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Review Article

Exosomes May Be the Potential New Direction of Research in Osteoarthritis Management

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Osteoarthritis (OA) is a joint degenerative disease, which is prominent in the middle-aged and elderly population, often leading to repeated pain in the joints of patients and seriously affecting the life quality of patients. At present, the treatment of OA mainly depends on the surgery and drug treatment. Nevertheless, these treatments still face many problems, such as surgical safety, complications, and drug side effects. Exosomes can be secreted and released by multiple cell types and have lipid bilayer membranes and contain abundant biological molecules, including proteins, lipids, and nucleic acids. Moreover, exosomes play a critical role in local and distal intercellular and intracellular communication. In recent years, several studies have found that exosomes can regulate the progression of OA and have a potential efficacy for OA treatment. Thus, in this article, we summarize and review the relevant research of exosomes in OA and emphasize the importance of exosomes in the development of OA.

1. Introduction

OA is a clinical disease involving the entire joint, including cartilage, subchondral bone, meniscus, ligaments, and muscles [1]. The main onset of OA is in the middle-aged and elderly population, which is characterized by cartilage degradation, subchondral bone sclerosis, osteophyte formation, synovial inflammation, and angiogenesis, and key risk factors include trauma, age, obesity, genetic and joint damage, and metabolic diseases [1–4]. At present, surgical treatment and drugs have achieved certain effects in patients with OA, but the accompanying surgical safety and complications and drug side effects are still clinical problems [5]. In addition, OA has caused huge public health resources [6]. Therefore, it is urgent to explore new strategies to protect cartilage and delay OA development.

Exosomes are an extracellular vesicle (EV) that functions as signaling molecules between cells [7]. In present studies, exosomes are closely related to OA, including promoting cartilage formation and tissue repair and regulating inflammatory response and homeostasis [8–10]. These studies have revealed the significant role of exosomes in OA. Besides, the clinical application of exosomes has received extensive attention. Therefore, it is very important to explore the role of exosomes in the OA process. In this review, we describe the characteristics of exosomes, biological functions, and related studies in osteoarthritis. Also, we discuss the diagnostic value and therapeutic potential of exosomes in OA.

2. Exosomes: An Overview

EVs were divided into microvesicles, exosomes, and apoptotic bodies in accordance with morphological features and content [11]. The most studied are the exosomes, which are a kind of EV and can be secreted and

released by multiple cell types (usually, exosomal size ranging from 30 to 150 nm) [12]. Exosomes were first found by R. M. Johnstone et al. when studying the formation of vesicles during the process of mature reticulocytes in sheep. Exosomes were widely distributed in peripheral blood, urine, saliva, ascites, milk, cerebrospinal fluid, and other body fluids and were usually extracted by ultracentrifugation, filtration centrifugation, density gradient centrifugation, chromatography, immunomagnetic beads, and polyethylene glycol precipitation [13, 14]. More importantly, the isolation and identification of high-purity exosomes are essential for elucidating its mechanism of action and its biological function. At present, a variety of techniques have been used to identify exosomes, including nanoparticle tracking analysis (NTA), dynamic light scattering (DLS), resistive pulse sensing, flow cytometry, electron microscopy, and atomic force microscopy (AFM) [15]. In general, the formation of exosomes involves three stages (Figure 1): (a) involution of cell membranes to form endosomes; (b) the endosomal membrane sprouts inward to form intraluminal vesicles (ILVs), and the endosomal body becomes multivesicular body biogenesis (MVBs); (c) exosomes are secreted to extracellular space by fusion of MVBs and plasma membrane [16]; extracellular exosomes have lipid bilayer membranes and contain abundant biological molecules, including proteins, lipids, and nucleic acids [17]. Since the first discovery of sheep erythrocyte supernatant, exosomes have been extensively studied and found to be closely associated with the occurrence and development of various diseases, including cancer, immune diseases, and neurodegenerative diseases [18–20]. The critical reason is that exosomes play a key role in local and distal intercellular and intracellular communication [21]. Exosomes are known to have a wide range of biological functions, such as regulating angiogenesis, apoptosis, antigen presentation, and receptor-mediated endocytosis. In addition, exosome can be used as a biomarker for the diagnosis and prognosis of the disease and shows great clinical value [22].

