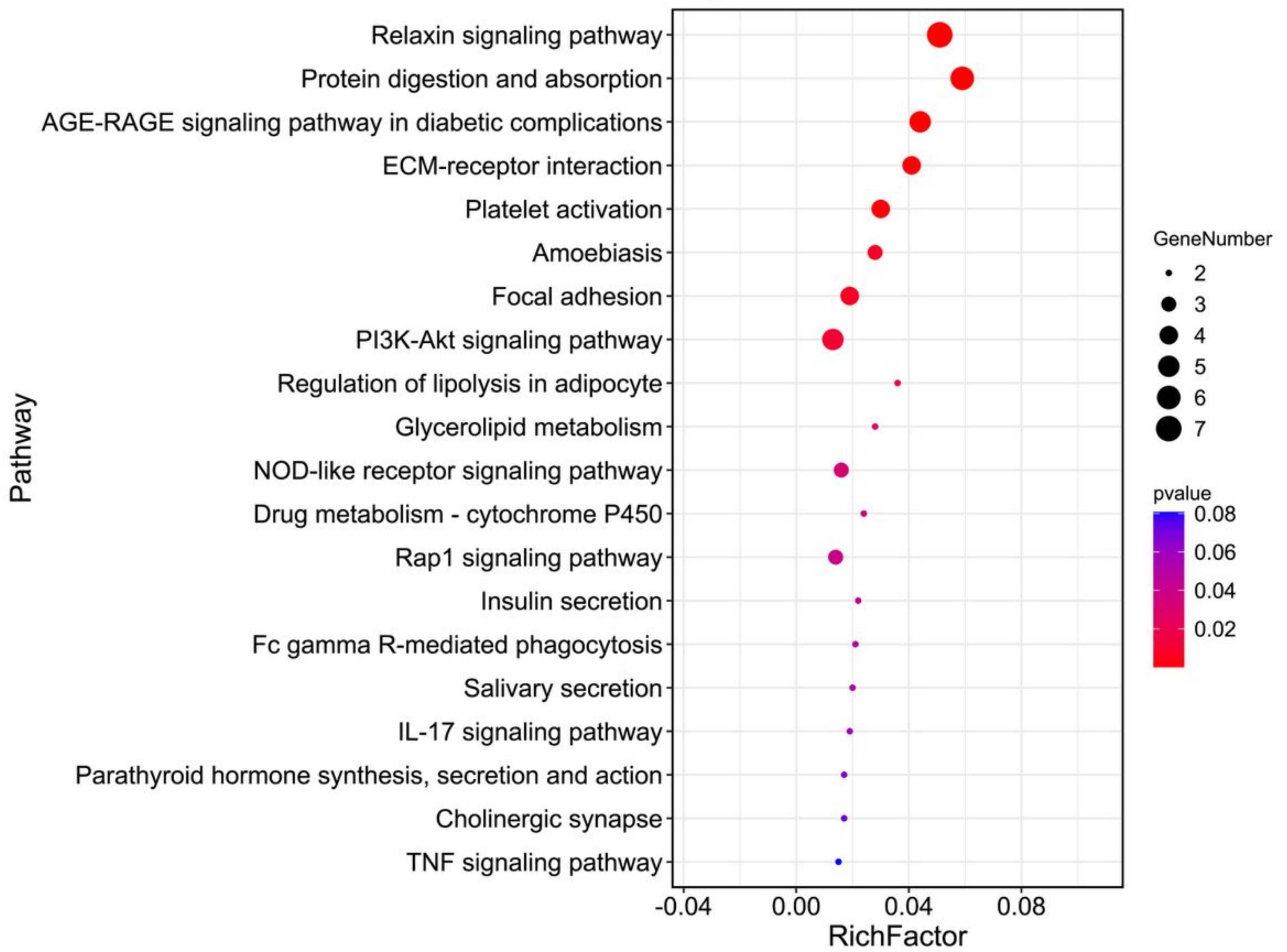

Figure 4

KEGG pathway enrichment analysis of the DEGs

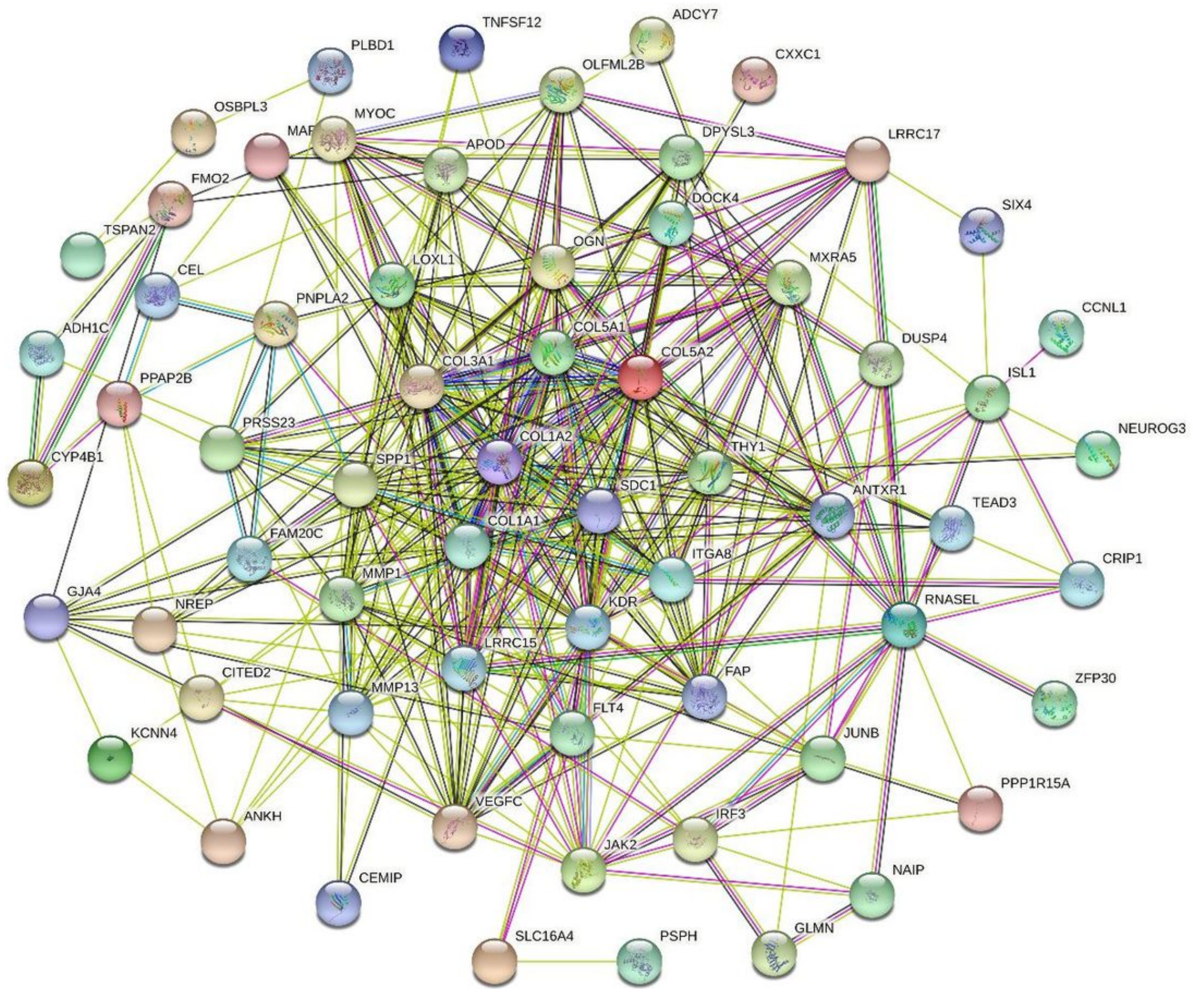

Figure 5

PPI network map of DEGs in ONFH, OA and RA

