

# Mechanism and means of exosomes in the treatment of osteoarthritis

Jialin Huang<sup>1,†</sup>, Yuru Su<sup>2,\*,†</sup>

<sup>1</sup> Physical Education, Physical Education Institute, Huanggang Normal University

<sup>2</sup>Department of Rehabilitation Therapeutics, School of Health Fjmu University, Fujian, China

\* Corresponding Author Email: 3180400128@caa.edu.cn

†These authors contributed equally

**Abstract.** Osteoarthritis is a chronic and degenerative disease for which effective early diagnosis and treatment have not been established. Exosomes represent a useful value in the clinical trial phase of OA. This article discusses the relationship between different sources of exosomes and the pathogenesis of OA, and describes the characteristics of exosomes and their application in the diagnosis and treatment of OA. Exosomes may be directly involved in antigen presentation, interact with the endogenous immune system to regulate immune function, or influence cellular function through their miRNAs; T cell-derived exosomes may inhibit the activity of other T cells and prevent excessive inflammation. Apoptosis of chondrocytes leads to proliferation and hypertrophy of articular cartilage, which accelerates the development of osteoarthritis. Exosomes are biomarkers and can be used as diagnostic tools for early diagnosis of OA. Therapeutically, exosomes contain miRNAs that can be used as regulatory targets for drug delivery to treat OA, and exosomes can be injected into the joint cavi.

**Keywords:** Osteoarthritis, Exosomes, diagnosis, treatment.

## 1. Introduction

Osteoarthritis (OA) is a chronic degenerative disease. It affects not only the knee joint but also the spine, hand and temporomandibular joints. It is characterized by degeneration of articular cartilage, synovitis, subchondral bone remodeling and osteophyte formation [1]. OA affects 250 million people worldwide, which represents an annual economic burden of more than \$891 billion.

The exact pathogenesis of OA remains unclear. Available evidence suggests that the etiology of OA is related to inflammatory factors, abnormal apoptosis of chondrocytes and extracellular matrix degradation; during the development of OA, abnormal expression of inflammatory factors such as TNF- $\alpha$ , IL-1 and IL-6 leads to increased chondrocyte apoptosis and extracellular matrix degradation. In addition, the treatment of osteoarthritis is the subject of ongoing medical research. Cartilage damage due to OA is extremely difficult to repair due to the lack of blood supply to the cartilage and its poor ability to repair itself [2]; there is still no effective means to diagnose and treat OA early.

Recent studies have shown that exosomes contain high levels of miRNAs and mRNAs that can enter cells and promote or inhibit inflammatory diseases and have good drug delivery properties, which may play a role in the clinical trial phase of OA and in the early diagnosis and treatment of OA. This could be an effective approach. Therefore, this paper discusses the relationship between different sources of exosomes and OA and their pathogenesis, and describes the characteristics of exosomes and their application in the diagnosis and treatment of OA [3].

## 2. The role of exosomes in the pathogenesis of osteoarthritis

Exosomes are lipid layers of intracellular multicellular bodies that fuse with the plasma membrane, then detach and are secreted into the extracellular matrix. Vesicles range from 30 to 150 nm in diameter [4]. Exosomes are commonly used as carriers of intercellular transfer of cytoplasmic proteins, nucleic acids and lipids and are widely distributed in biological fluids, such as blood, urine and saliva. They transmit information from donor cells to recipient cells and ensure intercellular

communication. Exosomes contain proteins, cytokines, transcription factor receptors and RNA, as well as other bioactive substances. Exosomes contain proteins and RNA, as well as biologically active substances such as proteins, cytokines, transcription factor receptors and RNA. their functions are thought to be involved in the body's immune response, cell migration and cell differentiation [5].

In fact, exosomes come from different sources such as miRNAs from mesenchymal cells, miRNAs from chondrocytes, phagocytes and T cells. Exosomes from different sources also contain protein molecules specific to that source. For example, exosomes from neurons contain high levels of glutamate receptors. Exosomes from intestinal epithelial cells contain various enzymes, and exosomes from dendritic cells activate acquired immunity [6]. Exosomes from different cell lines have different mechanisms in the development of OA. The aim of this study was to determine the mechanisms by which exosomes from different cell lines are involved in the pathogenesis of OA.