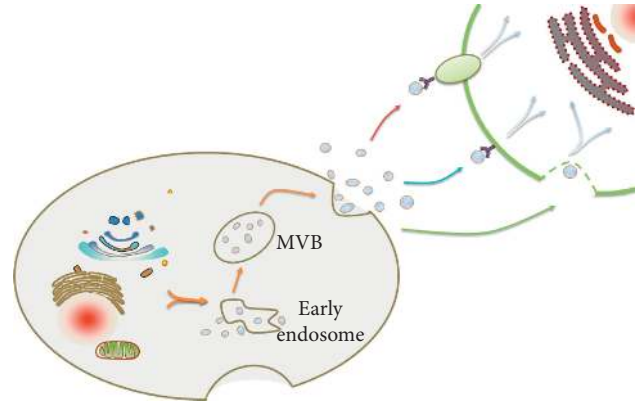

Figure 1: Exosomal formation, release, and intercellular transmission. The formation of exosomes includes three stages: form endosomes, form ILVs and MVBs, and further are secreted to extracellular space. When exosomes are released, exosomes act as intercellular signaling molecules that interact with receptor cells, including binding to cell membrane surface proteins, direct fusion, and endocytosis.

3. Exosome-Derived miRNAs in OA

Exosomes contain various RNAs including miRNA, lncRNA, circRNA, and mRNA. miRNAs are a kind of tiny, highly conserved RNAs with a length of about 22 nucleotides [23]. miRNAs have been studied for more than ten years in noncoding RNA. In the past years, miRNAs were extensively studied in diverse disciplines. With the in-depth study, the biological function of miRNAs has been gradually clarified. Critically, miRNAs contain miRNA response element, which can complement downstream target genes and degrade them [24]. This is an important function of miRNA.

Mesenchymal stem cells (MSCs) are derived from mesodermal cells and have the ability to differentiate into many kinds of cells, including osteogenic differentiation, adipogenic differentiation, and chondrogenic differentiation [25]. In addition, MSCs had better immune tolerance and immune regulation. These advantages are used to incorporate a new strategy to control the intervention of inflammation. In recent years, the studies and treatment of mesenchyme in OA have been extensively reported. MSCs have shown important functions in cartilage repair and inflammation regulation of osteoarthritis in some studies [26, 27]. Further, exosomes driven from MSCs have recently attracted widespread attention. For example, in the infrapatellar fat pad (IPFP) MSC-derived exosomes (MSCIPFP-Exos), miR-100-5p regulates MSCIPFP-Exos-mediated protection of articular cartilage via the mTOR signaling pathway [28]. After TGF-β1 induced MSCs, MSC-exosome-derived miR-135b was significantly increased in chondrocyte and overexpression of mir-135b promoted cartilage proliferation and repair. In the mechanism, miR-135b can bind with the transcription factor, specificity protein 1 (SP1), which is a protein that regulates apoptosis and proliferation of cells, targeting the degradation of SP1 to promote cartilage proliferation [29]. The procartilage repair effect of miR-135b has also been confirmed in the SD rat inflammation model. Similarly, through the verification of cell levels and animal models, the MSC-exosome-derived miR-92a-3p/wnt5a axis has a significant effect in increasing cartilage proliferation, slowing the progression of OA, maintaining cartilage stability, and inhibiting cartilage degradation [30]. Moreover, human synovial mesenchymal stem cell (hSMSC)-derived miR-140-5p can delay the progression of early OA and prevent knee cartilage damage, but the effect of hSMSC-derived miR-140-5p is finite [31]. On the other hand, miRNA-95-5p is significantly expressed in normal human cartilage by miRNA microarray analysis of normal cells and OA chondrocytes in human chondrocyte-derived exosomes. Exogenously derived miRNA-95-5p overexpression can delay the progression of OA and maintain cartilage development and homeostasis. Mechanistically, miRNA-95-5p-HDAC2/8 pathway plays

a key role [9]. Therefore, these studies bring a potential new approach to the prevention and treatment of OA.

In the above studies, miRNAs are closely related to cartilage proliferation, slowing the progression of OA, maintaining cartilage stability, and inhibiting cartilage degradation. To elucidate the specific mechanism of action of exosome-derived miRNAs has provided a guiding direction for OA treatment in the future.

4. Exosome-Derived lncRNAs in OA

Lncrna is a class of RNA that is more than 200 nt in length and does not encode proteins [32]. lncRNA exists in the nucleus or cytoplasm, and its function depends on the location of the subcellular [33]. Diverse lncRNA expression can regulate the cell proliferation, migration, invasion, immunobiology, and differentiation [34, 35]. In addition, lncRNA can perform its biological functions through different mechanisms, including decoys, signals, guides, and scaffolds [36]. In recent years, lncRNA is closely associated with the progression of OA and a variety of lncRNAs have been found to regulate the proliferation, repair, and formation of articular cartilage [37, 38]. The classical pathway of lncRNA is that lncRNA acts as competitive endogenous RNA (ceRNA) by binding to specific miRNAs [35]. In previous studies, MSC-Exos have the function of improving cartilage and bone regeneration [39, 40]. In a study by Liu et al., exosomal KLF3-AS1 derived from MSCs exhibits significant promotion of cartilage growth and reduced inflammation-induced cartilage damage. Among them, lncRNA KLF3-AS1 plays an important role in promoting GIT1 expression by sponge to miR-206 as a ceRNA [41].

