# Role of crosstalk between synovial cells and chondrocytes in osteoarthritis (Review)

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**Abstract.** Osteoarthritis (OA) is a low-grade, nonspecific inflammatory disease that affects the entire joint. This condition is characterized by synovitis, cartilage erosion, subchondral bone defects, and subpatellar fat pad damage. There is mounting evidence demonstrating the significance of crosstalk between synovitis and cartilage destruction in the development of OA. To comprehensively explore the phenotypic alterations of synovitis and cartilage destruction, it is important to elucidate the crosstalk mechanisms between chondrocytes and synovial cells. Furthermore, the updated iteration of single-cell sequencing technology reveals the interaction between chondrocyte and synovial cells. In the present review, the histological and pathological alterations between cartilage and synovium during OA progression are described, and the mode of interaction and molecular mechanisms between synovial cells and chondrocytes in OA, both of which affect the OA process mainly by altering the inflammatory environment and cellular state, are elucidated. Finally, the current OA therapeutic approaches are summarized and emerging therapeutic targets are reviewed in an attempt to provide potential insights into OA treatment.

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*Abbreviations:* OA, osteoarthritis; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; ECM, extracellular matrix; PCM, pericellular matrix; MMP, matrix metalloproteinase; ADAMTS, a desintegrin-like and metalloproteinases with thrombospondin motifs; SFCs, synovial fibroblasts; scRNA-seq, single-cell RNA sequencing; TLR, Toll-like receptor; ER, endoplasmic reticulum; ROS, reactive oxygen species; EVs, extracellular vesicles; FLS, fibroblast-like synoviocytes; CWP, cartilage wear particles; lncRNA, long-stranded non-coding RNA; AM, activated macrophage; OAC, osteoarthritic chondrocytes; MSC, mesenchymal stem cell; BM-MSC, MSC derived from bone marrow; AD-MSC, MSC derived from adipose tissue; SM-MSC, MSC derived from synovial membranes; PDMSC, placenta-derived mesenchymal stem cell; hUC-MSC, human umbilical cord MSC; UCD-MSC, umbilical cord-derived MSC

*Key words:* cellular interaction, OA, exosomes, chondrocytes, synovial cells

**Contents**



## 1. Introduction

Osteoarthritis (OA) is a chronic, non-specific inflammatory disease that, under the influence of a chronic inflammatory environment, can result in joint deterioration and deformity, leading to pain and limited mobility (1). There are 240 million individuals worldwide suffering from OA, and some specific populations (elderly, women, Asian population) face higher prevalence rates (2). This not only poses a threat to patient health, but also imposes a significant medical burden (3). An individual is at risk of OA due to aging, obesity and trauma, while chronic inflammation, metabolic disorders, and damage-associated molecular patterns (DAMPs) are also important factors in the occurrence of OA (4,5). As the most common joint disease, OA affects the entire joint, causing damage to articular cartilage, synovium, subchondral bone, and the fat pads beneath the patella (6-8).

Pathological crosstalk among different joint tissues actively contributes to OA development (9). Synovium-cartilage crosstalk leads to OA symptoms and may also contribute to OA development (10). Therefore, elucidating the specific crosstalk

mechanism between synovium and cartilage is crucial for in-depth research on the development process and pathogenic mechanism of OA. Moreover, current OA treatments exhibit limited efficacy in symptom relief, underscoring the need for a deeper understanding of OA pathogenesis to establish a foundation for the discovery of treatments.

Therefore, this article presents an exploration of the anatomy of normal and OA joint tissues, integrating imaging, biological information, and basic experimental evidence to substantiate the existence of an important link between synovium and cartilage. Additionally, it outlines the important injury phenotypic changes associated with injury, primarily synovitis and cartilage destruction, between cartilage and synovium. The literature on the crosstalk between synovial cells (fibroblasts and macrophages) and chondrocytes in OA is then collected and summarized to outline the mechanisms of their interaction. Finally, current and promising therapeutic modalities are presented to provide insights into new molecular mechanisms and facilitate the discovery of effective therapeutics.

## 2. Overview of joint structure and biology

*Synovial membrane*. The normal synovial membrane comprises two layers, the inner layer and the lining layer (11). Macrophages and fibroblasts are typically located in the external layer of the synovial membrane, jointly maintaining synovial homeostasis (12). The lining layer of the synovial tissue contains mesenchymal stem cells (MSCs), immune cells, heterogeneous macrophages, and fibroblasts (13). Under normal conditions, synovial fibroblasts (SFCs) produce synovial fluid, mainly composed of lubricants and mucins (14). Both of these molecules play a vital role in maintaining the normal structure of the joint cartilage by lubricating the cartilage surface and reducing friction (15). Additionally, lubricants, mainly lubricin, can inhibit the deposition of pathological proteins on the joint surface (16). Since joint cartilage lacks an inherent supply of nutrients, the synovium also helps to provide nutrition to chondrocytes and maintain joint soft homeostasis (17).

Synovial abnormalities in patients with OA are characterized by thickening of the inner synovial layer, inflammatory cell aggregation, interstitial vascularization, and fibrosis of the underlying layer (18-20). Synovitis is considered a potential precursor to the development of OA (21). MRI and ultrasound have often been used in the evaluation of OA (22,23), and imaging findings have revealed hyperplasia of the synovial lining in patients with early-stage OA (22). Synovial biopsy serves as the gold standard in diagnosing of synovitis (10), and patients with early-stage OA often present with synovial thickening and infiltration of inflammatory cells (20). In inflammatory situations, synovial lining cells are usually proliferated and accompanied by an inflammatory cell infiltrate consisting mainly of macrophages, and a few but significant number of T and B cells (24). During the OA process, synovial macrophages are involved in innate immune response, producing pro-inflammatory cytokines that interact with other synovial cells and chondrocytes (25). An important factor in the pathogenesis of OA is the disturbance of cytokine balance, with an increase in the secretion of pro-inflammatory cytokines initiating a vicious cycle that causes damage to cartilage and other intra-articular structures by activating catabolic enzymes, thereby exacerbating OA progression (8). In addition, pro-inflammatory cytokines can further activate chemokines, such as chemokine (C-C) motif ligand (CCL)2 and CCL5, attracting inflammatory cells to the joints, further promoting the secretion of inflammatory factors and disease progression (9). In addition, synovitis promotes angiogenesis (26), which may lead to osteophyte formation and ossification, which in turn accelerates inflammation (27). In the advanced stages of OA, over-proliferation of fibroblasts, differentiation into myofibroblast-like cells, and impaired extracellular matrix (ECM) anabolism promote fibrosis of the synovium (28). Thus, the pathological process of the synovium is crucial for the development of OA.

*Cartilage*. Articular cartilage is a connective tissue covering the ends of bones, composed of ECM and chondrocytes, which lubricate joints and withstand loads (29). Proteoglycans (aggregated proteoglycans and chondroitin sulfate) are the main constituents of the matrix and together with collagen (mainly collagen II) form the ECM, which is involved in cartilage synthesis and degradation (6). In a previous study, pericellular matrix (PCM) was proposed as the matrix encasing chondrocytes within cartilage, maintaining the mechanical load of chondrocytes and regulating molecular interactions (30). This finding provides deeper insights into the microstructure, physical properties, and chemical composition of cartilage. Further exploration of ECM and PCM facilitates a better understanding of how to regulate chondrocyte metabolism and maintain cartilage homeostasis.