## 2.1. Mesenchymal cell-derived miRNA and OA

MicroRNAs (miRNAs) are endogenous non-coding RNA molecules in eukaryotes whose gene expression is regulated by transcription (20-25 bases). They are involved in almost all life activities and in the pathogenesis of inflammatory diseases. miRNAs are increasingly being studied to show that they can play an active role in the treatment of osteoarthritis with MSC-EXO. miRNAs are considered to be highly conserved. They regulate gene expression and modulate inflammatory messengers, thereby regulating cell differentiation and apoptosis. It plays a regulatory role on target genes [7].

In recent years, molecular biology has progressed and the important discoveries of miRNAs, lncRNAs and Exo in inflammatory diseases have also led to important new ideas for the treatment of OA devices. In this paper, we focus on potential theoretical explanations of miRNAs and Exo for the pathogenesis of OA as an important approach for early diagnosis and treatment.

Exosomes from mesenchymal stem cells (MSCs) can play a lubricating and anti-inflammatory role in OA and reduce the development of arthritis in OA. The differentiation function of MSCs leads to the formation of chondrocytes in vitro, which in some cases have a secretory function. There is growing evidence that this secretory function confers immunomodulatory properties to inflamed joints, supporting indirect evidence for immunomodulatory properties of indirect histiocytes in the context of joint injury. xos-MSCs increase type II-alpha collagen and aggregates, thereby enhancing cartilage. MMP-13 (matrix metalloproteinase 13) and Runx2 (short-state-associated transcription factor 2), which were found to be important properties of cellular hypertrophy, were both reduced [8]. Intratumoral injection of synovial mesenchymal stem cell-derived exosomes also had anti-inflammatory effects: in a rat model of osteoarthritis, it promoted chondrocyte migration and proliferation and reduced the extent of cartilage damage. This shows great potential for the clinical application of exosomes. However, Li et al. found that mir-27a-3p was downregulated in OA patients and increased the expression of ADAMTS-5, leading to degradation of MSC and thus promoting OA [9]. Currently, miRNAs offer new ideas for the treatment of OA, but they are still in the early stages of research.

## 2.2. Chondrocyte-derived miRNA and OA

In addition to the increasing research on mesenchymal stem cell-derived miRNAs in osteoarthritic inflammatory diseases, the therapeutic effects of chondrocyte-derived exosomes in osteoarthritis have also attracted the attention of researchers. Osteoarthritis is a disease that is closely associated with mechanical degeneration and wear of articular cartilage. Previous studies have shown that the paracrine mechanism of exosomal miRNA sends signals to articular cartilage through the cell gap; Mir-155-5p exosomes regulate chondrocyte differentiation and migration, thereby inhibiting chondrocyte apoptosis and OA disease progression [10].

An important feature of OA is cartilage degeneration, which is caused by external injury, mechanical wear and tear, abnormal cartilage nutrient metabolism and long-term stress imbalance due to cartilage wear. Previous studies have shown that stable articular cartilage is synthesized and

degraded by chondrocytes in ECM (collagen type  $\alpha 2$ , proteoglycan polymerase), maintaining the normal homeostasis of articular cartilage. Chondrocytes rely on ECM material for nutrition. The internal cartilage structure is closed and hypoxic, resulting in low chondrocyte turnover and difficulty in repairing damaged articular cartilage in osteoarthritis, there is substantial evidence that chondrocyte apoptosis affects the structure and maintenance of cellular tissue. Apoptosis is a natural and programmed process of cell death, and excessive chondrocyte apoptosis is a pathological feature of OA. Previous studies have shown that miRNAs can regulate the pathological state of excessive apoptosis of chondrocytes in OA by regulating key elements of the apoptosis information pathway. However, the therapeutic effects of miRNAs in OA need further investigation.

### 2.3. Phagocyte and OA

Exosomes are directly involved in antigen presentation, can interact with the human immune system, regulate immune function and influence cellular function through their miRNAs [11].

