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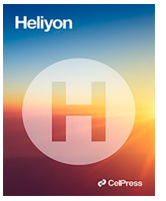

Research article

Identification and validation of immune-related genes in osteoarthritic synovial fibroblasts

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ABSTRACT

Objective: OA was generally considered as a non-inflammatory disease dominated by articular cartilage degeneration. However, the role of synovitis in OA pathogenesis has received increasing attention. Recent studies support that OA patients have a pro-inflammatory/catabolic synovial environment similar to RA patients, promoting the occurrence and development of OA. Therefore, we investigated the co-immune-related genes and pathways of OA and RA to explore whether part of the pathogenesis of RA synovitis can be used to explain OA synovitis.

Methods: Data of GSE29746 and GSE12021 were downloaded from the Gene Expression Omnibus (GEO) database. Compared with control group, differentially expressed genes (DEGs) of OA and RA groups were screened separately by R software, Venny website was used to screen co-DEGs. Metascape was used to screen the common enriched terms and pathways between OA and RA. STRING website and Cytoscape software were used to map protein–protein interaction (PPI) networks and screen co-hub genes. GSE29746 was selected as the test dataset, and GSE12021 as the validation dataset for validate the co-hub genes. The results were validated by western blotting (WB) and real-time quantitative polymerase chain reaction (qPCR) of clinical synovial samples.

Results: We identified 573 OA-related DEGs, 148 RA-related DEGs, and 52 co-DEGs, revealing 14 common enriched terms, most of which were related to immune inflammation. *IL7R* was the only upregulated co-hub gene between OA and RA in the PPI network, consistent with the validation dataset. IL7R was highly expressed in clinical osteoarthritic synovial samples ($P < 0.001$).

Conclusion: Our findings suggested that *IL7R* is a critical co-DEG in OA and RA and confirmed the involvement of immune inflammation in disease pathogenesis. Furthermore, it confirms the role of *IL7R* in synovial inflammation in RA and OA synovitis and provides evidence for further investigation of OA immune inflammation.

1. Introduction

Osteoarthritis (OA) is the most common type of arthritis and is a major cause of morbidity and disability that substantially reduces the quality of life in the older adult population. OA is estimated to affect approximately 250 million people, resulting in a considerable economic and societal burden [1]. OA commonly occurs in the knee, hip, and hand joints and is characterized by cartilage

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degeneration, subchondral bone remodeling, osteophyte formation, and synovitis [2]. Traditionally, OA was taken as a typical non-inflammatory joint disease caused by mechanical stress on joint cartilage due to various reasons, including age, obesity, trauma, and joint deformation [2]. However, as studies have been reported, increasing evidence indicates that inflammation plays a very important role in the pathology of OA, affecting the disease progression and painful symptoms [3].

Synovial changes play a crucial role in the pathogenesis and progression of OA, as confirmed by imaging and histological evidence [4]. OA often leads to synovitis, which manifests as immune cell infiltration, synovial fibroblast phenotypic changes, and inflammatory cytokine overexpression [5,6]. These osteoarthritic synovial pathologies substantially contribute to the initiation and maintenance of an inflammatory microenvironment in OA joints. IL1β, TNFα and IL6 are the most important inflammatory mediators of OA, and also activators of other cytokines, chemokines, and signaling pathways such as MAPK pathway and NF-κB pathway, leading to proteoglycan degradation, collagen breakage, and inhibition of proteoglycan and collagen synthesis [7,8]. Macrophages are the main source of IL1β and TNFα, and synovial fibroblasts (SFs) are the main source of IL6 [9]. Macrophages and T cells were most abundant in the inflammatory infiltrate of OA synovial tissue. The degree of pain in OA was positively correlated with the proportion of T cells [10]. Enrichment of macrophages in OA synovial fluid was also strongly associated with joint hypofunction and decreased quality of life [11]. The transcriptional switch of the fibroblast phenotype is correlated with the progression of OA and the development of early OA pain. Synovial fibroblasts subsets differ in OA disease stage and pain presence. Subsets of fibroblasts enriched in painful sites in early OA patients promote fibrosis, inflammation, neuronal growth and nociceptive signaling pathways [12].

Rheumatoid arthritis (RA) is the most common autoimmune arthritis that systematically affects the lining cells of the synovial joints, leading to synovitis, cartilage degradation, and bone destruction, and its major pathophysiology is autoimmune response and inflammation [13]. Synovitis is the most important pathological manifestation of RA joints. The inflammatory infiltrate of RA synovial tissue contains innate immune cells such as monocytes, and adaptive immune cells such as T-helper-1 and T-helper-17 cells and B cells. The synovial fibroblasts cause a strong tissue response, manifested as aggressive inflammation, matrix regulation, and enhanced chondrocyte catabolism and synovial osteoclastogenesis [9].

Synovial fibroblasts are located in the synovial lining. In healthy joints, SFs produce joint lubricants such as hyaluronic acid that directly promotes the composition of synovial fluid, providing nutrients to the underlying articular cartilage, and produce matrix components and extracellular matrix (ECM) degrading enzymes to help shape and maintain the synovial ECM [9]. In arthritis, SFs interacting with T cells, B cells and macrophages, lead to synovial inflammation, synovial hyperplasia and blood vessel formation, and promote osteocast formation to enhance bone destruction, as well as secrete excess MMPs that invade adjacent cartilage leading to joint degeneration [14]. These pathological changes go through a series of physiological processes-Local SFs in the lining are activated by large amounts of pro-inflammatory cytokines, chemokines, and growth factors produced by highly activated macrophages. "Activation and priming of SFs induces chromatin remodeling and epigenetic changes that enhance accessibility at a number of gene loci encoding proteins mediating inflammation, bone remodeling, cellular metabolism, and components of the complement system." [15] Furtherly, local inflammatory tissue priming is driven by the complement system through the metabolic reprogramming of SFs, irrelevant to synovial macrophages [16].