When cartilage is damaged by external forces, chondrocytes, SFCs, and synovial macrophages produce a desintegrin-like and metalloproteinases with thrombospondin motifs (ADAMTS) or matrix metalloproteinases (MMPs), the former scavenging proteoglycans (31) and the latter cleaving collagen (32), disrupting cartilage tissue structure and biological function. Not only does catabolism of the ECM cause cartilage degeneration, changes in chondrocyte status are equally important for cartilage degeneration. Chondrocyte response patterns in OA include proliferation and cell death, anabolic imbalance, and phenotypic regulation (33). Early in the OA process, chondrocytes proliferate and synthesize ECM to aid in injury healing (34). After sufficient catabolic signals are provided to articular chondrocytes, this leads to their eventual phenotypic loss (35). These phenotypes include hypertrophy, apoptosis, autophagy and senescence, with hypertrophy being the most common phenotype of chondrocytes. The normal bone joint structure and OA tissue structure are depicted in Fig. 1.

*Association between synovium and cartilage*. The synovium establishes a connection with cartilage through the secretion of synovial fluid, introducing the concept of molecular interaction across this region during OA (36). During the progression of OA, an important network links synovitis and cartilage destruction (1,37).

An arthroscopic score for knee OA from a multicenter, longitudinal study showed that the intensity of synovitis inflammation is strongly related to the severity of cartilage

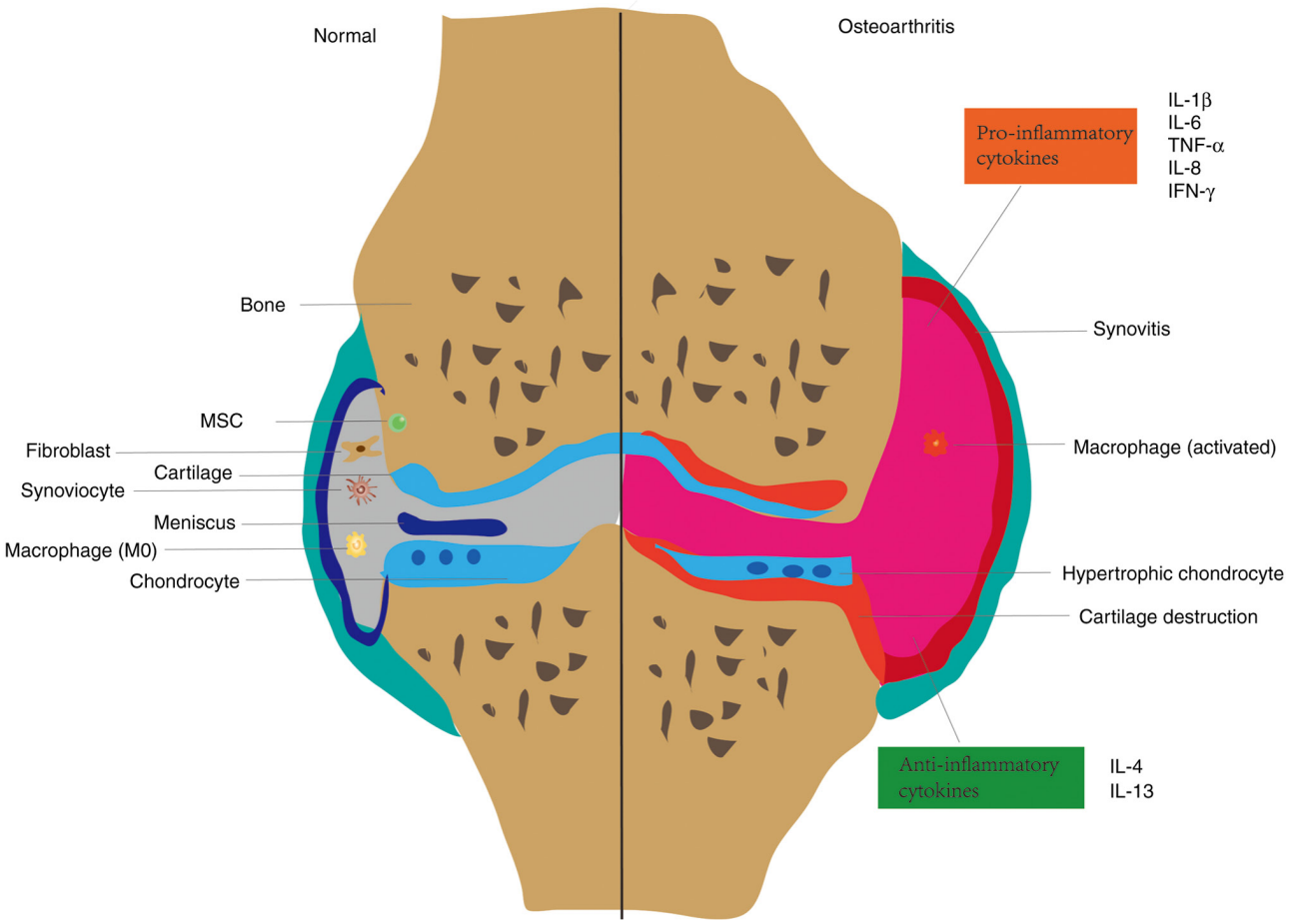


Figure 1. Structure of joints and mechanism of injury in osteoarthritis. The left side of the image shows the normal joint structure; following inflammatory stimulation, a series of changes such as synovitis, cartilage destruction, macrophage activation and chondrocyte hypertrophy are carried out. MSC, mesenchymal stem cell.

destruction, which may have potential in predicting disease progression (38). Another study involving multicenter patients with OA demonstrated a significantly higher frequency of cartilage loss in cases with grade 3 or 4 effusion synovitis compared to those with grade 0 or 1 effusion synovitis (39). In OA, bioinformatics is employed to identify the central genes and immune environment characteristics of OA (40). By analyzing gene expression profiles, novel diagnostic biomarkers for OA and possible associations between key genes and infiltrating immune cells may be identified. A transcriptomics-based study by Wang *et al*, integrated data from different tissues of the knee joint in patients with OA, clarified the relationship between synovium and cartilage, and combined with synovial proteomics data, constructed a crosstalk spectrum according to predicted ligand-receptor interactions (40). Basic experiments have shown that some secreted glycoproteins, such as MFG-E8, whose deletion leads to progressive cartilage destruction and synovial proliferation, are two pathological processes that may jointly crosstalk through the NF-κB pathway (41). Notably, specific medicinal plants, such as curcumin, a rooted plant of the ginger family, have been shown to alleviate synovitis and cartilage damage through the NF-κB pathway (17).

The aforementioned evidence from clinical experiments, bioinformatics and basic research demonstrates a close relationship between synovium and cartilage. However, the exact mechanism remains unclear. Hence, it is particularly important to explore the specific mechanisms of crosstalk between the two and help discover new therapeutic modalities for OA.

## 3. Immune response in OA

The activation of immune cells induces changes in the environment for cartilage survival. Factors released by immune cells continuously influence the inflammatory microenvironment, regulating its complex balance (42). The response of chondrocytes in the immune response is increasingly attracting interest. Single-cell RNA sequencing (scRNA-seq) and mass cytometry, render it possible to investigate chondrocyte heterogeneity and intercellular communication in detail, and to identify subgroups with different functions and phenotypes of these cells, targeting molecular mechanisms to understand OA (43). In this section, the activation of different subpopulations of chondrocytes involved in autoimmune response and subsequent mediating of OA inflammation and structural damage, are elucidated.