The main feature of OA is synovitis. The main pathological changes in the synovium include an inflammatory synovial response with macrophage, T-cell and B-cell infiltration, proliferation of the canalicular layer, interstitial fibrosis and neovascularization.

Macrophages are the most important immune cells in the body. Activated phagocytes produce various inflammatory factors (interleukin-1) and chemokines (interleukin-8), which can promote or suppress the inflammatory response. Various factors and metabolites differentiate the phenotype and function of phagocytes so that they are mainly divided into M1 and M2 macrophages, i.e. macrophage polarization. Mesenchymal stem cell-derived exosomes have been shown to slow the progression of OA by modulating phagocyte polarization towards M2, with the opposite effect on M1.

Studies have shown that exosomes derived from the synovial fluid of patients with OA can activate macrophage differentiation to M1 type, secrete inflammatory and chemokines, and promote OA progression.

### 2.4. OA and T cells

In synovial fluid (SF), extracellular vesicles (EVs) are abundant, mainly from monocytes, granulocytes and T cells.

According to research, exosomes could be released when T cells are activated, and the exosomes produced by T cells can inhibit dendritic cells (DC). This is a self-regulation mechanism of the human immune system. T cell-derived exosomes can inhibit the activity of other T cells from avoiding excessive inflammation. In the human body, it manifests as chronic bone and joint inflammation, preventing multiple stimulations of antigen-presenting cells (APC) [12].

## 3. Diagnosis and treatment

### 3.1. Diagnosis

In the early stages of OA, the disease is asymptomatic. Even when symptoms are recognized, there is no effective treatment: X-rays are the most common and widely used imaging technique for the routine diagnosis of OA, but they are not sufficiently clear to provide accurate images of the internal structures of the joints. CT is another imaging technique that indirectly assesses the degenerative features of cartilage in advanced OA through three-dimensional imaging of the joint cavity stenosis. Three-dimensional imaging of articular cartilage can be performed directly with CT scans, but this method is invasive because it requires the injection of a contrast agent directly into the joint cavity. In general, contrast agents are safe for humans. However, side effects of contrast agents, such as anaphylaxis, neurotoxicity, vascular toxicity, and in some cases nephrotoxicity, can occur due to individual differences in humans.

In recent years, biomarkers have been developed to diagnose OA at an early stage. biomarkers are biochemical indicators that can indicate structural or functional changes or potential changes in a system, organ, tissue, cell or subcellular. They can be used for a variety of applications. Examples

include disease diagnosis, disease classification, and the assessment of the safety and efficacy of new drugs and therapies in target populations. These markers have been experimentally shown to contribute to bone loss, chondrocyte erosion, and inflammation of joint tissue. Some biochemical markers are components of extracellular matrix molecules that are normally released into the blood and body fluids. They usually occur as by-products of cartilage degradation, bone and lipid metabolism, and tissue regeneration. Thus, biomarkers can detect not only destructive changes in cartilage OA, but also diagnose functional, structural and biochemical changes in subchondral tissues and associated pathologies. However, the detection of biomarkers remains a challenge: specific and sensitive biomarkers must be found for the early diagnosis of OA.

Exosomes are a biomarker for the early diagnosis of OA. Exosomes contain many specific protein biomarkers associated with OA. Exosomes consist of a surface "shell" and an internal "content". The surface of exosomes is marked with various proteins whose properties depend on the source of the exosome and the pathology of the body. Many exosomal miRNAs in plasma have been found to be associated with common diseases such as psoriatic arthritis, psoriasis vulgaris, rheumatoid arthritis (RA), and gouty arthritis. Analysis of potential target genes has shown that these miRNAs are associated with immune and bone damage. Furthermore, Tsuno et al. demonstrated that serum exons from patients with active RA have a different protein quality profile than those from patients with inactive RA, osteoarthritis, and healthy blood donors [13].

### 3.2. Treatment methods

According to the Chinese guidelines for OA treatment, early to mid-stage OA treatment mainly consists of pharmacological and non-pharmacological therapies. The main pharmacological treatments include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), joint pain relief with Chinese herbs (such as bone marrow and yifeng), and intra-articular injections of corticosteroids and hyaluronic acid. Non-pharmacological therapies mainly include physical therapy and exercise therapy. Recent studies have shown that traditional rehabilitation therapies, such as acupuncture, massage and acupuncture injections, which can relieve pain and improve physical function, can have a significant impact on OA. A treatment strategy for advanced OA is joint replacement. These treatments can relieve OA symptoms and improve the patient's quality of life (QOL), but they do not stop the progression of OA symptoms.