Bioinformatics analysis is the science of searching and analyzing biological information in the research of life science. In clinical research, it is mainly used to find the hub genes, RNA and molecular markers, which play an essential role in disease pathogenesis, diagnosis and treatment and other aspects. Multiple bioinformatic studies have attempted to elucidate the pathogenesis of OA and RA, and substantial progress has been made. However, the current study mostly uses OA as the control group of RA, and cannot find commonalities between the two.

All of the above evidence support that, similar inflammatory microenvironments have been identified between OA and RA synovitis and SFs are at the center of inflammatory tissue priming of synovitis. Therefore, we investigated the roles of common hub genes and pathways of SFs in OA and RA using publicly available data and clinical synovium samples to explore whether part of the pathogenesis of RA synovitis can be used to explain OA synovitis.

2. Materials and methods

2.1. Bioinformatic analysis

Data were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) of the National Center for Biotechnology Information (NCBI). Because no in vivo experiments were performed on humans or animals, no ethical approval was required for the bioinformatics analysis. In the GEO database, 27 datasets were retrieved using the search keywords "osteoarthritis," "synovial fibroblasts," and "Homo sapiens." Datasets with experiment type "expression profiling by array" and a consistent analysis platform were preferred. The GSE29746 dataset [17] was finally selected. This dataset was based on the GPL4133 Agilent-014850 Whole Human Genome Microarray 4 × 44K G4112F platform, comprising eleven normal control (NC) samples, eleven OA, and nine RA samples; the latest update was made in 2018. To avoid age bias, array data of ≥45-year-old individuals were used, and two samples from individuals <45 years in the NC group were excluded [18].

As no other eligible SF datasets were obtained, synovial sample datasets were chosen for external validation. We searched eligible datasets using the keywords "osteoarthritis," "synovium," and "Homo sapiens," and obtained the GSE12021 dataset [19], including five NC samples and 10 OA samples, based on the GPL96 [HG-U133A] Affymetrix Human Genome U133A Array platform.

2.2. Data processing

Matrix data for the GSE29746 dataset were obtained from the GEO database. R software (version 4.1.0, The R Foundation, Vienna, Austria) was used for the statistical analysis. The limma, dplyr, and Tibble R packages were used for differentially expressed gene (DEG) screening, with a threshold of $P < 0.05$ and $|\log_2$ fold change (FC)$| > 1$. The ggplot2 and ggrepel R packages were used for data visualization.

2.3. Identification of co-DEGs and gene enrichment analysis

Venny 2.1.0 was used to identify and visualize the co-DEGs shared between OA and RA. Gene ontology (GO) analysis was conducted to obtain the biological process (BP), cell component (CC), and molecular function (MF) terms, and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was performed to identify the enriched pathways, with significance set at $P < 0.05$. The Database for Annotation, Visualization, and Integrated Discovery (DAVID, version 6.8) [20] was used for functional enrichment of the co-DEGs. The figure drawing was plotted by websites (https://www.bioinformatics.com.cn) to make a bubble chart of the results. Gene enrichment analysis was again performed on a web-based tool of Metascape (https://metascape.org) [21]. Firstly, individual OA-DEGs and RA-DEGs list were inputted respectively for viewing top-nonredundant enrichment clusters. Then multi-gene-list meta-analysis was performed to visualize shared pathways and pathway clusters. The online tool of bioinformatics websites(https://www.bioinformatics.com.cn) was used to construct a Chord Diagram combining the co-DEGs and shared pathway clusters.

2.4. Protein–protein interaction (PPI) and network analysis

The PPI networks of the DEGs were constructed using the online database STRING (version 11.5) and Metascape. RA- and OA-hub-genes were screened using the Degree algorithm of the Cytohubba plugin [22] of Cytoscape software (version 3.9.0). The Molecular Complex Detection (MCODE) algorithm of Metascape was applied to obtain OA-MCODE clusters, which were visualized and functionally annotated using Cytoscape.

2.5. External dataset validation

Matrix data of the GSE12021 validation dataset were analyzed with limma, as described in Data Processing, and the outcomes were visualized using the ggpubr and ggplot2 R packages. To validate the identified hub genes, expression levels were compared between OA and NC and visualized. The Wilcoxon test was used to compare the differences in co-hub gene expression between the OA and NC groups, with statistical significance set at $P < 0.05$.

2.6. Selection criteria for OA and RA synovium samples

Clinical samples were collected from Shengjing Hospital of China Medical University (Shenyang, China) and were approved by the Ethics Committee of Shengjing Hospital Affiliated with China Medical University (Shenyang, China; Ethics Approval No. 2021PS772K). The ethical approval covers the consent waiver because discarded joints were used. Synovial samples were collected from six patients with knee OA who underwent total knee replacement and six patients who underwent partial synovectomy after joint trauma. All OA patients met the following inclusion criteria: 1) OA diagnosis met the diagnostic criteria of the American Rheumatic Association (ACR) [23]; 2) no coexisting joint inflammatory diseases were diagnosed. The clinical criteria of ACR for knee OA include knee pain plus the presence of at least three of the following six: ① Age> 50 years; ② morning stiffness time <30min; ③ crepitus on active motion; ④ bone tenderness; ⑤ bony enlargement; ⑥ No palpable warmth of synovium [24].

