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Review Article

Exosomes: critical mediator and therapeutic target for osteoarthritis

Peng Jiang[1,3,4], Jie Liu[2], Huiying Li[5], Huarong Shao[2,3], Haining Tan[2], Fei Liu[2,3], Peixue Ling[2,3], Qiuju Han[4], Xixi Dou[2,5]

[1]Department of Joint Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China; [2]Shandong Provincial Key Laboratory of Carbohydrate and Glycoconjugate Drugs, Shandong Freda Pharmaceutical Group Co., Ltd, Ji'nan, Shandong, China; [3]Postdoctoral Scientific Research Workstation, Shandong Academy of Pharmaceutical Science, Ji'nan, Shandong, China; [4]Institute of Immunopharmaceutical Sciences, School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, Ji'nan, Shandong, China; [5]College of Biological Sciences and Technology, Beijing Key Laboratory of Food Processing and Safety in Forestry, Beijing Forestry University, Beijing, China

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Abstract: Osteoarthritis (OA) is characterized by articular cartilage degradation and chondrocyte injury. Increased cell apoptosis of chondrocytes and inflammation are features of degenerating cartilage. Recently, exosomes are considered as important mediators of the pathogenesis and progression of OA. Importantly, exosomes originating from different cells, especially mesenchymal stem cells (MSC), have been shown to delay the progression of OA by different mechanisms. These exosomes derived from MSC harbor several proteins, lipids, nucleic acids, and cytosolic material that promote chondrocyte proliferation and migration and prevent the apoptosis of chondrocytes. Based on these findings, exosomes may serve be diagnostic biomarkers and therapeutic targets for OA. In this review, we summarize the role of exosomes and their key components in mediating OA development and therapy.

Keyword: Osteoarthritis, exosomes, MiRNA, mesenchymal stem cells, cartilage repair

Introduction

Osteoarthritis (OA), a chronic inflammation-related joint disease, is characterized by repeated attacks of joint pain, joint movement disorders, and eventual aggravation [1-3]. Several risk factors including aging, obesity, trauma, and genetic predisposition are associated with OA, while the pathogenesis of OA has not been fully elucidated [4-7]. Chondrocytes are reported as the only cells residing in cartilage tissue that participate in the production of cartilage extracellular matrix (ECM), which serves an important role in the maintenance of cartilage structure and function [8-10]. Currently, non-steroid anti-inflammatory drugs and analgesics are used to relieve OA symptoms, but these drugs cannot ameliorate the disease and its symptoms effectively. Therefore, it is of great significance to explore the mechanism of chondrocyte injury and OA pathogenesis, and to develop more effective strategies.

In recent years, studies have implicated that exosomes derived from several types of cells (chondrocyte, macrophage) contributed to the pathogenesis and progression of OA [11, 12]. Importantly, exosomes isolated from mesenchymal stem cells (MSCs) have a potential to maintain chondrocyte homeostasis and ameliorate the pathological severity of OA, this providing novel therapeutic strategies for OA treatment [13, 14].

Exosomes, secreted by almost all cell types under both normal and pathologic conditions, are nano-sized (40-100 nm) membrane-bound vesicles. Exosomes are usually present in biological fluids like blood, urine and ascetic fluid, and carry various biomolecules, such as proteins, mRNAs, microRNAs (miRNAs) and long

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non-coding RNAs (lncRNAs) [15], circular RNAs (circRNAs) and common exosomal markers including heat shock protein 70 (HSp70), cluster of differentiation-9 (CD9), cluster of differentiation-63 (CD63) and cluster of differentiation-81 (CD81) [16-18]. Exosomes have demonstrated clinical potential in the development of innovative therapy for complex clinical diseases including tumors and infectious diseases.

Although exosomes have been studied for decades, their biological significance in the pathogenesis and therapy of OA has only recently begun to be elucidated. Here, we summarize the role of exosomes and their key components in mediating OA development and therapy.

Exosomes contribute to the pathogenesis and progression of OA

In recent years, the pathophysiologic functions of exosomes in OA have been explored. Various components harbored by exosomes exert important regulatory functions during different stages of OA.