In recent years, the significant progress of extracellular vesicles (EVs) in medical regeneration has attracted the attention of medical researchers. Based on their composition and origin, EVs can be classified into three types. Exosomes, intracellular microvesicles, and apoptotic bodies. Exosomes are mainly involved in intercellular signaling processes, have physiological functions such as antitumor immunity and promotion of angiogenesis, and play important roles in various physiological and pathological processes such as antigen presentation, promotion of tumor growth and migration, and repair of damaged tissues. Exosomes have also shown unique advantages in the early diagnosis and targeted treatment of many diseases and are considered to be the most promising therapeutic approach for repairing articular cartilage damage.

Exosomes are most often used as targets for drug delivery in the treatment of osteoarthritis, which leads to three problems due to the arrangement of synthetic polymers of conventional drugs with other biomolecules (proteins) in the bloodstream. Toxicity, immunogenicity and rapid excretion by the monocyte phagocytic system (MPS).

Exosomes are highly biocompatible compared to conventional carriers. The advantage of exosomes as drug carriers over existing artificial liposomes is their good biocompatibility. Liposomes are the most important transport medium for siRNA and other RNAs. They cause toxic immune responses in vivo, leading to cumulative toxicity in the liver and other parts of the body, and do not achieve the desired effect. Exosomes are biocompatible and can compensate for the disadvantages of liposomes, such as immunogenicity and cumulative toxicity in vivo. Exosomes are also characterized by their high loading capacity. They contain various bioactive substances such as proteins, cytokines, transcription factor receptors and RNA, as well as proteins and RNA and low immunogenicity. On

the other hand, liposomes are often used as nanoparticles for drug delivery and, after multiple injections, interact with immune cells in the blood to produce the corresponding antibodies, a phenomenon known as "ABC (accelerated blood clearance)".

As a carrier for specific drug delivery, exosomes can reduce the immediate elimination function of the monocyte-macrophage system, achieve the desired concentration without multiple injections, increase the drug dose, and ensure the maximum efficacy of the drug [14].

In addition, Liu et al. created cell-free exosomal tissue patches using stem cell-derived exosomes and lightly cross-linked imine hydrogels that could release exosomes for 14 consecutive days. The new cartilage tissue regenerated from the tissue patch was found to be hyaluronic acid cartilage, similar to the rabbit model of articular cartilage defects. In addition, Hu et al. prepared Germa/nanoclay hydrogels (gel-nano-sevs) into which small cellular exocapsules from human umbilical cord mesenchymal stem cells (hUC sEVs MSCs) were incorporated. In this study, miR-23a-3p, highly expressed in hUC sEVs MSCs, activated the serine/threonine kinase (AKT) pathway and chromosomal homologs of 10-phosphatase and Tamsin (PTEN) to promote cartilage regeneration. The results showed that it promotes cartilage regeneration. It has been shown that nanoSEV gel can release exosomes continuously for about 30 days to promote cartilage regeneration.

#### 4. Conclusions

Macrophages are the most important immune cells in the body. Mesenchymal stem cell exosomes have the opposite effect on M1, regulating the polarity of phagocytes to M2 and slowing the progression of OA.

T cell-derived exosomes are a self-regulatory mechanism of the human immune system, suppressing the activity of other T cells and preventing excessive inflammatory responses.

Without early diagnosis, the clinical manifestations of OA are not obvious, and most patients with OA are detected in the late stages of the disease. At this stage, pharmacological treatment can only relieve pain and cannot prevent the development of OA. Therefore, in recent years, a relatively clear method for early diagnosis of OA has been established, focusing on exosomes as biomarkers. Exosomes can also be used as drug delivery carriers for the treatment of OA devices. Compared to other drug carriers, exosomes offer unique advantages in terms of biocompatibility, good payload capacity and low immunogenicity.

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