2.7. Western blot analysis

Synovial samples were lysed in RIPA buffer (C5029, Bioss, Beijing, China) containing 1% protease inhibitor PMSF (D10411, Bioss, Beijing, China), the supernatant was centrifuged in centrifuge tubes at 12,000 rpm in a 4 °C centrifuge for 30 min, and the protein concentration was measured using a BCA quantitative kit (BL521A, Biosharp, Hefei, China). After denaturation, the proteins were separated using SDS-PAGE gel (P0015, Beyotime, Shanghai, China) electrophoresis, and the target protein was transferred to a PVDF membrane (0.45μm, GE, USA), with a constant current of 200 mA. The membranes were incubated with IL7R antibody ABP53336 (1:1,000, Abbkine, Wuhan, China) and GAPDH antibody A19056 (1:1,000, ABclonal, Woburn, MA, USA) on a shaking ice bed at 4 °C for 14 h overnight to obtain the primary antibody. The next day, the primary antibody was recovered and incubated with the secondary antibody. Luminescence was performed on a light-emitting machine to capture strip images, and ImageJ software (National Institutes of Health, Bethesda, MD, USA) was used for densitometric analysis of western blots.

2.8. qPCR-based mRNA analysis of co-hub genes

Total RNA was extracted using a total RNA extraction reagent (Trizol; TaKaRa Bio, Kusatsu, Japan) according to the manufacturer's instructions. Reverse transcription to cDNA was performed using an RNA Two-Step Reverse Transcription Kit (TaKaRa Bio, Kusatsu, Japan). A qPCR SYBR Green amplification kit (TaKaRa Bio, Kusatsu, Japan) was used for qPCR analysis, the internal reference was

β-Actin antibody A01011 (1:1,000, Abbkine, Wuhan, China); RNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method. The qPCR primers used in this study were: *IL7R* upstream primer 5′-TGCGTGACATTAAGGAGAAGCTGTGG-3′, *IL7R* downstream primer 5′-AGTTGAAGGTAGTTTCGTGGATGCC-3′, *ACTB* upstream primer 5′-CCCTCGTGGAGGTAAAAGTGC-3′, *ACTB* downstream primer 5′-CCTTCCCGATAGACGACACTC-3′.

2.9. Statistical analysis

Data are presented as the mean ± standard deviation and statistically analyzed using SPSS 24.0 (IBM SPSS, Armonk, NY, USA). Differences between groups were assessed using Student's *t*-test, with significance set at $P < 0.05$. GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) was used for data visualization.

3. Results

3.1. Determination of DEGS in OA and RA

A total of 573 DEGs were identified in the OA dataset (234 upregulated and 339 downregulated), and 148 DEGs were identified in the RA dataset (75 upregulated and 73 downregulated) (Fig. 1a and b); the top 10 up- and downregulated DEGs are displayed in Tables 1 and 2. We identified 52 co-DEGs between OA and RA (24 upregulated and 28 downregulated) (Fig. 1c and d). The functional annotation of co-DEGs by DAVID identified "extracellular matrix organization" (BP), "plasma membrane" (CC), and "calcium ion binding" (MF) as significantly enriched terms ($P < 0.05$, Fig. 1e).

3.2. Co-hub DEG identification

The PPI networks of DEGs contained 496 nodes and 1020 edges for OA and 131 nodes and 67 edges for RA. The top 10 hub-DEGs of OA and RA are shown in Table 3, and their PPI network map are shown in Fig. 2a and b, and *IL7R* was detected as a co-hub DEG of OA and RA. The expression level of *IL7R* is presented in Table 4.

3.3. DEG pathway enrichment

The top 20 most significant GO and KEGG terms for OA and RA are presented in Fig. 3a and b. The DEGs in OA were significantly enriched in "*trans*-synaptic signaling" (BP) as well as the "cytokine-cytokine receptor interaction" and "amoebiasis" KEGG pathways, whereas DEGS in RA were significantly enriched in "skeleton system development," "modulation of chemical synaptic transmission," and "ossification" (BPs).

3.4. Multi-gene-list meta-analysis

Multiple gene lists analysis of OA- and RA-related DEGs was performed with Metascape. We identified 14 shared enriched GO and KEGG terms from the heatmap of enriched terms across input gene lists, including "positive regulation of T cell activation," "response