*Macrophage activation*. The first step in initiating the immune response involves the recognition of foreign objects by immune

cells (44). Macrophages, recognized as crucial players in OA, are distributed throughout the body, swiftly moving towards inflammatory sites (45), participating in both innate and acquired immunity (46). During the innate immune process, macrophages express pattern recognition receptors (PRR), including Toll-like receptors (TLR) and NOD-like receptors (NLR) (47,48), binding to pathogen-associated molecular patterns (PAMP) or DAMPs, mainly cartilage degradation products (49). Further activation of the transcription factors NF-κB and MAPK induce genes encoding cartilage-degrading ECM enzymes and inflammatory factors, ultimately leading to cartilage catabolism (47). The adaptive immune process in OA involves the activation of B cells and T cells, which assist macrophages (50). Some stimulators (IFN-γ, TNF-α, and LPS) and transcription factors (STATA and NF-κB) promote M1 polarization of macrophages, releasing pro-inflammatory cytokines (51), thereby accelerating the pathogenesis process of synovitis and cartilage destruction (52). By contrast, Th2 cells promote macrophage M2 polarization and mitigate OA by releasing IL-4 and IL-13 (42). *In vivo* experiments in mice have shown that inhibiting synovial macrophage M1 polarization helps reduce cartilage damage (53). In addition to immune responses, some metabolic changes, especially glucose metabolism, as well as energy metabolism affect macrophage processes leading to cartilage destruction.

Regarding material metabolism, glycolysis metabolism appears to promote OA development. Firstly, the addition of glycolysis inhibitors under the M1 polarized cell model of macrophages induced by alkaline calcium phosphate crystals was revealed to effectively reverse M1 macrophage polarization (54). This suggests that metabolic changes, particularly increased glycolysis in synovial macrophages, have the potential to exacerbate cartilage destruction. Additionally, the SIRT6 inhibitor, a member of the deacetylase protein family, has been demonstrated to exacerbate cartilage damage by enhancing the glycolytic process (55). Introducing RNAi targeting SIRT6 into cells induced RAW264.7 to release pro-inflammatory cytokines, promoting the M1 phenotype while inhibiting the M2 phenotype. In *in vivo* experiments, a significant cartilage deficit can be observed in mice (55). Given that the endoplasmic reticulum (ER) is the site where various metabolisms, such as gluconeogenesis and lipid metabolism, occur, it is involved in regulating the progression of OA. GRP78, an ER stress molecular chaperone and polymeric hyaluronan was revealed to inhibit synovial inflammation and the M1 phenotype of macrophages stimulated by IL-1β through the GRP78-NF-κB pathway. Further investigation is needed to elucidate these findings (56).

Experiments conducted in mitochondria indicated that GLX351322, an inhibitor of NADPH oxidase 4, reduces synovitis cartilage destruction through the MAPK/NF-κB pathway, thus attenuating teporomandibular joint OA (57).

In terms of epigenetic modifications, extracellular vesicles (EVs) from human umbilical cord MSCs (hUC-MSCs) were demonstrated to reduce NLRP3 mRNA methylation in macrophages by releasing miR-1208 to interact with METTL3, thereby attenuating knee OA in a mouse model (58).

In conclusion, metabolic reprogramming and epigenetic modifications play important regulatory roles in molecular alterations and polarization states of macrophages. The exploration of metabolic activators or inhibitors, along with targeted molecular epigenetic regulation, may effectively maintain the balance of cell survival and physiological processes (56-58).

*Fibroblast activation*. Fibroblast-like synoviocytes (FLS) represent a heterogeneous population of invasive fibroblasts and are considered important in OA (59). Activated FLS are one of the key participants in OA joint destruction, secreting pro-inflammatory mediators including IL-1β and TNF-α (60,61). Pro-inflammatory mediators have the function of maintaining cartilage homeostasis (62), and chondrocytes are stimulated by the pro-inflammatory mediators released by FLS, thereby exacerbating inflammation (59,63). IL-1β promotes chondrocyte synthesis of MMPs, mainly MMP1 and MMP13, thereby shearing and disrupting ECM synthesis by articular cartilage (64). TNF-α promotes chondrocyte mitochondrial dysfunction and leads to death, resulting in cartilage destruction (65). In addition, ECM is cleaved into substances such as fibronectin and type II collagen after the increase of the activities of MMPs and ADAMTS, which further activates FLS as DAMPs through the integrin and TLR pathways (66,67). A study showed that under the stimulation of cartilage wear particles (CWP), OA-FLS cultures increased the levels of pro-inflammatory mediators (NO, PGE2), cytokines (IL-6, IL-8) and MMPs (MMP9, MMP10, MMP13), which modify the inflammatory microenvironment (68,69).

Metabolic reprogramming and epigenetic modifications have important regulatory roles in fibroblast molecular alterations and polarization states.

Glucose metabolism appears to be crucial for fibroblast activation. According to a study, hyperglycemia increases AGEs expression through the HIF-1α-GLUT1 pathway, leading to an increase in inflammatory factors in FLS and subsequent chondrocyte degradation and OA promotion (70). Additionally, overexpression of pyruvic acid dehydrogenase kinase can inhibit the metabolic reprogramming of OA SFCs, thereby reducing the secretion of FLS cytokines, which may be the mechanism to mitigate cartilage degeneration (71).

Epigenetic modifications mainly include DNA methylation, histone modifications, chromosome remodeling and regulation of non-coding RNAs (72). Epigenetic modifications of FLS have an impact on cartilage phenotype. In terms of methylation, ATG7 mRNA methylation modifications mediated by METTL3 were demonstrated to regulate FLS cell senescence through the autophagy-GATA4 axis. In an *in vivo* animal model, METTL3 knockdown ameliorated DMM-induced cartilage destruction (73). Notably, METTL3 also has an important role in macrophage regulation. In terms of microRNA (miRNA or miR), miRNA expression is increased in FLS, and a previous study revealed a protective effect in DMM-induced OA mice using miR-34a-5p mimics (74). However, the specific mechanisms of miRNA regulatory molecules need to be further elucidated. In terms of histone modification, histone modification regulates molecular expression and pathway changes in fibroblasts. For example, spermidine inhibits TNF-α-induced pro-inflammatory cytokine release from the NF-κB/p65 pathway in OA by activating RIP1 deubiquitination, thereby alleviating synovitis and cartilage degeneration (75).

*Chondrocyte activation*. Activation of chondrocytes arises from alterations in the inflammatory microenvironment, characterized by cell phenotype adjustment, molecular changes, and ECM disruption (76), which disrupts the anabolic-catabolic balance of chondrocytes (77), tilting this balance towards catabolism, which in turn promotes cartilage degeneration and OA pathological progression. Chondrocytes are the only surviving cells in cartilage, synthesizing matrices and fibers to maintain normal cartilage function (78). Proliferation, viability, and secretion of chondrocytes change as OA progresses. Various behavioral phenotypic changes are acquired, such as cell death, and hypertrophy, which produce important changes in OA (79). At the same time, during the progression of OA, marked changes in metabolism occur, with a shift to glycolysis in the glycolytic pathway, which leads to impaired ECM synthesis and anabolic processes, in addition to some lipid metabolism (lipid deposition and elevated cholesterol), and oxidative stress, which also play an important role (80).

Recent single-cell sequencing techniques have revealed heterogeneous populations of chondrocytes induced by different factors. Different chondrocyte heterogeneous populations exist at different stages of disease development, have different cartilage anatomical localizations, mediate different phenotypes (hypertrophy, apoptosis), and perform different functions (9). The focus of the present review was on the chondrocyte heterogeneous subpopulations associated with immune response and fibrosis.