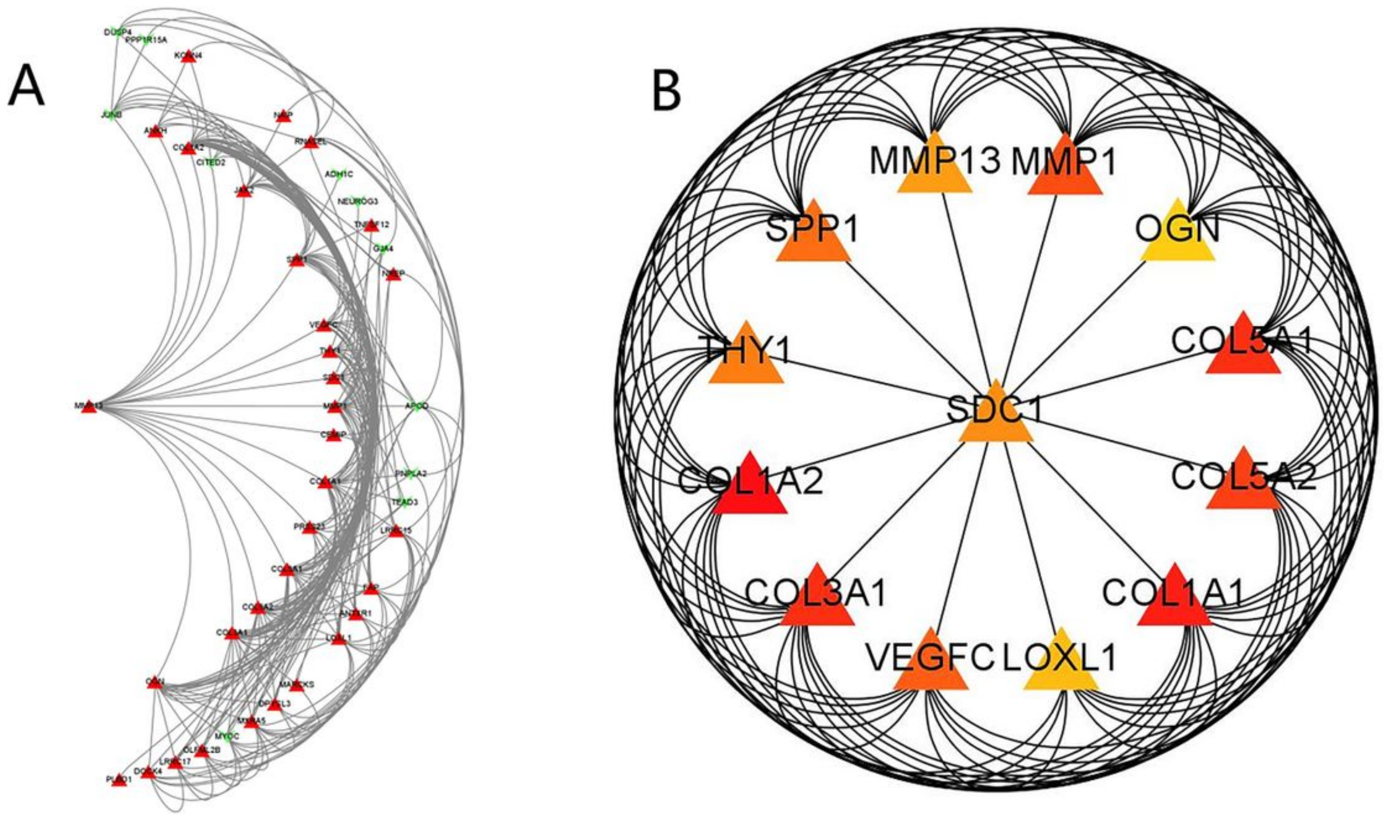

Figure 6

The PPI network shows the most significant DEGS module. (A) The PPI network of DEGs was constructed using Cytoscape. (B) The PPI network composed of 15 HUB genes was screened by cytohubba and the most significant module was obtained. Up-regulated genes are marked with red upward arrow.