Exosomes derived from chondrocytes during OA

Articular cartilage depends solely on the chondrocytes for the maintenance of extracellular matrix, thus the compromise of chondrocyte function and survival would lead to failure of the articular cartilage [19, 20]. Early studies have found that the matrix vesicles (MVs) derived from OA chondrocytes displayed annexins II, V, and VI, which is critical in pathologic mineral formation in OA [21].

The miRNA profiles of exosomes isolated from the supernatants of OA and normal chondrocyte cultures are different. Mao et al. found that 22 miRNAs were up-regulated (fold change >2) and 29 miRNAs (including miR-95-5p) were down-regulated (fold change <-2) in OA-secreted exosomes compared to levels in normal chondrocyte-secreted exosomes. Exosomal miR-95-5p-mediated cartilage development and degradation by histone deacetylase-2/8 (HDAC2/8) was found to regulate OA development [22, 23]. Another study revealed that exosome-like vesicles from osteoarthritic chondrocytes enhanced the production of mature interleukin-1β (IL-1β) partially through miR-449a-5p/autophagy-related protein 4B (ATG4B)-mediated autophagy inhibition in macrophages, which may further aggravate the synovitis and cartilage erosion in OA [24].

Also, circRNAs, as a type of non-coding RNA (ncRNA), have been demonstrated to be involved in the pathogenesisof OA [25, 26]. Recently, circular bromodomain and WD repeat domain containing 1 (circ-BRWD1) was reported to be increased in the exosomes derived from IL-1β-treated chondrocytes. Besides, circ-BRWD1 serves as a sponge for miR-1277 to positively regulate TRAF6 expression, which regulates OA development [27]. Currently, the exosomal circRNA profile has not been investigated yet. Considering that various circRNAs like circular ring finger protein 121 (circRNF121), circRNA.33186, and circular transmembrane bax inhibitor motif containing 6 (circTMBIM6) can delay or aggravate diverse aspects of the OA process [25, 26], the functional circRNAs in exosomes need to be identified.

Furthermore, the proteomics in OA chondrocyte exosomes are different from normal chondrocyte cultures. Zheng et al. performed proteomic analysis and found fewer mitochondrial-associated proteins and immune response-related proteins in exosomes from IL-1β induced inflammatory chondrocytes [11]. It is well-recognized that mitochondria exert various regulatory effects on OA pathogenesis, including bioenergetics metabolism, reactive oxygen species (ROS) production, calcium metabolism, inflammatory responses, apoptosis, and aging-related responses [28, 29]. Indeed, chondrocytes in OA exhibit reduced mitochondrial biogenesis [30].

Exosomes from OA synovial fluid

Synovial fluid is vital for monitoring pathophysiologic changes in the joint cavity, and a number of studies have investigated the role of synovial fluid content in pathophysiology during OA.

The exosomes from OA synovial fluid can increase the production of IL-1β and several chemokines such as C-C motif chemokine ligand 8 (CCL8), CCL15, CCL20 and CXCL1 in macrophages and cause obvious pro-inflammatory effects [31]. Importantly, chondrocytes were observed to readily endocytose extracel-

lular vesicles (EVs) and their RNAs, and OA-derived EVs could decrease chondrocyte survival and anabolic gene expression, and increase catabolic gene expression [32, 33]. Kolhe et al. also revealed that exosomes from OA synovial fluid significantly decreased the expression of anabolic genes and elevated the expressions of catabolic genes in chondrocytes [32].

Recently, exosomal lncRNAs in synovial fluid have been reported to be vital for OA development. Kirsch et al. found that the expression of exosomes was much higher in patients with OA than that of healthy people, with no significant difference between early OA and late-stage OA. This suggests that the expression of exosomes in synovial fluid was not suitable for identifying OA stages [21]. Another study observed that OA alters synovial EV miRNA expression in a gender-specific manner. Also, miRNA content of the EVs differs between OA and Non-OA groups. In males, 69 miRNAs were significantly down-regulated and 45 miRNAs were up-regulated, whereas in females, 91 miRNAs down-regulated and 53 miRNAs up-regulated. Notably, miR-504-3p was the only miRNA commonly up-regulated in both sexes [32]. Additionally, exosomal lncRNA prostate cancer gene expression marker 1 (PCGEM1) was proven to be related to the progression of OA [21, 34].