In a genomics study conducted by Ji *et al* (81), seven articular chondrocyte populations in human knee OA cartilage were defined for the first time, namely proliferative chondrocytes (ProCs), pre-hypertrophic chondrocytes (preHTCs), hypertrophic chondrocytes (HTCs), fibrochondrocytes (FCs), effector chondrocytes (ECs), regulatory chondrocytes (RegCs), and steady-state chondrocytes cells (HomCs). Of these, ECs are associated with metabolic responses, which lead to impaired ECM synthesis and anabolic processes. RegCs have functions such as antigen-presenting and immune cell receptor signaling, and some RegCs have high levels of immune system-specific markers, suggesting that they are similar to immune cells. FCs, labeled with fibroblast phenotypic markers, and with a high proportion of genes and vascularization capacity are associated with unfavorable OA outcomes. ECs and RegCs are predominantly present in early OA, and FCs are predominantly a late chondrocyte population. Functional ECs and RegCs protect cartilage from OA, while FCs mainly destroy cartilage to exacerbate OA.

Hu *et al* (82) further identified chondrocyte subtypes of patients with OA based on the research by Ji *et al* (81) and explored their immunogenicity. ECs have stronger immune reactivity and secretory activity, mediating and recruiting immune cells in OA, mainly through the regulation of various signaling pathways related to tissue inflammation and exerting immune cell effects. FCs have higher fibroblast characteristics and exhibit enhanced metabolic activity in energy metabolism, which may mainly induce cartilage degeneration by affecting fibrodegeneration and cartilage repair.

Gao *et al* (83) processed the data from Ji *et al* (81) and identified a subset of chondrocytes accordingly. The study focused on stress metabolism chondrocytes and ECM synthesis chondrocytes. Stress metabolic chondrocytes may actively participate in metabolic reprogramming (84). Chondrocytes related to matrix synthesis may promote cell apoptosis and neovascularization through the SLIT-ROBO pathway (85).

Articular cartilage consists of ECM and chondrocytes with different morphologies and functions. These findings suggest that heterogeneous subsets of chondrocytes involved in metabolic changes as well as immune responses are important for the progression of OA. Clarifying the classification and function of different chondrocyte subpopulations and exploring their communication with other cells will deeply expand knowledge in molecular biology and OA pathology. In addition, these aforementioned scRNA-seq studies identify the origins of crucial synthetic and decomposed mediators in OA. Further exploration of these mediators can help to identify targeted pathogenic cells and molecules more centrally, and develop more effective OA strategies.

According to Yuan *et al*, synovium regulates different metabolic subgroups of cartilage in the knee joint (86). The receptor-ligand crosstalk action was higher in number in synovial and cartilage inflammatory subtypes. Therefore, synovium may be a driver of these OA subpopulations. According to Ching *et al*, molecular phenotypic changes in synovial cells and chondrocytes cause crosstalk, and a model for crosstalk has been built to explain OA (87).

Identifying the association between chondrocyte heterogeneity and pathogenic synovial cells contributes to the understanding of the complexity and interactions of histopathology. The research methods include analyzing cell surface markers, bulk transcriptomics and single cell transcriptomics that identify a subpopulation of chondrocytes associated with disease that may ultimately serve as a specific target for therapy. Revealing therapeutic targets for disease and targeting chondrocyte subpopulations may complement therapeutic treatments.

Additional clinical studies are required to understand how alterations in these subpopulations affect the various clinical settings of OA, including severity of joint damage, disease prognosis, and patient response to treatment. Detailed phenotypic research has greatly expanded the understanding of chondrocyte plasticity, which helps with the development of targeted therapeutic strategies for chondrocytes. The mechanism of crosstalk between the three types of cells is summarized in Fig. 2.

*Crosstalk between cells*. The interaction between synovium and cartilage is ultimately between synovial cells and chondrocytes. It has been shown that treating articular chondrocytes with EVs derived from OA synovial fluid not only reduces cell survival, but also reduces anabolism and increases catabolism and pro-inflammatory effects (88,89).

Following the onset of OA, fibroblasts acquire an invasive phenotype and interact with chondrocytes through pro-inflammatory mediators to secrete MMPs to affect OA (37). Similarly, macrophages acquire a polarized phenotype and induce chondrocytes to produce pro-inflammatory mediators and phenotype changes by releasing pro-inflammatory mediators (18,90). At the same time, these mediators activate cartilage cells that produce MMPs, amplify the inflammatory cascade with synovial cells, and lead to a vicious cycle of an inflammatory microenvironment (91).

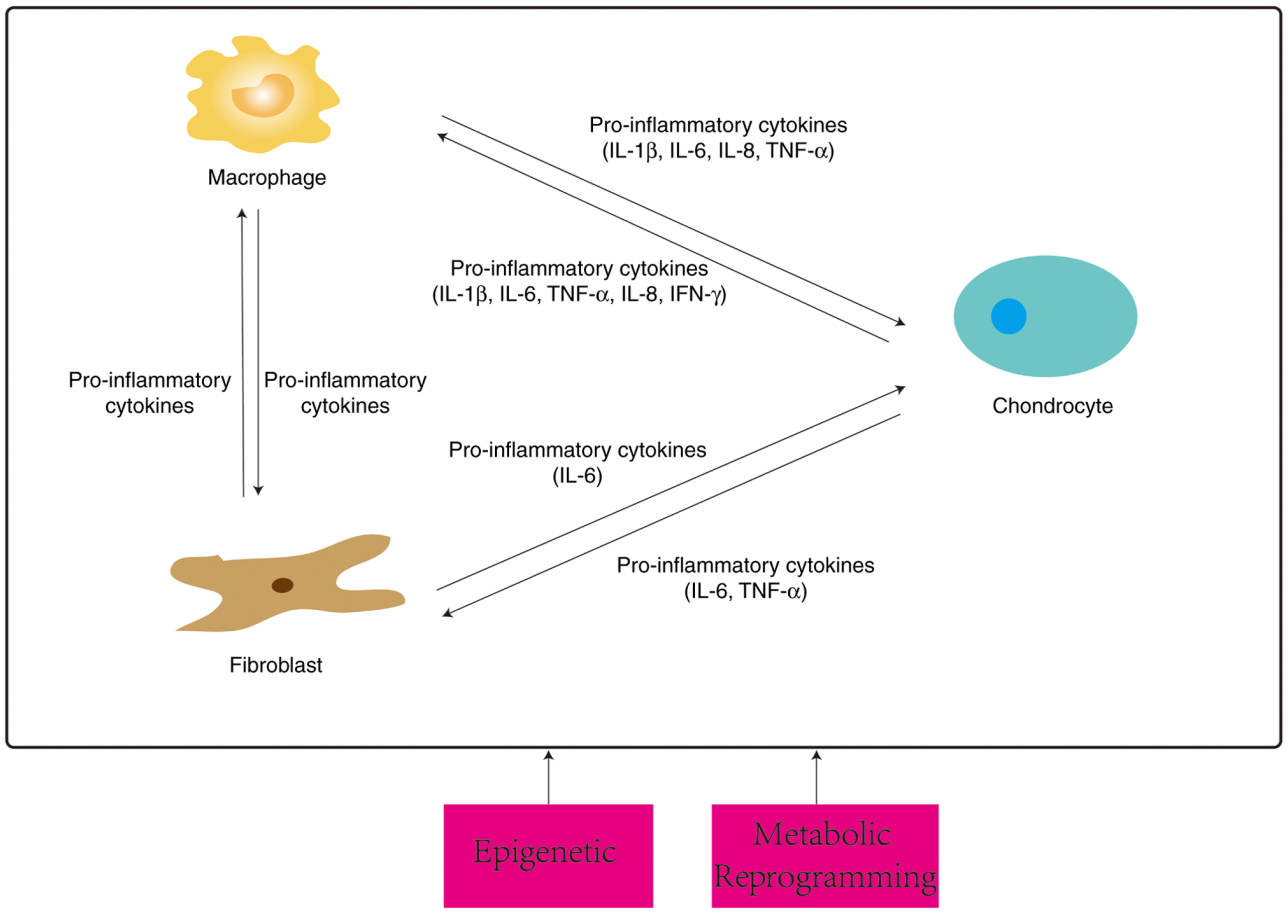


Figure 2. Mechanism of action of synoviocytes and chondrocytes. Macrophages, chondrocytes and fibroblasts interact through proinflammatory cytokines and chemokines. Epigenetics and metabolic reprogramming are the committed steps in regulating the interactions.