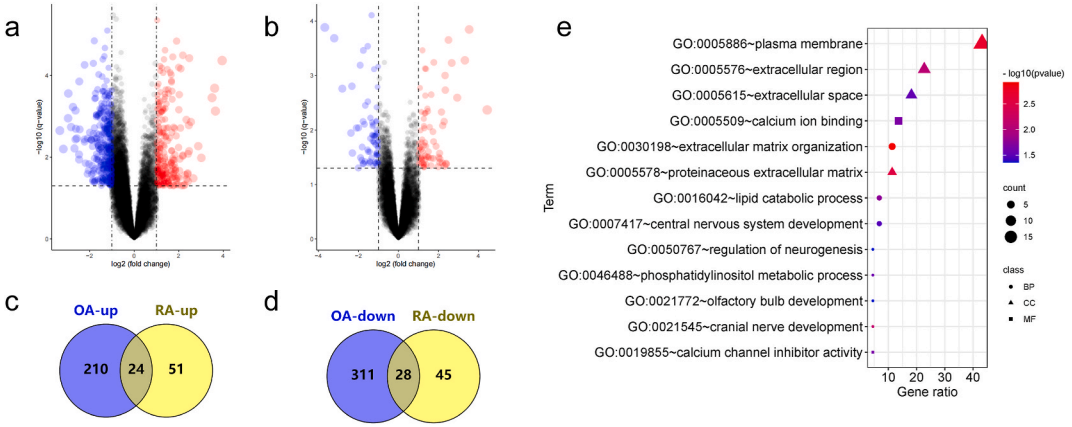

Fig. 1. Determination and functional enrichment of common (co)-DEGs in OA and RA. (a–b) Volcano plots of DEGs in OA and RA ($P < 0.05$ and $|\log_2 FC| > 1$ were set as thresholds). Red points ($\log_2 FC > 1$) represent upregulated DEGs, blue points ($\log_2 FC < -1$) represent downregulated DEGs, and black points represent non-DEGs. (c–d) Co-DEGs between OA and RA, upregulated and downregulated DEGs, and 24 upregulated and 28 downregulated co-DEGs. (e) Functional annotation of co-DEGs; The ● represents BP, ▲ represents CC, and ■ represents MF. The size of the shapes represents the number of genes involved, and the red color indicates higher significance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Top 10 up- and downregulated DEGs in OA.

Gene	log_2FC	*P*.Value	State
ITGB2	3.950049619	4.33E-05	up
SPINK6	3.648966874	0.000744647	up
SPINK5L3	3.614236624	0.000206157	up
SLC7A10	3.497140677	0.00035155	up
LRRN1	3.015084752	0.010399221	up
LOC100131014	2.875995619	0.005378152	up
LYPD6B	2.660388467	0.032825693	up
GRIN3A	2.54983639	0.001374621	up
LOC100128328	2.475848696	3.78E-05	up
DKFZP547L112	2.466513339	0.007092283	down
SCN3A	−3.338204536	0.002235951	down
HOXB3	−3.181155934	0.006299982	down
EPGN	−2.9696864	0.001115904	down
DIRAS2	−2.959314271	0.000276033	down
CDH18	−2.831644556	0.001835177	down
SLC6A15	−2.75059866	0.000592104	down
CLGN	−2.682593017	0.006091199	down
ANXA10	−2.635119433	0.000724278	down
COL4A5	−2.634097136	0.003674986	down
ADH1A	−2.616799907	0.00202163	down

Table 2
Top 10 up- and downregulated DEGs in RA.

Gene	log_2FC	*P*.Value	State
PRAME	4.43472157	0.004273354	up
SPINK5L3	3.533506294	0.000142252	up
ITGB2	3.317249877	0.000523735	up
SPINK6	2.934714208	0.002543525	up
PLCH2	2.661084402	0.000585561	up
CRTAM	2.497535109	0.000221771	up
SLC22A10	2.37655555	0.041132387	up
SMOC2	2.375605341	0.042462647	up
LOC387895	2.338961646	0.001844232	up
IL27RA	2.32759801	0.000994565	down
SCN3A	−3.684990093	0.000130416	down
COL4A5	−3.211915806	0.000205676	down
DIRAS2	−2.807175861	0.001736574	down
NPTX1	−2.376947207	0.011335857	down
SEMA3E	−2.32710838	0.001565381	down
RTN1	−2.303189151	0.026415479	down
LGI1	−2.101643985	0.009167453	down
EPGN	−2.004185359	0.049582246	down
PLA2G7	−1.993851302	0.009115322	down
PRPH2	−1.914817014	0.000643957	down

Table 3
Top 10 hub genes of OA and RA.

OA	Degree	RA	Degree
CD4	53	IL7R	5
PLK1	29	HOPX	5
CSF2	27	KMT2D	4
CENPE	26	GRM1	4
MKI67	25	GRIN3A	4
IL7R	24	EOMES	4
BUB1	23	ASCL2	4
KIF20A	23	ADAMTS4	4
BUB1B	22	MMP13	4
GRIN1	21	PTGS2	3

to lipopolysaccharide," "*trans*-synaptic signaling," "leukocyte differentiation," "synapse organization," "cell adaptation," "skeleton system development," "positive regulation of leukocyte differentiation," and "regulation of chemical synaptic transmission" (BPs); "glutamatergic synapse," "extracellular matrix" (CCs), "calcium ion binding," and "signaling receptor regulator activity" (MFs), along

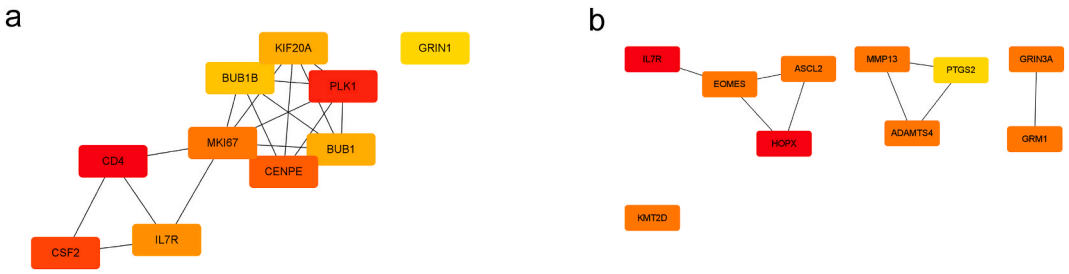

Fig. 2. PPI network of top 10 DEGs. *IL7R* was observed in OA (a) and RA (b) hub DEGs. The color depth of nodes represents the degree of significance; deeper coloration represents higher significance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
The expression level of *IL7R* in OA and RA.