Exosomes from synovial fibroblasts during OA

Early studies have reported the effects of MVs from synovial fibroblasts (SFB) [35]. OA alters the expression of miRNAs within synovial exosomes. IL-1β stimulation increased exosome secretion from SFB. Treatment of normal articular chondrocytes with exosomes from SFB-conditioned medium induced OA-like changes in both *in vitro* and *ex vivo* experimental systems. Notably, IL-1β exposure led to significant upregulation of 11 miRNAs and downregulation of 39 miRNAs in these exosomes [36].

Zhou et al. identified 12 upregulated and 7 downregulated miRNAs in synovial exosomes from OA patients relative to control patient synovial exosomes. Gene Ontology and Kyoto Encyclopedia of Genes and genomes functional enrichment analyses revealed pathways including proliferation, migration, metabolism, and signal transduction are involved. Notably, this study determined that exosomal miR-126-3p was downregulated 2.93-fold in synovial fluid [37].

Exosomes secreted from SFBs release their cargo into target cells (articular chondrocytes) and activate downstream effect/signaling pathways. Kolhe et al. found that estrogen signaling regulates EVs' miRNA cargo of primary SFB cells [32]. Exosomes derived from SFB under hypoxia were reported to aggravate rheumatoid arthritis by regulating Treg/Th17 balance [38], while this effect has not been observed in OA.

Exosomes from vascular endothelial cell during OA

Blood vessels are vital in the skeletal system, and the growth of vascular networks is controlled by osteoclasts, osteoblasts, and other bone cells.

Few studies reported exosomes from vascular endothelial cells during OA. Recently, Yang et al. revealed chondrocytes effectively internalized the exosomes from vascular endothelial cells (ECs-Exos). Mechanistically, EC-Exos downregulated autophagy and P21 expression, which decreased the ability of chondrocytes to resist oxidative stress, resulting in elevated cellular ROS content and inducing apoptosis [39]. Exosomes are reported as important nanocarriers transmitting genetic information in this milieu.

Exosomes from immune cells during OA

Macrophages play a key role in the pathogenesis of synovitis in OA, and macrophage-produced mediators drive inflammatory and destructive responses in OA [40, 41]. Activated macrophages were found in the majority of OA knees, significantly associated with pain severity and radiographic OA severity [42, 43]. Importantly, M1 polarization of synovial macrophages was demonstrated to remarkably exacerbate experimental OA [44, 45]. Whether exosomes derived from macrophage regulate OA remains uncertain.

In addition, microvesicles derived from activated monocytes and T cells induce the synthesis of metalloproteinases and cytokines/chemokines [46]. Exosomes derived from immature