In addition to the interaction between synovial cells and chondrocytes, a huge network encompasses three types of cells. SFCs have different functional properties in OA and secrete R-spondin-2 (92). R-spondin-2 activates the Wnt pathway and induces chondrocyte hypertrophy and differentiation (93). Notably, R-spondin-2 can also be secreted by M1 macrophages, and knockdown of R-spondin-2 was demonstrated to exacerbate cartilage destruction in mouse animal experiments (94,95). This suggests an important network linking the three together. Further research is required to identify common molecules and pathways of action to elucidate the specific mechanisms of the three interactions.

## 4. Cellular interaction

Direct evidence of the interactions between synovial cells (mainly macrophages and fibroblasts) and chondrocytes, which act as mutual donors and acceptor cells, has been amassed. The interactions take place by means of cell contact, paracrine secretion, and exocytosis. The main substances that interact are some amino acids and peptides/proteins, pro-inflammatory cytokines, secreted proteins, and microvesicles. Microvesicles are formed by budding from the cell membrane, with a particle size of 150-1,000 nm. They transfer bioactive RNA [miRNA, tRNA, mRNA, and fragmented mRNA, long stranded non-coding RNA (lncRNA), and tRNA], proteins, lipids, and metabolites from donor cells to recipient cells, and affect the biological characteristics of the latter (19). In terms of cellular communication, microvesicles mediate intercellular communication and regulate the spread of inflammation and cartilage destruction through miRNA and lncRNA. In terms of organizational communication, microvesicles can penetrate microcrack channels and vascular channels between bone and cartilage interfaces, promoting bone and cartilage communication (19).

*Cellular channels*. Connexins (Cxs) are subunits that form gap channels, and Cx43 is the most prominent Cx (96). It has been confirmed that articular chondrocytes in cartilage physically connect with distant chondrocytes through cytoplasmic extension mainly establishing intercellular communication through the gap junction channel composed of Cx43.

Carpintero-Fernandez *et al* (96) established a co-culture system (Transwell) to study crosstalk between synovial cells and chondrocytes and showed the presence of a cellular channel (Cx43) between the two cells to establish communication and exchange amino acids and peptides/proteins, including several chaperone proteins and cell surface proteins, which may indicate the involvement of chaperone and cell surface proteins in the pathological process in OA.

*Paracrine*. Previous research has identified the importance of IL-6 between cellular interactions. Chondrocytes are prompted to secrete IL-6 through IL-6R on IL-6 secretory junctions on fibroblasts under normal conditions or after leptin stimulation,

and IL-6 secreted by FLS upregulates the expression of MMP3 and MMP13 genes, and promotes ECM destruction (37). After IL-1β stimulates chondrocytes to bind IL-1R, the NF-κB pathway is activated and chondrocytes secrete IL-6 and act on IL-6R, upregulating STAT3 expression to promote IL-6 secretion by macrophages, thus promoting IL-6 and IL-8 re-release (97). IL-6 is derived from pro-inflammatory cytokine stimulation of chondrocytes, binding to macrophages or IL-6R on FLS cells causes a cascade effect, which proceeds to the facilitated expression of MMPs.

Subsequent studies have explored the types of pro-inflammatory cytokines in greater depth. A 3D culture system that cultured macrophages and chondrocytes found that activated macrophages (AMs) promoted osteoarthritic chondrocytes (OAC) to express more MMPs and ADAMTS as well as cytokines (IL-1β, IL-6, TNF-α, IL-8 and IFN-γ). Being affected by OAC, AMs express more IL-1β and VEGFA (98). Similarly, findings under Transwell co-culture conditions revealed that cartilage debris stimulated macrophages prompting them to release pro-inflammatory mediators (TNF-α, IL-6, NO), inducing chondrocytes to break down large amounts of pro-inflammatory metabolic factors (MMP13, IL-6, iNOS) and exacerbating OA progression (99). In addition, M1 polarization occurs after IL-1β stimulation of macrophages (100), which secrete pro-inflammatory factors (IL-1β, TNF-α, IL-6), upregulating the increase of catabolic factors (MMP13, ADATMS5) and decrease of anabolic factors (SOX9) in chondrocytes. In turn, chondrocytes receive stimulation to secrete PTX3, which acts on the CD32 receptor of M0 macrophages and activates the NF-κB pathway, preventing both M2 polarization and promoting the expression of iNOS. This also promotes the M1 phenotype (101).

Furthermore, a study revealed that synovial cells produce one or more soluble factors that may be released into cartilage via synovial fluid, inducing the expression of Prg4 (lubricating hormone) in surface regions, thereby inhibiting senescent chondrocyte hypertrophy and promoting their differentiation (102).

In conclusion, macrophages stimulated by DAMPs secrete pro-inflammatory mediators to induce catabolism in chondrocytes, and chondrocytes exacerbate OA by promoting further cascade or polarization of macrophages through pro-inflammatory cytokines or secreted proteins.

*Exosomes*. EVs secreted by synovial cells or chondrocytes contains abundant miRNAs, which affects downstream pathways, leading to the acquisition and deletion of changes in cell phenotype and molecular expression, thereby altering the inflammatory microenvironment and affecting OA.

In chondrocyte-fibroblast crosstalk, it was observed in a rat chondrocyte model that SFC secreted EVs rich in miR-126-3p, promoted functional changes in chondrocytes, mainly migration and proliferation, while inhibiting chondrocyte apoptosis and expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) (103). Overexpression of miR-150-3p was revealed to reduce the expression of Trim14 while suppressing secretion of immune factors (NF-κB, IFN-β), leading to a decrease in the concentration of inflammatory mediators (IL-1β, IL-6, TNF-α), and anabolic factors (COL2, ACAN) (104). MiR-106b-5p was demonstrated to be downregulated by lncRNA-H19 and inhibited TIMP2 expression, thereby disrupting MMPs. In addition, in the *in vitro* chondrocyte model, proliferation and migration were enhanced, and ECM synthesis (increase in MMP13, ADAMTS5 and decrease in COL2A1, ACAN) was weakened (61). Fibroblasts act on chondrocytes via miRNA and regulate their secretion of ECM degradation enzymes as well as pro-inflammatory factors by affecting the phenotype of the cells, subsequently influencing the progression of OA.

In macrophage and chondrocyte crosstalk, LPS and IFN-γ stimulate macrophages after extracting EVs, and miR-1246 enriched in EV was shown to promote chondrocyte secretion of proinflammatory mediators (IL-1β, IL-6, TNF-α) and MMPs by inhibiting the expression of GSK3β and Axin2 through the Wnt/β-catenin signaling pathway (105). Another study showed that LPS stimulation of macrophage THP-1 downregulates hsa_circ_0005567 expression and upregulates miR-492 expression of chondrocytes, inhibiting SOCS2 and promoting chondrocyte apoptosis (106). Furthermore, EVs were extracted after IL-1β stimulation of chondrocytes and added to LPS-stimulated macrophages, and these vesicles inhibited LPS-triggered autophagy of macrophages by downregulating ATG4B via miR-449a-5p. Autophagy inhibition has been revealed to exacerbate synovitis and promote OA progression by increasing mitochondrial ROS (mitoROS) production and promoting macrophage IL-1β secretion (100).