Disease	Degree	log_2FC	*P*.Value	State
OA	24	1.492774843	0.018265166	up
RA	5	1.289843538	0.019048097	up

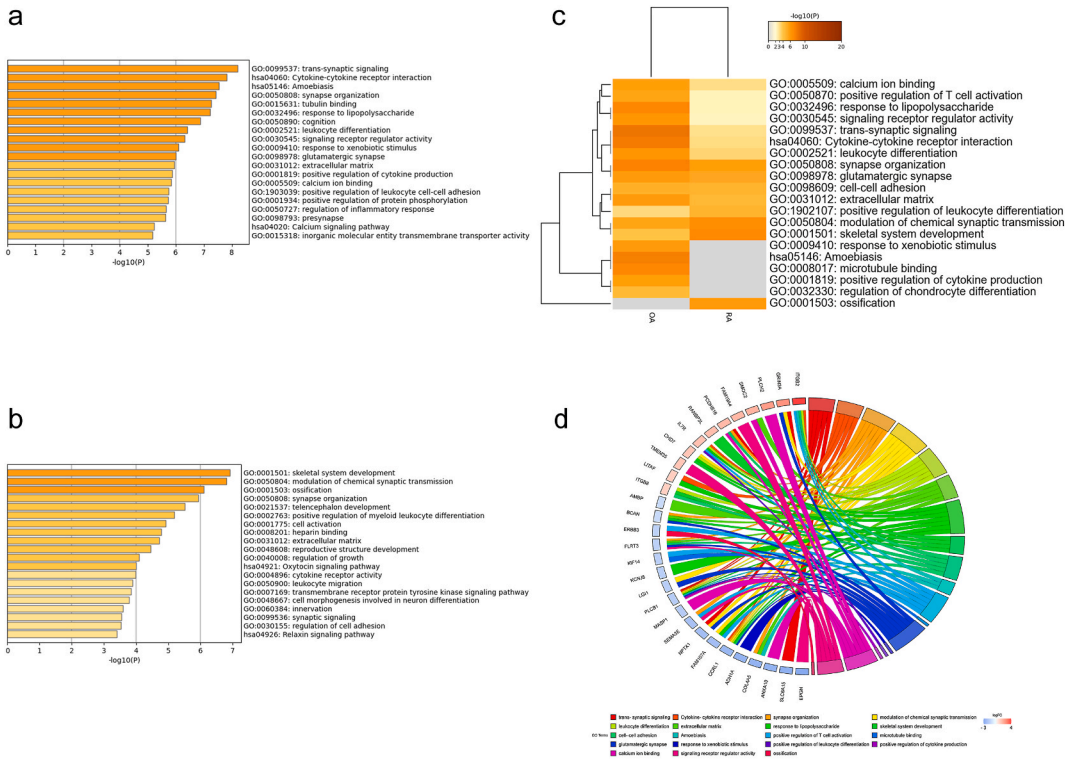

Fig. 3. Enrichment analysis of DEGs in OA and RA with metascape. (a) Enrichment analysis of individual DEGs list in OA and (b) RA. (c) Heatmap of co-enriched terms; 14 co-enriched terms were observed between OA and RA; deeper coloration indicates a lower P-value and higher significance, and gray coloration represents non-significant terms. (d) Chord diagram displaying the correlation between co-DEGs and co-enriched terms. Lines indicate correlations between genes and enrichment terms; a total of 30 co-DEGs were involved in the shared enrichment terms.

with the shared "cytokine-cytokine receptor interaction" KEGG pathway (Fig. 3c). The chord diagram was used to correlate the co-DEGs in the enrichment analysis with each enriched term and showed that 30 co-DEGs were involved in 19 enrichment terms. *IL7R* was involved in five co-enrichment terms, including "leukocyte differentiation," "response to lipopolysaccharide," "positive regulation of T cell activation," and "positive regulation of leukocyte differentiation" (BPs), along with the enriched KEGG pathway "cytokine-cytokine receptor interaction" (Fig. 3d).

A network plot was then rendered to further capture the relationships between the terms, where terms with a similarity >0.3 are connected by edges. The most significantly enriched cluster subset corresponded to 20 enriched terms mentioned in Fig. 3c. Each node represents an enriched term and is colored first by its cluster ID (Fig. 4a) and then by its p-value (Fig. 4b). The third plot (Fig. 4c) was divided by clusters to visualize whether the terms are shared by multiple lists or unique to a specific list. We observed that all subset terms in clusters of "leukocyte differentiation" and "glutamic synapse," contained both OA- and RA-DEGs. The network connections of the clusters were centered around these two clusters and were aggregated based on functional similarity.