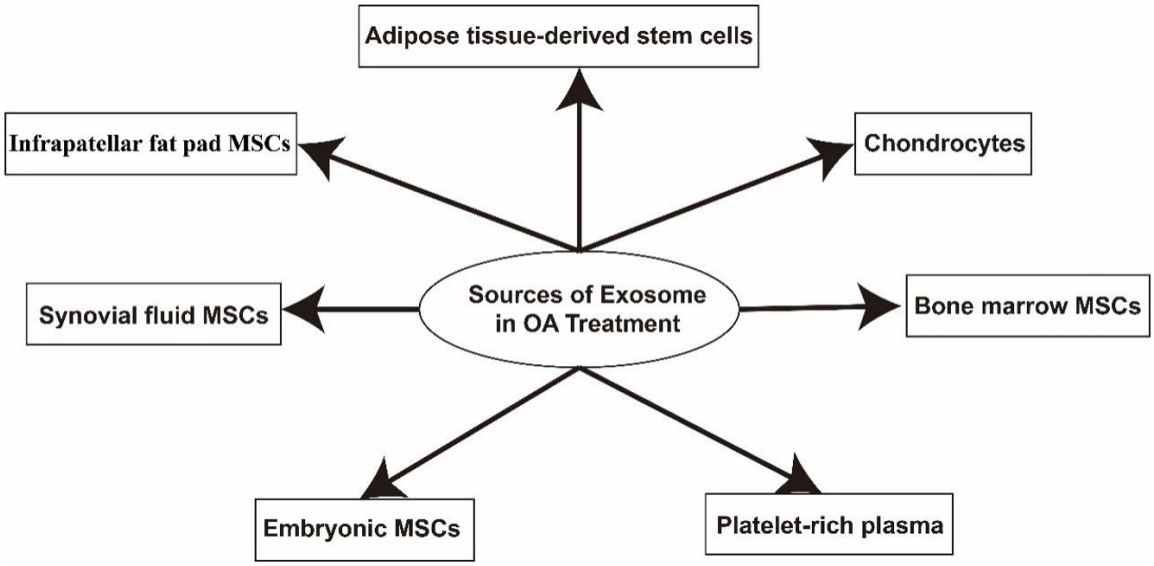

Figure 1. Exosomes derived from different cells and tissues used for the treatment of OA. Various exosomes were obtained and used in OA therapy to have a better understanding of the development of OA. Note: MSCs: Mesenchymal stem cells. OA: Osteoarthritis.

dendritic cells (DCs) treated with interleukin-10 (IL-10) produce anti-inflammatory exosomes that suppress the onset of murine collagen-induced arthritis (CIA) and reduce the severity of established arthritis. Interestingly, the DC-derived exosomes are more immunosuppressive than their parental DCs. DCs transduced with an adenoviral vector expressing Fas-ligand or IL-4 produce exosomes that suppress inflammation in a murine model of delayed-type hypersensitivity and partially reverse established CIA through a class II major histocompatibility complex (MHC)-dependent, but class I MHC-independent, mechanism [47-49]. Indoleamine 2,3-Dioxygenase expression in DCs leads to the generation of immunosuppressive exosomes [50].

Recently, neutrophils have been considered to have both short-lived inflammatory effector functions and long-term homeostatic roles [51]. The role of neutrophils during OA development is intriguing. Neutrophils accumulate in large numbers in the synovial space during acute and transient RA flares, contributing to ≥30% of total synovial fluid MVs during active phases of the disease [52-54].

Although neutrophil depletion in experimental arthritis models attenuates inflammatory markers, it also decreases cartilage proteoglycan synthesis. Notably, neutrophil-derived MVs can penetrate cartilage and exert joint-protective effects in inflammatory arthritis.

Exosomes are therapeutic for OA

MSCs are multipotent adult stem cells of mesodermal origin, isolated from various tissues including adipose tissue, bone marrow, dental pulp, skin, and synovial fluid [55, 56]. Due to their robust chondrogenic potential, MSCs have been extensively investigated as a key cell source for cartilage regeneration. MSC-based therapy has shown promise in preventing OA progression, reducing inflammation, and alleviating pain, emerging as a possible novel approach for OA management [57, 58].

Accumulating evidence indicates that MSC-derived exosomes (MSC-Exos) can relieve joint pain in OA patients and play a vital role in modulating cell migration, proliferation, differentiation, apoptosis, ferroptosis, and ECM synthesis (**Figures 1** and **2**). Unlike parent MSCs, exosomes exhibit no apparent side effects such as immunogenicity or tumorigenicity. Importantly, the therapeutic effects of MSCs and endothelial colony-forming cells can be recapitulated by their derived exosomes. MSC-based therapy for OA are currently under clinical evaluation, with promising results reported