Macrophages stimulated to undergo M1 polarization affect chondrocytes encoding proinflammatory factors and ECM-degrading enzymes, as well as induce chondrocyte apoptosis and oxidative stress via miRNA.

Notably, small extracellular vesicles derived from OA-derived chondrocytes, containing the Cx43 protein, regulate the epithelial-mesenchymal transition (EMT) signaling program through NF-κB and ERK pathways, ultimately inducing the loss of a fully differentiated phenotype and aging of synovial cells (107).

The mechanism of the interaction between exosomes secreted by three types of cells is depicted in Fig. 3. Paracrine factors and exosomes are summarized in Table I.

## 5. Clinical application

MSCs are somatic cells that can self-renew and differentiate in multiple directions. They are generally separated from a variety of adult or neonatal tissues, such as bone marrow (BM), adipose tissue (AD), placenta or umbilical cord (108). Recent evidence suggests an 'ecological niche' role for synovial membranes (SMs) as a rich source of pluripotent MSCs capable of differentiating into a wide spectrum of mature cells, including cartilage, bone, muscle, and AD (108-110).

Through its paracrine signaling secretion, MSCs are not only capable of differentiation into different cells, but also have anti-inflammatory and immunosuppressive properties (111).

In OA, MSCs have a therapeutic function (112). MSCs derived from the umbilical cord were administered intraarticularly to patients with active OA (Phase I/II trial) by Matas *et al* (113). Soler *et al* used isolated expanded autologous MSCs to treat knee OA, evaluating its feasibility and effectiveness through pain scores and imaging evidence. According to their findings, cell-based therapy exhibited favorable tolerability, although some adverse effects were reported (for

Table I. Paracrine factors and exosomes.

| Phenotypic changes | Interaction mode | Donor cell | Recipient cell | Culture system | Mechanism | (Refs.) |
|---|---|---|---|---|---|---|
| Pro-inflammatory, decomposing | Exosomes | Synovial fibroblasts | Chondrocyte | Transwell co-culture | FLS-derived extracellular vesicle lncRNA H19 promotes cell viability and migration, and prevents IL-1β-induced phenotypic changes in chondrocytes by regulating miR-106b-5p and TIMP2 expression ECM degradation in induced chondrocytes | (61) |
| Unknown | Cell contact | Chondrocyte | Synovial cells | Transwell co-culture | The three kinds of cells can establish intercellular connections and communicate through gap junction channels to exchange some essential amino acids, peptides and proteins (including calnexin, calreticulin or CD44 antigen) and other substances | (96) |
| Pro-inflammatory, decomposing | Paracrine | Synovial fibroblasts | Chondrocyte | Transwell co-culture | TNF-α produced by chondrocytes upregulates the expression of metabolic factors in FLS, while IL-6 derived from FLS plays an important role in regulating MMP3 and MMP13 in chondrocytes | (37) |
| Pro-inflammatory, decomposing | Paracrine | Chondrocyte | Macrophage | Conditional medium cultivation | IL-1β activates NF-κB in chondrocytes, inducing IL-6 secretion | (97) |
| Decomposing | Paracrine | Macrophage | Chondrocyte | Transwell co-culture | Increased production of pro-inflammatory molecules and expression of chondrocyte catabolic factors in macrophage culture | (98) |
| Pro-inflammatory | Paracrine | Macrophage | Chondrocyte | Transwell co-culture | Increased release of matrix metalloproteinases and proinflammatory mediators from chondrocytes | (99) |
| Autophagy | Exosomes | Chondrocyte | Macrophage | Conditional cultivation | Chondrocytes secrete miR-449a-5p to inhibit autophagy of synovial macrophages by inhibiting the expression of ATG4B | (100) |
| Pro-inflammatory, M1 polarization | Paracrine | Macrophage | Chondrocyte | Conditional cultivation | Reduced miR-224-5p promotes the secretion of PTX3 by M1 polarized OA macrophages and chondrocytes. The increased PTX3 promotes | (101) |

Table I. Continued.

| Phenotypic changes | Interaction mode | Donor cell | Recipient cell | Culture system | Mechanism | (Refs.) |
|---|---|---|---|---|---|---|
| | | | | | the polarization of M1 in synovial macrophages and the secretion of inflammatory cytokines that disrupt the homeostasis of chondrocytes, accelerating the progression of OA | |
| Aging and hypertrophy | Unknown | Synovial cells | Chondrocyte | Conditional cultivation | Synovial cells secrete soluble factors to induce surface region Prg4 expression | (102) |
| Pro-inflammatory, apoptosis | Exosomes | Synovial fibroblasts | Chondrocyte | Conditional cultivation | SFC-miRNA-126-3p-Exos can inhibit apoptosis, cell death, and related inflammation of chondrocytes | (103) |
| Pro-inflammatory, decomposing | Exosomes | Synovial fibroblasts | Chondrocyte | Transwell co-culture | H-FLS-EVs inhibit the Trim14/NF-κB/IFN-β axis to regulate innate immune response, thereby protecting chondrocyte function and maintaining joint homeostasis | (104) |
| Pro-inflammatory, decomposing | Exosomes | Macrophage | Chondrocyte | Conditional cultivation | MiR-1246 inhibits GSK3β and Axin2 expression, inducing activation of the Wnt/β-catenin signaling pathway and promotion of the expression of proinflammatory factors and matrix metalloproteinases in chondrocytes | (105) |
| Apoptosis | Exosomes | Macrophage | Chondrocyte | Conditional cultivation | Downregulation of hsa_ circ_ 0005567 expression and upregulation of miR-492 expression in chondrocytes, induce inhibition of SOCS2 expression and promotion of chondrocyte apoptosis | (106) |

FLS, fibroblast-like synoviocytes; OA, osteoarthritis; SFC, synovial fibroblast; miR, microRNA.

example, mild arthralgia and gastrointestinal reactions) (114). OA can therefore be treated with MSCs, which secrete different factors (cytokines, chemokines, growth factors, EVs) (115). Stem cells of different origins have the potential to treat OA (116), and the present review describes their mechanism of action in OA through their mode of action.

*Paracrine secretion of MSCs*. Proteomic analysis revealed common secreted proteins of MSCs including BM-MSCs, AD-MSCs and SM-MSCs, classified by function as anti-inflammatory, MMP inhibitory, ECM homeostasis, and chondrocyte anti-death and promoting proliferation, suggesting that secreted proteins may affect OA through several of these aspects.