3.5. MCODE clustering analysis

The three MCODE clusters with the highest scores were identified in the OA-PPI network. MCODE_1 cluster mainly comprised "G protein-coupled peptide receptor activity," "peptide receptor activity," (MFs) and "neuroactive ligand-receptor interaction" KEGG pathway; MCODE_2 Cluster involved "PI3K-Akt signaling pathway" and "cell adhesion molecules," KEGG pathways and "enzyme-linked receptor protein signaling pathway" (BP); and MCODE_3 Cluster mainly involved "ionotropic glutamate receptor complex," "neuron receptor complex," and "plasma membrane signaling receptor complex" (CCs) (Fig. 4d–Table 5). IL7R was determined to be a member of the MCODE_3 cluster that participates in the BPs.

3.6. External dataset and clinical validation

We identified DEGs between the OA and NA groups of the GSE12021 dataset to validate our analyses. The co-hub DEG, *IL7R*, was validated. *IL7R* expression was significantly higher in the osteoarthritic synovium samples ($P = 0.04$) than estimated in the test dataset (Fig. 5a).

In clinical synovial samples, IL7R levels were determined using western blotting. IL7R expression was higher in osteoarthritic synovial samples than in NC samples ($P < 0.001$) (Fig. 5b), which was consistent with the qPCR analysis ($P < 0.001$) (Fig. 5c).

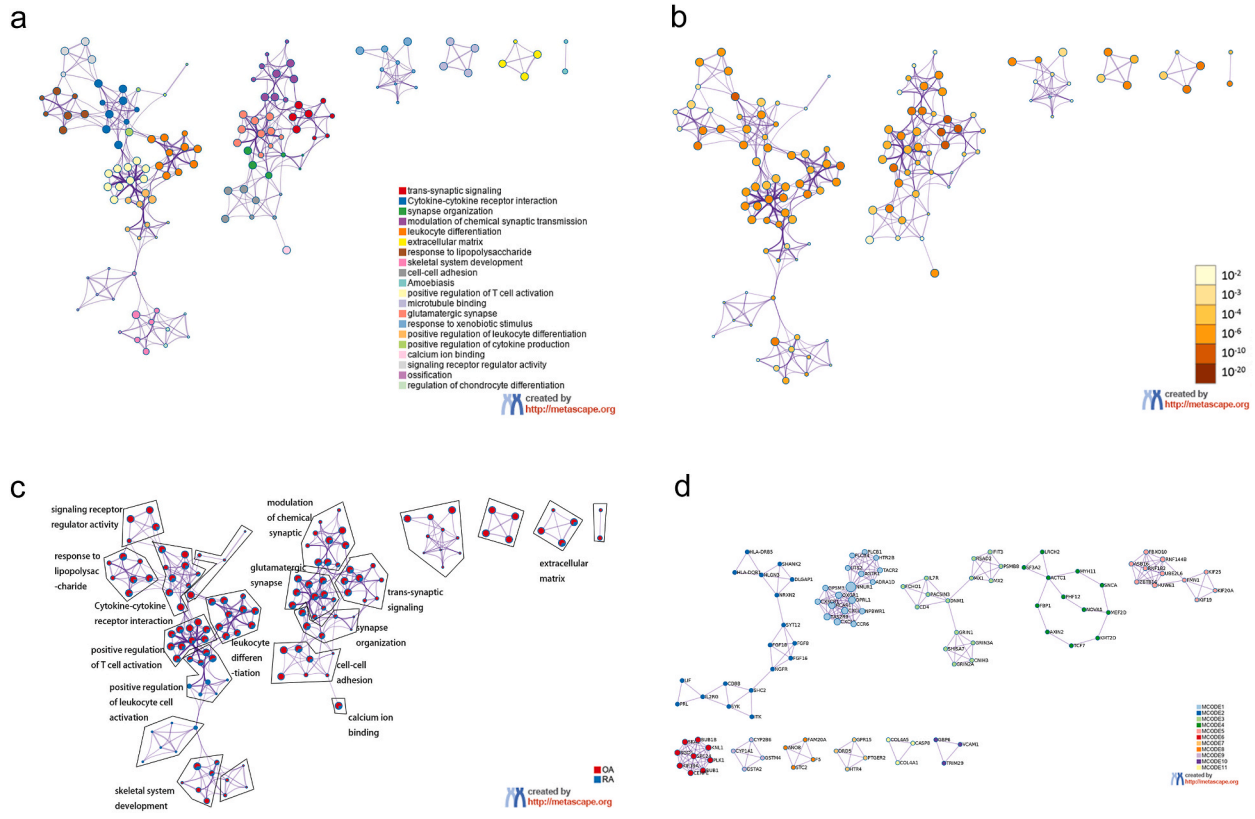

Fig. 4. Network plots of enriched terms in multi-gene-list analyze and MCODE complex classification for OA. Each node represents a enrichment term, grouped into a cluster based on genetic member similarity, and clusters are assembled based on functional similarity. (a) Colored by cluster ID, terms belonging to the same cluster are same in color; (b) Colored by P-value, DEG count contained in the enrichment term was negatively correlated with the size of the P-value; (c) Nodes are represented by pie charts with sizes proportional to the DEG count in the enriched terms. The section size represents the percentage of OA or RA DEGs in each enriched term. Specific clusters were labled with Adobe Photoshop software (Adobe, San Jose, CA, USA). (d) MCODE complex representing nine closely related protein groups in the OA PPI, classified by color. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Enrichment analysis in MCODE_1、MCODE_2 and MCODE_3.