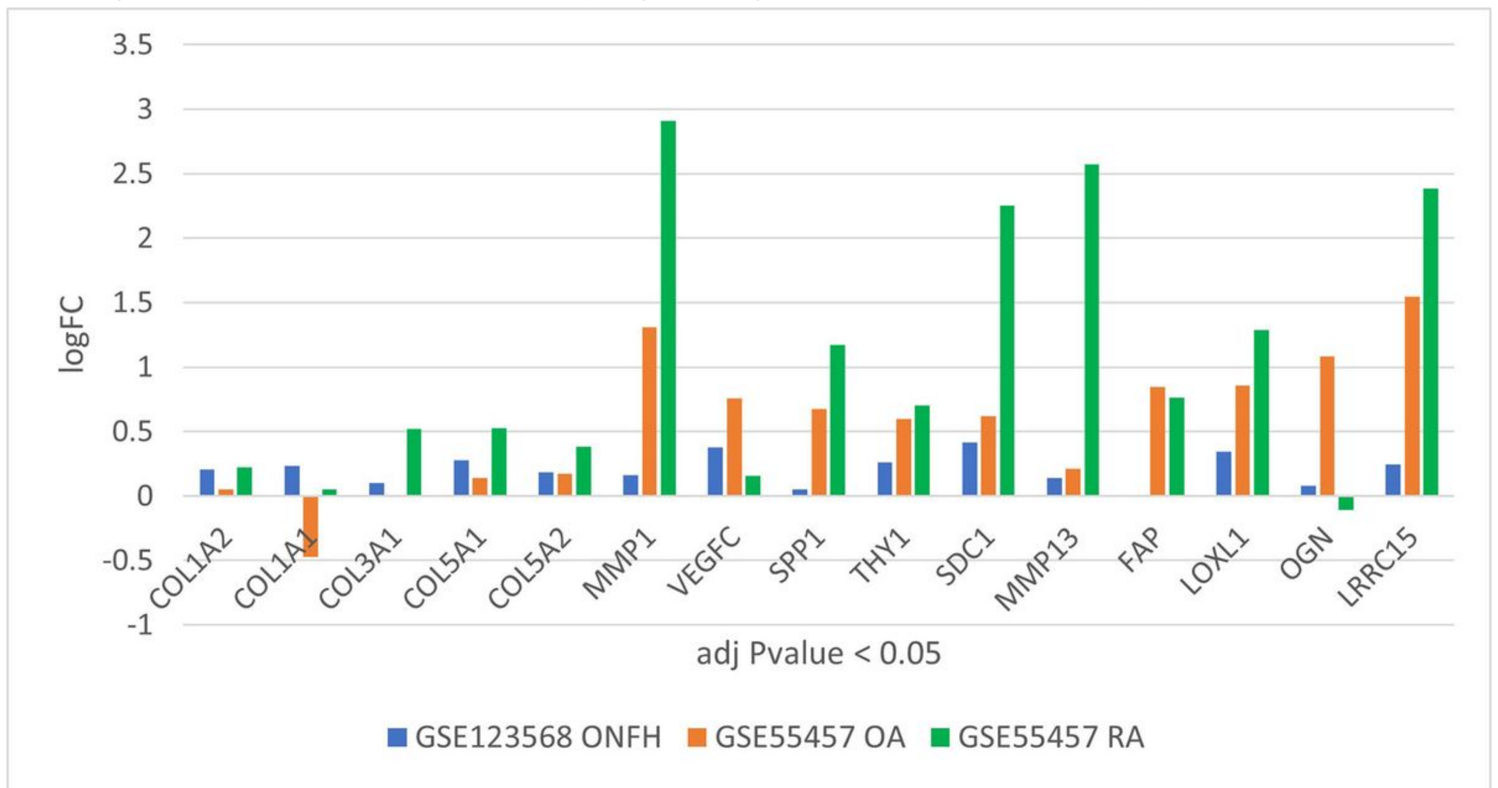

Figure 7

GEO validation of the hub genes. The X-axis represented the ONFH, OA, RA groups and the Y-axis represented the relative expression levels. ONFH, osteonecrosis of the femoral head; OA, osteoarthritis; RA, rheumatoid arthritis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- cytohubba.csv
- GOKEGG20210709120006.docx
- GSE55235OAFigclusterProfiler.pdf
- VennY.xlsx
- GEOvalidationofthehubgenes.xlsx
- GSE74089Fig1.pdf
- GSE55235OADegresult.csv
- GSE55235RADegresult.csv
- GSE74089Degresult.csv
- GSE55235OAFigclusterProfiler.pdf
- GSE74089Fig1.pdf