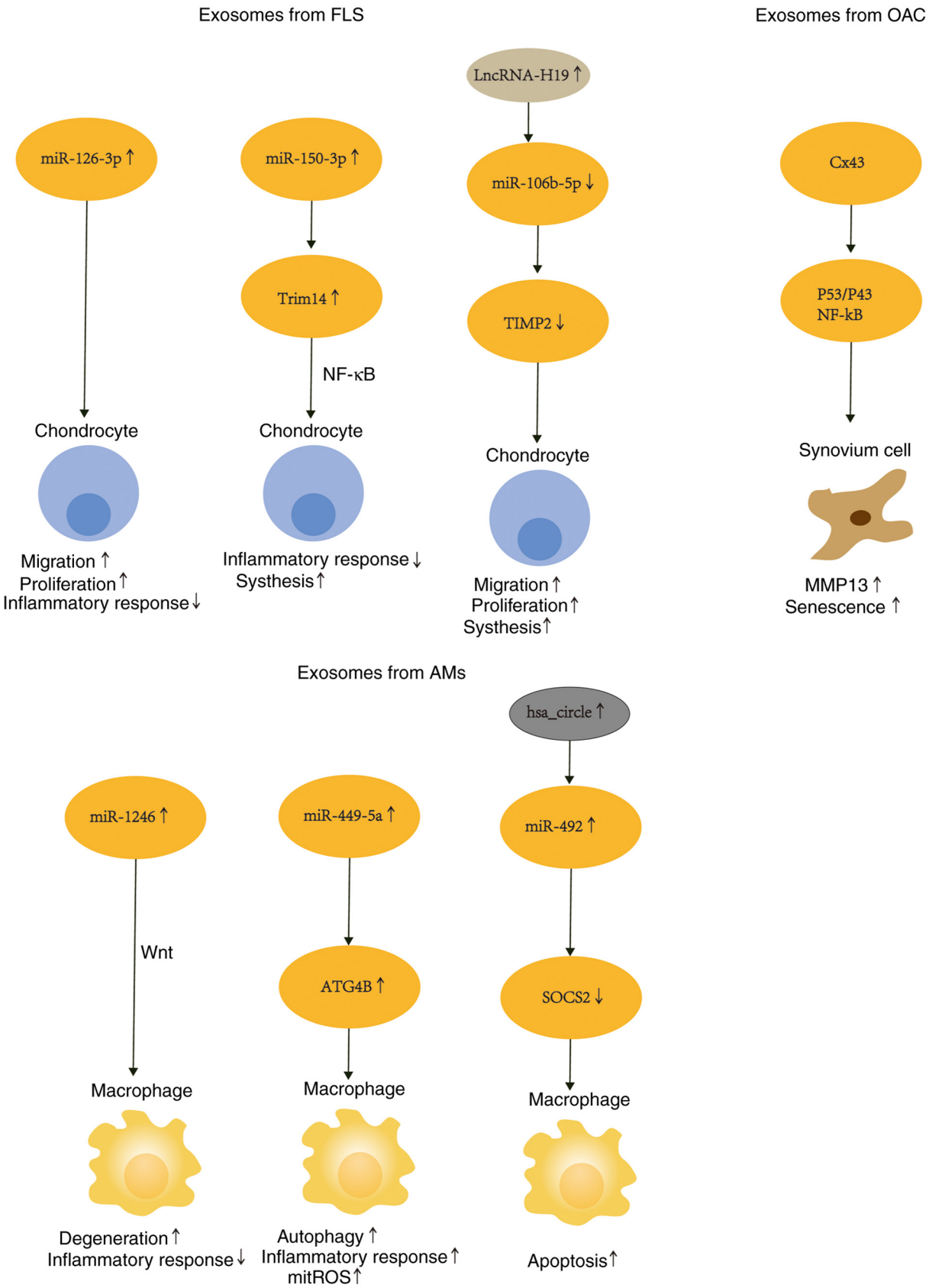


Figure 3. Mechanism of secretion of EVs between three types of cells. EVs secreted by FLS and AM cells contain microRNAs, which undergo a series of changes in the phenotype of chondrocytes, including migration, proliferation, changes in synthesis and decomposition, apoptosis and autophagy. EVs, extracellular vesicles; AMs, activated macrophages; FLS, fibroblast-like synoviocytes.

Proteomic data from BM-MSC, AD-MSC and SM-MSC samples revealed that TSG-6 and TSP-1 proteins reduce the concentration of inflammatory factors and MMPs by regulating the NF-κB pathway, and enhance COL2

expression, which is involved in cartilage repair and maintenance of cartilage homeostasis (117). Similarly, treatment with 12-Epi-Napelline, induced the metabolic secretion of chondrocyte-repair-promoting growth factors by BM-MSCs through modulation of the TGF-β/BMP pathway and shifted to differentiated chondrocytes (118).

In terms of anti-inflammation and inhibition of MMPs, intra-articularly injected AD-MSCs were revealed to inhibit chondrocyte MMP-13 release by homing to the synovium and releasing fluid factors with chondroprotective effects (chondrocyte proliferation and chondrogenic matrix protection) (119). The cell mixture Nanofat is extracted from AD, and Nanofat conditional medium treatment increased chondrocyte viability and proliferation and reversed the upregulation of the expression of catabolic markers and decreased the expression of synthetic metabolic markers induced by IL-1β (120). In addition, intra-articular injections of SMUP cells secreted by PTX-3 induced macrophage polarization to an M2 anti-inflammatory phenotype as well as upregulated ARG-1 expression, attenuating osteoarthritic destruction (121).

Placenta-derived MSCs (PDMSCs) were shown to enhance chondrocyte proliferation and migration by paracrine means, significantly restoring IL-1β-induced COL2, MMP13, ADAMTS4, ADAMTS5 and SOX9 aberrant gene expression, and chondrocyte COL2, MMP13 and SOX9 aberrant protein expression (122).

*Exosome secretion of MSCs*. Exosomes are endocytosis-derived nanoscale vesicles (30-140 nm) that play an important role in regenerative medicine (123). They carry numerous proteins and nucleic acids (124). KLF3-AS1, an exosome-derived noncoding RNA derived from MSCs, was demonstrated to inhibit autophagy and apoptosis in OA chondrocytes (125).

Different miRNAs have important therapeutic roles in MSCs (126). Synovial MSC-derived EVs contain different miRNAs. An *in vivo* study revealed that overexpression of miR-31 downregulates KDM2A, increases chondrocyte proliferation and migration, and attenuates cartilage damage and inflammation (127). MiR-155-5p overexpression was shown to prevent OA by increasing chondrocyte proliferation and migration, attenuating apoptosis and targeting Runx2 (128). OA cartilage damage was demonstrated to be ameliorated by miR-555A-26a-5p inhibition of PTEN, which suppressed chondrocyte apoptosis and inflammation (129). In addition, miR-130b-3p, which originated from SM-MSCs, attenuated chondrocyte apoptosis and ECM during OA degradation and exerted anti-inflammatory effects via inhibition of the LRP12/AKT/β-catenin axis (130).

The EVs of BM-MSCs containing lncRNA-NEAT1 were demonstrated to stimulate the Sesn2/Nrf2 axis through miRNA-122-5p and stimulate chondrocyte proliferation and autophagy, but inhibit their apoptosis (124). Notably, parathyroid hormone (PTH) (1-32) enhanced the treatment outcome of BM-MSC-derived exosomes on chondrocyte regeneration by inhibiting pro-inflammatory cytokine expression (131,132). Exosomes derived from BM-MSCs have also been revealed to reduce OA by promoting M1 to M2 conversion of synovial macrophages (116).

AD-MSCs act by regulating chondrocyte status and macrophage polarization. On the one hand, exosomes secreted by AD-MSCs promote cell proliferation and prevent chondrocyte apoptosis via the lncRNA-KLF3-AS1/miR-206 axis (131). On the other hand, osteoarthritic synovial fluid-treated AD-MSCs secrete factors and EV-embedded miRNAs that play a role in M2 macrophage polarization and cartilage repair (133).

Exosomes originated from OA chondrocytes have significantly lower miR-92a-3p expression than those secreted by normal chondrocytes. MiR-92a-3p was shown to inhibit the activity of the 3'-UTR-containing reporter construct and directly target WNT5A to suppress expression in MSCs and chondrocytes (134).

In conclusion, MSCs of different origins regulate the pathological process of OA by promoting various phenotypic changes in chondrocytes through exosomes or by influencing macrophage polarization status to regulate the release of pro-inflammatory cytokines. The mechanism of action of various MSCs in secreting EVs is depicted Fig. 4. The mechanism of action of MSCs is summarized in Table II.