MCODE	GO	Description	Log 10(*P*)
MCODE_1	GO:0008528	G protein-coupled peptide receptor activity	−11.7
MCODE_1	GO:0001653	peptide receptor activity	−11.6
MCODE_1	hsa 04080	Neuroactive ligand-receptor interaction	−10.9
MCODE_2	hsa 04151	PI3K-Akt signaling pathway	−9.1
MCODE_2	hsa 04514	Cell adhesion molecules	−7.7
MCODE_2	GO:0007167	enzyme linked receptor protein signaling pathway	−7.5
MCODE_3	GO:0008328	ionotropic glutamate receptor complex	−11.0
MCODE_3	GO:0098878	neurotransmitter receptor complex	−10.8
MCODE_3	GO:0098802	plasma membrane signaling receptor complex	−8.3

4. Discussion

OA is the most prevalent type of arthritis [1], and RA is the most common form of autoimmune inflammatory arthritis [25]. Synovitis is a common pathological manifestation in OA and RA and maybe have a common driver in pathogenesis [26,27]. Based on their similarities and the crucial role of SFs in the pathogenesis of arthritis, we investigated the co-DEGs and roles of SFs between OA and RA. Our findings revealed 52 co-DEGs (24 upregulated and 28 downregulated); IL7R was an upregulated co-hub-DEG that may be a potential biomarker for inflammatory SFs.

Functional annotation of the DEGs in OA showed that they were enriched in BPs or pathways related to signal transduction, leukocyte differentiation and adhesion, and the extracellular matrix. In contrast, DEGs in RA were involved in bone development, signal transduction, leukocyte differentiation and migration, and cell adhesion. The co-DEGs of OA and RA were involved in the CCs "extracellular matrix organization," "extracellular space," and "extracellular region"; therefore, the extracellular matrix (ECM) was the key CC affected by SF-related cytokines. The ECM is an essential microenvironment for maintaining cell survival, migration, proliferation, and differentiation and is closely related to immunity [28]. A chronic inflammatory microenvironment may contribute to ECM degeneration and remodeling [29].

OA and RA shared 14 significantly enriched terms, with each term containing five or more co-DEGs. The cluster network of enriched terms was centered around "leukocyte differentiation" and "glutamatergic synapse," and its functions revolved around positive regulation of leukocyte differentiation, chemical synaptic transmission, and cell adhesion. Seven terms were more significantly enriched in OA than in RA, including "positive regulation of T cell activation," "response to lipopolysaccharide," "*trans*-synaptic signaling," "leukocyte differentiation" (BPs), "calcium ion binding," "signaling receptor regulator activity" (MFs), and "cytokine receptor interaction" signaling pathways. This may indicate that OA has a high degree of synovitis, and the co-DEGs participate in the inflammatory processes of OA and RA through the same immunobiological pathways.

Closely connected cytokine clusters in the OA-PPI network were identified using MCODE cluster analysis. We identified nine terms that were highly correlated with inflammatory signaling pathways, cell adhesion, and signal transduction, including the terms "G proton-coupled peptide receptor activity," "PI3K-Akt signaling pathway," and "ionotropic glutamate receiver complex." G-protein-coupled receptors—transmembrane receptors that play pivotal roles in inflammation and immune responses [30], including in RA and OA—are involved in various OA pathologies, such as cartilage matrix degradation, synovitis, subchondral bone remodeling, and osteophyte formation [31,32]. Inhibition of G protein binding suppresses collagen-induced arthritis by reducing CD4+T cell productions [33]. Abnormalities in the PI3K-Akt signaling pathway have been associated with multiple human diseases, including cancer, RA, and nervous system diseases [34]; the normal functioning of this pathway is critical for joint-tissue metabolism and cartilage resistance against degeneration and synovitis [35]. This study demonstrates the role of inflammation in the pathogenesis of OA, which is consistent with the findings of previous studies.

We confirmed that *IL7R* is a co-hub DEG in OA and RA. IL7R is a heterodimer composed of two subunits, including an α chain and common cytokine receptors on a γ chain [36]. IL7R is the receptor for the inflammatory cytokine IL7. After interacting with IL7R, IL7 forms a ternary complex that participates in the JAK-STAT signaling pathway; activates downstream PI3K, Akt, Bcl-2, and Src kinases; participates in immune regulation; affects the growth and function of immune cells; and maintains lymphocyte homeostasis [37]. T cells are the major cells expressing IL7Rα, including CD4+T cells, CD8+T cells, γδ T cells, and natural killer T cells [38]. The binding of IL7 to IL7R stimulates the proliferation of memory T cells and the secretion of other cytokines, regulating the homeostasis of the T-cell population. The IL7/IL7R pathway is required for T cell survival, proliferation, and metabolism. Loss of the IL7/IL7R pathway directly leads to the loss of T lymphocytes [39], causing severe immunodeficiency [36]. This is consistent with the results of our study—IL7R was significantly enriched in "leukocyte differentiation," "response to lipopolysaccharide," "positive regulation of T cell activation," "positive regulation of leukocyte differentiation," (BPs) and "cytokine-cytokine receptor interaction" KEGG pathway.