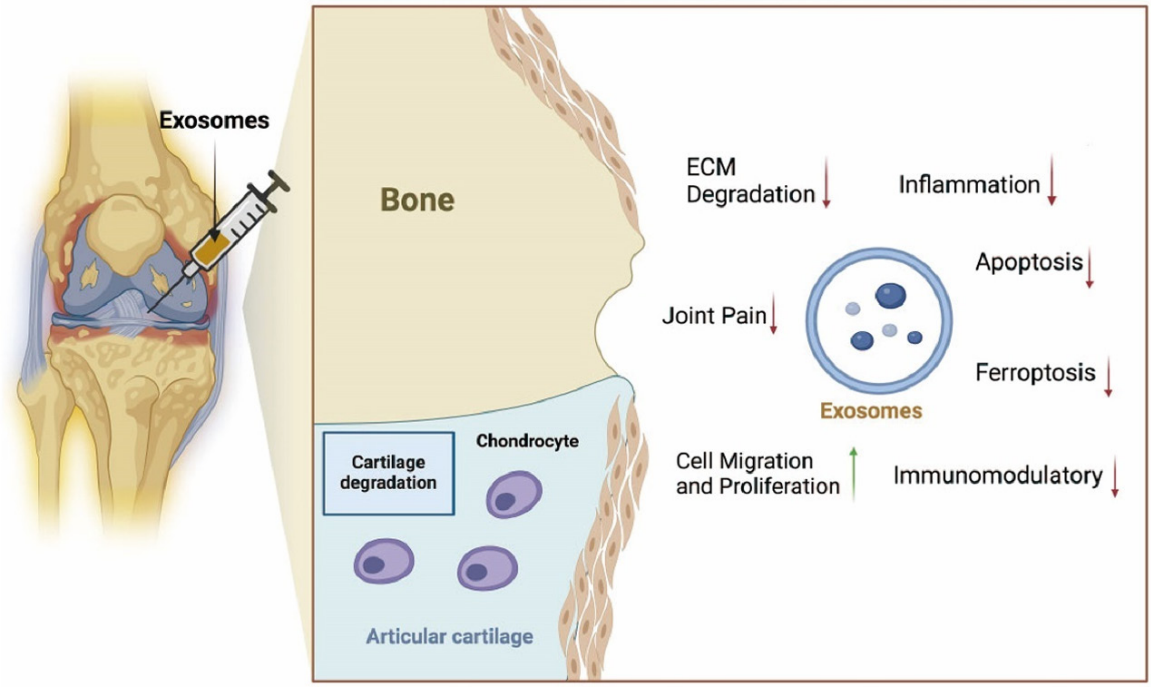

Figure 2. Exosomes play a vital role in the pathologic processes of OA and relieve it by inhibiting the inflammatory response, reducing ECM degradation, regulating the immune system, decreasing abnormal angiogenesis, promoting cell proliferation and migration, and suppressing cell apoptosis. Note: OA: Osteoarthritis; ECM: Extracellular matrix.

regarding pain reduction and attenuation of inflammation [13, 59, 60].

Exosomes from MSC are therapeutic for OAare

Bone marrow MSCs (BMSC)-derived exosomes & OA: BMSCs have been widely applied in cartilage regeneration studies and are proposed as potential therapeutic agents for knee OA, with satisfactory outcomes in clinical trials [60-62]. Although BMSCs have demonstrated efficacy in multiple disease models, BMSC-derived exosomes (BMSC-Exos) have only recently been explored for OA therapy.

BMSC-Exos are efficiently internalized by chondrocytes [63], and have been shown to promote cartilage repair, enhance ECM synthesis, and alleviate OA knee pain in rats [60]. BMSC-Exos inhibit mitochondrial-mediated apoptosis in response to IL-1β, through the involvement of p38, ERK, and Akt [63, 64].

ncRNAs including miRNAs and circRNAs, in BMSC-Exos regulate chondrocyte function and OA progression. Mao et al. identified nine significantly upregulated miRNAs (miR-8075, miR-92a-3p, miR-320c, miR-1263, miR-668-5p, miR-548a-3p, miR-6750-5p, miR-3619-5p, and miR-628-5p) in paired MSC-derived exosomal samples [65]. Another study demonstrated that exosomal miR-136-5p eBMSCs inhibits chondrocyte degeneration in traumatic OA by targeting E74-like factor 3 (ELF3) [66]. In addition, Mao et al. elucidated that exosome-transported circRNA_0001236 enhances chondrogenesis and suppresses cartilage degradation by the miR-3677-3p/sex-determining region Y-box 9 (Sox9) axis both *in vitro* and *in vivo* [39].

BMSC-Exos also regulate macrophage polarization. For instance, Wang et al. found that transforming growth factor-beta 1 (TGF-β1)-modified MSCs secrete exosomes highly expressing miR-135b, which promote M2 synovial macrophage polarization by targeting mitogen-activated protein kinase 6 (MAPK6), thereby enhancing chondrocyte proliferation [67, 68]. Furthermore, ECM/gelatin methacryloyl (GelMA)/exosome scaffolds effectively restore chondrocyte mitochondrial dysfunction, enhance chondrocyte migration, and polarize synovial macrophages toward an M2 phenotype [69].

In addition, BMSC-Exos directly regulate the activation of various immune cells. Cosenza et al. reported that both exosomes and microparticles (MPs) inhibit *in vitro* activation of CD4+ and CD8+ T lymphocytes and B lymphocytes. However, only exosome injection attenuated clinical signs of arthritis by inhibiting plasmablast differentiation and inducing IL-10-expressing Breg cell induction [70].