## 6. Conclusions

Synovial cell-chondrocyte interactions are important in the osteoarthritic process. Functionally, the main effects are through anti-inflammation, cell phenotype changes, ECM-cell interactions, homeostasis and inhibition of degradation enzymes. Therefore, it is important to further elucidate the mechanisms of action between synoviocytes and chondrocytes and their effects on synovitis and cartilage destruction. Immune cells begin to activate, mainly through macrophage polarization, secreting some pro-inflammatory factors as well as exosomes which act on chondrocytes, thus influencing the pathological process of OA. Fibroblasts, through invasive changes, act on chondrocytes. Therefore, further research is required to elucidate the effects of macrophages and fibroblasts on chondrocyte homeostasis.

scRNA-seq has confirmed the heterogeneity of cell subsets. Analyzing the similarities and differences between pathogenic and normal cell populations from aspects of cell function, phenotypic changes and molecular regulation, will expand knowledge on OA targeted therapy. In terms of treatment, it is worth considering the restoration of joint architecture by maintaining chondrocyte homeostasis and targeting the pathogenic synoviocyte-chondrocyte axis. Single cell technology provides a new means of studying the crosstalk mechanism of OA by elucidating the communication of synoviocytes and chondrocytes. In order to combine scRNA-seq analysis results with clinical treatment, it is necessary to carry out *in vivo* experiments to verify the function loss, such as inducing specific gene deletion in mouse OA models and observing the pathological process of OA. It is also important to elucidate how MSCs contribute to joint damage in OA. Integrating electronic technology and *in vivo* studies may provide thorough and comprehensive insights of the immune cell-fibroblast-chondrocyte triad in OA, generating a molecular basis for the development of effective therapeutic strategies aimed at providing protection against structural damage and repair of damaged joints.

Table II. Mechanism of action of MSCs.

| Molecule | Donor cell | Recipient cell | Phenotypic changes | Mechanism | (Refs.) |
|---|---|---|---|---|---|
| Unknown | BM-MSCs | Macrophage | M2 polarization ↑ | Unknown | (116) |
| miR-122-5p | BM-MSCs | Chondrocyte | Proliferation↑ Autophagy↑ Apoptosis↓ | Sesn2/Nrf2 | (124) |
| miR-31 | SM-MSCs | Chondrocyte | Proliferation and migration↑ | KDM2A/E2F1/ PTTG1 | (127) |
| miR-155-5p | SM-MSCs | Chondrocyte | Proliferation and migration↑ ECM synthesis↑ Apoptosis↓ | Runx2 | (128) |
| miR-555A-26a-5p | SM-MSCs | Chondrocyte | Apoptosis and inflammation↓ | PTEN | (129) |
| microR-130b-3p | SM-MSCs | Chondrocyte | Apoptosis↓ ECM degradation↓ | LRP12/AKT/Wnt-β | (130) |
| miR-206 | AD-MSCs | Chondrocyte | Proliferation↑ Apoptosis↓ | GIT1 | (132) |
| Unknown | AD-MSCs | Macrophage | M2 polarization ↑ | Unknown | (133) |
| miR-92a-3p | Chondrocyte | MSCs | Unknown | WNT5A | (134) |

BM-MSCs, MSCs derived from bone marrow; AD-MSC, MSCs derived from adipose tissue; SM-MSCs, MSCs derived from synovial membranes; MSCs, mesenchymal stem cells.

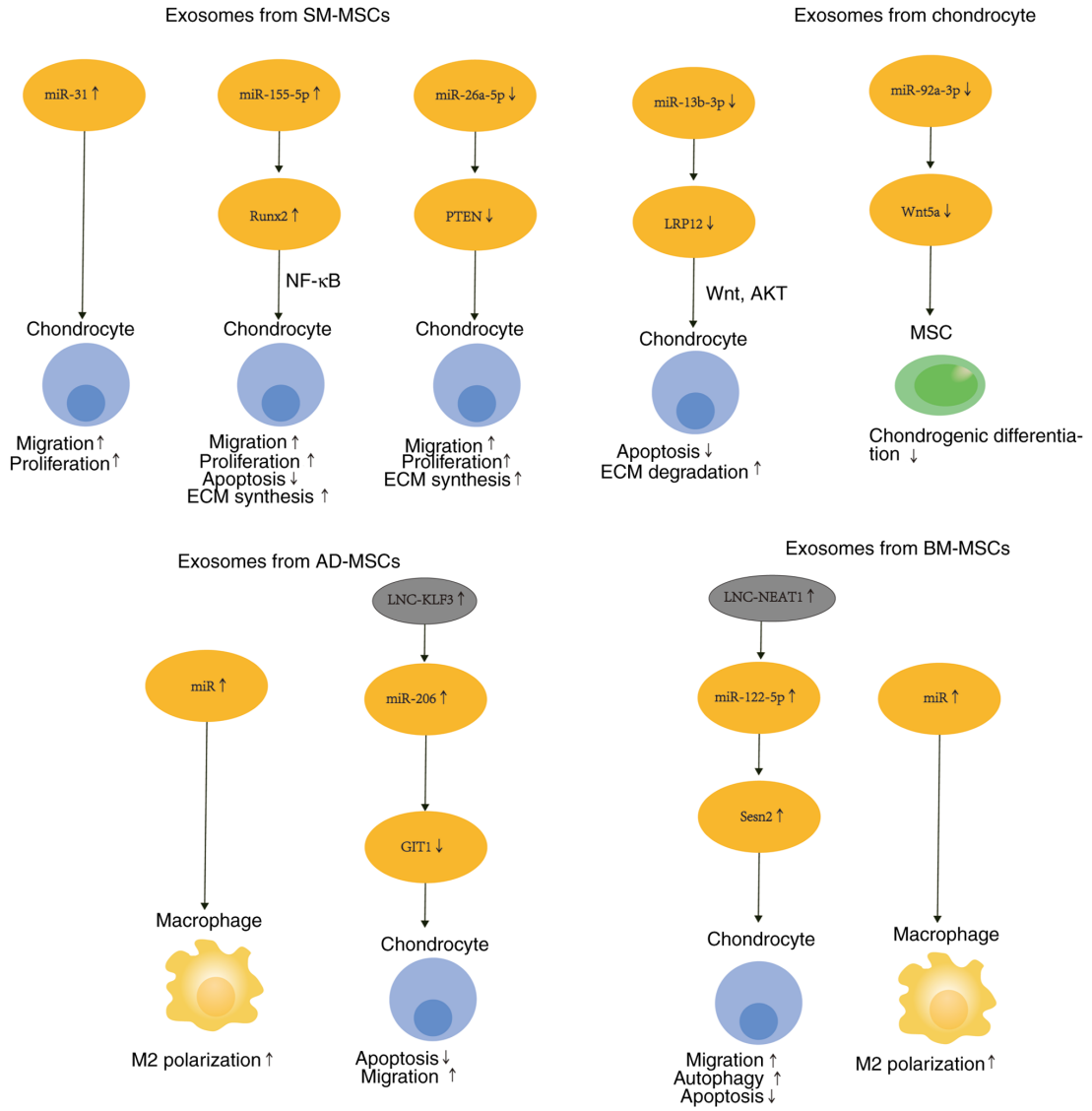


Figure 4. Mechanism of secretion of EVs by different MSCs. EVs secreted by various MSCs contain microRNAs, which undergo a series of changes in the phenotype of chondrocytes, including migration, proliferation, changes in synthesis and decomposition, apoptosis, autophagy and polarization. EVs, extracellular vesicles; MSCs, mesenchymal stem cells; SM-MSCs, MSCs derived from synovial membranes; AD-MSCs, MSCs derived from adipose tissue; BM-MSCs, MSCs derived from bone marrow.

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**Authors' contributions**

BC wrote the original draft of the manuscript. ZC and YS reviewed and edited the manuscript. JJ, GX, WZ and CW created the figures, and reviewed and improved the language of this manuscript. PX and ZC reviewed and edited the manuscript, supervised the project and obtained funding. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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