The IL7/IL7R system has been identified to be involved in the regulation of RA [40]. IL7 and IL7R are highly expressed on RA synovial tissue lining fibroblasts and sublining macrophages and endothelial cells. And the soluble form of IL7R (sIL7R) is produced by fibroblasts, with elevated levels in the serum and synovial fluid [41,42]. Existing studies have found that the IL7/IL7R pathway can activate T cells and monocytes/macrophages in joints, stimulate the expression of pro-inflammatory cytokines such as TNFα, interferon γ (IFNγ), IL1β, and IL6 to promote the production of inflammatory metabolic microenvironment in RA [43], and promote bone destruction by stimulating RANKL expression to affect the formation of osteoclasts meanwhile promoting macrophage differentiation into osteoclasts through the STAT5 signaling pathway [44], and also promote angiogenesis by activating IL8 and Ang 1 secretion of RA

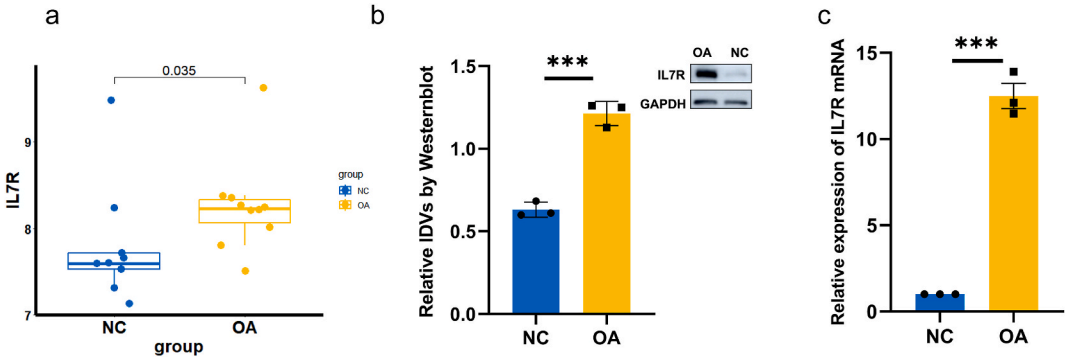

Fig. 5. IL7R was upregulated in OA synovium. (a) Based on validation with the GSE12021 dataset, higher levels of *IL7R* were observed in the OA group than in the NC group ($P < 0.05$). (b) Based on validation with clinical synovium samples, IL7R levels were significantly higher in OA clinical samples than in NC samples ($P < 0.001$, $n = 3$); western blots are displayed on the right, with GAPDH used as the internal reference (Images of the original drawings are shown in supplementary material 1). (c) Similar outcomes were observed in the qPCR analysis ($P < 0.001$, $n = 3$). ***. $P < 0.001$. Data was statistically analyzed using SPSS 24.0. Differences between groups were assessed using Student's *t*-test, with significance set at $P < 0.05$. GraphPad Prism 8 was used for data visualization.

macrophages and endothelial cells [45].

Previous researches have shown that the expression of *IL7R* is much higher in RA than OA, and *IL7R* is considered as an inflammatory marker that can be used to distinguish RA from OA [46,47]. However, we investigated the gene expression of OA and RA separately and found that *IL7R* is the hub gene in the synovitis of both diseases. Moreover, the external validation confirmed that *IL7R* expression in the synovial membrane of OA patients was much higher than that of normal patients, which enriched the results of previous studies.

Multiple relevant clinical studies support our results. IL7Rα was expressed on B cells with equal percentage in the synovial tissue of both OA and RA patients, playing proinflammatory effects [48]. Ratneswaran et al. demonstrated that the cytokine level of IL7 is the target to distinguish the severity of trapeziometacarpal osteoarthritis [49]. Min et al. detected that IL7R was significantly expressed in the synovial membrane of knee OA, promoting the expression of angiogenic factors [50]. This study reports the high expression of IL7R in OA and RA synovial fibroblasts using bioinformatics analyses. Through external dataset validation and qPCR and Western blot analyses of clinical synovial tissue, the results showed that the mRNA and protein expression levels of *IL7R* in OA synovial tissue were significantly higher than those in NC synovial tissue. OA and RA had common hub gene of *IL7R* and common enrichment terms, which suggest that both may promote the occurrence and development of arthritis through the same mechanisms. Future studies should expand the sample size and further explore the role of IL7R in the pathogenesis of OA.

This study had some limitations. First, in our outcomes, the co-enrichment cluster of OA and RA scored significantly higher in OA than in RA, possibly owing to the small sample size. Second, owing to the limited number of gene counts in the GEO database, for sample tissues of synovial fibroblasts that included normal control samples, we used a dataset of gene expression in synovial tissue for external validation. Third, due to difficulties of clinical sampling, our validation experiment only used synovial tissue of OA patients.

In conclusion, we used bioinformatics to identify co-DEGs of SFs in OA and RA and found that *IL7R* was a key inflammatory gene associated with the pathogenesis of OA and RA, which was validated using external datasets and clinical samples, suggesting that IL7R may be a potential target for OA treatment. This study indicated that the pathogeneses of OA and RA might share common immune characteristics, providing new insights into the biological mechanisms and molecular targets of OA immune inflammation.

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Data availability

The data that support the findings of this study are available from public databases.

CRediT authorship contribution statement

Yaduan Dai: Conceptualization, Data curation, Methodology, Software, Validation, Writing – original draft. **Lin Chen:** Methodology, Supervision, Validation, Visualization, Writing – original draft. **Zhan Zhang:** Data curation, Investigation, Methodology, Software, Supervision, Writing – review & editing. **Xueyong Liu:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28330.

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