Recently, Zhou et al. isolated a unique MSC population from the bone marrow of surgically resected polydactyly tissue (pBMSCs), which exhibited greater chondrogenic differentiation potential than conventional BMSCs. Furthermore, pBMSC-derived exosomes (pBMSC-Exos) showed superior therapeutic efficacy compared to BMSC-Exos in an OA mouse model [71]. However, the specific components in pBMSC-Exos that regulate OA progression remain to be elucidated.

Infrapatellar fat pad (IPFP) MSCs-derived exosomes & OA: Adipose-derived MSCs present promising therapeutic prospects in regenerative medicine, including the treatment of OA [72]. IPFP-derived MSCs (IPFP-MSCs) combined with chitosan/hyaluronic acid nanoparticles have been shown to promote chondrogenic differentiation both *in vitro* and *in vivo* [73]. Wu et al. demonstrated that IPFP-MSCs secrete exosomes enriched in miR-100-5p, which specifically targets the 3' untranslated region (3'UTR) of mammalian target of rapamycin (mTOR) in chondrocytes [74]. This targeting inhibits cell apoptosis, promotes anabolism in IL-1β-induced chondrocytes, and improves gait patterns in destabilization of the medial meniscus (DMM)-induced OA mice Considering the convenience of obtaining human IPFP from OA patients by arthroscopic procedures, IPFP-MSC-Exos represent a novel potential therapeutic strategy for OA.

Synovial fluid derived-MSCs-derived exosomes & OA: Synovial fluid is a viscous fluid secreted by the inner layer of the synovial membrane. The synovial fluid share similar characteristics (size, surface markers, miRNA content) with exosomes from other body fluids.

Synovial fluid-derived MSCs (SF-MSCs) offer new prospects for stem cell-based therapy. As articular MSCs isolated from the joint cavity synovial fluid, they exhibit higher chondrogenic differentiation capacity but lower adipogenic, osteogenic, and neurogenic potentials compared to other types of MSCs [75, 76]. Kartogenin (KGN) is a small molecule that promotes the specific differentiation of SF-MSCs into chondrocytes [77]. Due to its low water solubility and forming precipitates in the cell, its chondrogesis-promoting activity is limited. Recently, Xu et al. engineered exosomes to efficiently and specifically deliver KGN into SF-MSCs prior to transplantation to the joints of OA rats [59].

SF-MSC-derived exosomes protect against OA through various miRNAs. For example, miR-155-5p prevents OA progression by enhancing chondrocyte proliferation and migration, attenuating apoptosis, and modulating ECM secretion [78]. miR-129-5p, enriched in human synovial MSC exosomes (HS-MSC-Exos), suppresses IL-1β-mediated OA by inhibiting high mobility group box-1 protein (HMGB1) release [79].

Notably, OA prevalence is higher in women than in men. Using miRNA microarray analysis, Kolhe et al. identified differentially secreted exosomes and their miRNA expression pattern in the synovial fluid of OA patients. Female OA-specific miRNAs are estrogen-responsive and target Toll-like receptor signaling pathways [32]. The discovery of additional gender-specific exosomal miRNAs holds significant promise for personalized OA therapy.

Embryonic MSCs-derived exosome & OA: MSCs derived from pluripotent embryonic stem cells (ESC-MSCs) represent another potential source for OA therapy. Injection of ESC-MSCs alleviates cartilage destruction and matrix degradation in the DMM model. As early as 2007, Wang et al. demonstrated that exosomes from embryonic mesenchymal stem cells (EMSC-Exos) modulate chondrocytes to maintain collagen II (Col II) expression and decrease A Disintegrin and Metalloproteinase with Thrombospondin Motifs 5 (ADAMTS5) expression under IL-1β stimulation [80]. However, the underlying mechanisms of their therapeutic effects on OA remain unexplored.

Exosomes from non-MSC sources for OA therapy

Exosomes derived from platelet-rich plasma (PRP) & OA: PRP, is an autologous derivative of whole blood with a higher platelet count than

peripheral blood. It has been reported to enhance bone regeneration, and intra-articular injections of PRP provide a non-surgical approach for advanced OA [81]. PRP-derived exosomes (PRP-Exos) increase proliferation and migration while decreasing apoptosis of IL-1β-induced OA chondrocytes. The potential mechanism involves activation of the Wingless/Integrated (Wnt)/β-catenin signaling pathway [82].

Exosomes derived from Adipose-derived stem cells (ADSCs) and OA: ADSCs exhibit self-renewal capacity and can differentiate into various connective tissue cells (osteoblasts, adipocytes, chondrocytes, and myocytes) under specific inductive conditions [83]. ADSCs are abundant and easily obtainable by liposuction with minimal donor morbidity, making them attractive for clinical and experimental OA treatment. Zhao et al. found that ADSC-derived exosomes (ADSC-Exos) effectively promote chondrocyte proliferation and migration, and prevent H_2O_2-induced chondrocyte apoptosis. Mechanistically, ADSC-Exo treatment increased the levels of chondrogenic miRNAs (miR-145 and miR-221) and chondrogenic markers in periosteal cells [84].

Exosomes derived from chondrocytes and OA: Zhen et al. recently investigated the therapeutic effect and underlying mechanism of exosomes derived from primary chondrocytes (D0 exosomes) in OA. They found that D0 exosomes facilitate OA therapy by restoring mitochondrial dysfunction and modulating immune reactivity. D0 exosomes contain 65 mitochondrial proteins, which increase intracellular adenosine triphosphate levels. Additionally, D0 exosomes induce higher infiltration of $CD163^+$ M2 macrophages and reduce the number of inducible nitric oxide synthase positive M1 macrophages [11]. However, the specific components in D0 exosomes that regulate the immune system and induce an anti-inflammatory phenotype during OA treatment remain unclear.

Research development and clinical translation challenges

Investigating the role of exosomes from different cellular sources in OA pathology may facilitate the development of novel therapeutic approaches. However, current clinical applications face several challenges including predominance of e studies limiting translational relevance, uncertainty about the optimal exosome type, clinical dosages and administration frequencies, a lack of standardized research methods, a need for clinical trials adhering to rigorous protocols, andscarcity of multi-center studies comparing the efficacy of exosomes from different sources.

Beyond extraction, scalable production, and long-term storage, key issues requiring resolution include targeted delivery, functional optimization, and precise modulation of the joint microenvironment. Compared to conventional exosomes, local injection of chondrocyte-affinity peptide-loaded exosomes offers advantages such as enhanced targeting, prolonged intra-articular retention, and reduced side effects. Given the complexity and diversity of exosomal sources, their mechanisms of action and therapeutic potential in OA warrant further investigation. Developing pharmaceutical products featuring stem cell-derived exosomes with stable quality, significant efficacy, and scalable production capacity - alongside enhancing their drug-like properties - represents a critical clinical translation challenge and a valuable research direction.

Conclusion

MSC-based therapy is limited by tumorigenicity, immune incompatibility, and chromosomal aberrations. Thus, strategies that leverage MSC properties while avoiding these shortcomings are urgently needed. As reviewed herein, MSC-Exos mediate cartilage repair and regeneration through multiple pathways. Compared to MSC therapy, MSC-Exos transplantation offers several advantages, including non-immunogenicity, non-tumorigenicity, and convenient storage and transportation. With technological advancements, exosome-based therapeutic approaches may come to benefit many OA patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Xixi Dou, College of Biological Sciences and Technology, Beijing Key Laboratory of Food Processing and Safety in Forestry, Beijing Forestry University, No.35, Qinghua East Road, Beijing City 100083, China; Shandong Provincial Key Laboratory of Carbohydrate and Glycoconjugate Drugs, Shandong Freda Pharmaceutical Group Co., Ltd, No. 989, Xinshuo Street, Ji'nan 250013, Shangdong, China. Tel: +86-010-62336964; +86-0531-81213034; Fax: +86-010-62336964; +86-0531-81213034; E-mail: douxx@163.com; Qiuju Han, School of Pharmaceutical Sciences, Shandong University, No. 44, Wenhuaxi Road, Ji'nan 250101, Shangdong, China. Tel: +86-0531-88381980; Fax: +86-0531-88382548; E-mail: hanqiuju@sdu.edu.cn

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