4.1. Exosome-Derived lncRNA as Molecular Markers. Clinically, the diagnosis of early and advanced osteoarthritis lacks simple and accurate marker detection and the identification and utilization of a molecular marker as a specific clinical value of staging diagnosis of OA. In a study by Zhao and Xu, the subjects were divided into three groups: the control group, the early OA group, and the late OA group (patients in the late-stage OA). Blood samples from the elbow vein and synovial fluid samples from the knee joint were collected from all subjects. Exosomes were extracted by ultracentrifugation, and the expression of several exosomal lncRNAs was measured using RT-PCR. With the development of OA, the expression of exosomal lncRNA PCGEM1 is gradually increasing. This shows that exosome-derived lncRNA can be an important indicator of the progression of osteoarthritis and provides a new molecular marker for the accurate and effective monitoring of the progress of osteoarthritis [42]. Numerous molecules in exosomes play an important role in regulating the development of OA and detecting the progress of OA, and we list all OA-related exosome-derived miRNAs and lncRNAs in Table 1.

5. Exosomes Regulate the Progression of OA

5.1. Exosomes Regulate Cellular Senescence of OA. Aging is a key factor for inducing the progression of OA, and age-related proinflammatory state may act as a vital role in OA [43]. In addition, OA cartilage can be detected by the senescence-associated secretory phenotype (SASP) and oxidative stress is a key process in inducing cellular senescence [44, 45]. Researchers found that EV derived from adipose-derived mesenchymal stem cells (ADMSCs) reduces inflammation and oxidative stress. These data show that conditioned medium (CM) and exosome mediate anti-senescence effects in OA osteoblasts. Of note, osteoblasts participate in the regulation of cartilage metabolism and bone remodeling in OA [46]. Therefore, regulation of OA cellular senescence and metabolism provides new targets for the prevention or treatment of OA.

5.2. Exosomes Regulate Cartilage Development and Homeostasis. In the rat model, for rats with large segmental cartilage defects, the function of cartilage was detected by intra-articular injection of embryonic mesenchyme-derived exosomes. After 12 weeks of treatment, the study showed that defects in treated exosomes revealed cartilage and complete recovery of subchondral bone characterized by hyaline cartilage with good surface regularity, complete binding of adjacent cartilage, and extracellular matrix deposition very similar to age-matched unoperated controls. In contrast, in the control group treated with PBS, only fibrous repair tissue was found in the cartilage defect [39]. This research first discovered the effectiveness of exosomes for cartilage repair. Next, Wang et al. showed in mouse OA model that the injection of embryonic stem cell-derived exosomes into the joint cavity can slow the progression of OA and maintain the cartilage matrix [8]. However, MSC-derived exosomes effectively relieve temporomandibular joint osteoarthritis (TMJ-OA) pain and promote regeneration [47]. These studies provide a feasible solution for the clinical treatment of cartilage defects and repair of cartilage, indicating that the new prospect of exosome treatment as OA is worthy of expectation. The repair effect of exosomes in OA is significant. Is the effect of exosomes from different sources on OA different? In one study, the authors compared the effects of exosomes from induced pluripotent stem cell-derived MSCs (iMSCs) and synovial membrane mesenchymal stem cells (SMMSCs) in the mice OA model. The study found that iMSC-Exos has a better therapeutic effect after the same injection of iMSC-Exos or SMMSC-Exos. Furthermore, although both iMSC-Exos and SMMSC-Exos stimulate chondrocyte migration and proliferation, iMSC-Exos has a greater effect than SMMSC-Exos [48].

5.3. Exosomes Regulate Inflammation. Synovial membrane is required for normal cartilage and joint function. Synovial inflammation (synovitis) plays a key role in the development of symptoms and progression of OA, and a model of Toll-like receptor and complement activation as an important mechanism contributes to the synovitis and enhances cartilage erosion in OA [49]. On the one hand, inflammation can stimulate angiogenesis, and on the other hand, angiogenesis can promote inflammation.

Table 1: Exosome-derived miRNAs and lncRNAs in OA.

Names	Function	Mechanism	Ref
miR-100-5p	Maintains cartilage homeostasis	mTOR signaling pathway	[28]
miR-135b	Promotes chondrocyte proliferation and cartilage repair	miR-135b/SP1	[29]
miR-92a-3p	Regulates cartilage development and homeostasis	miR-92a-3p/Wnt5a	[30]
miRNA-95-5p	Regulates cartilage development and homeostasis	miRNA-95-5p-HDAC2/8	[9]
miR-140-5p	Enhances proliferation and migration of chondrocytes	miR-140-5p/RALA	[31]
KLF3-AS1	Promotes cartilage repair and chondrocyte proliferation	KLF3-AS1-miR-206/GIT1 axis	[41]
PCGEM1	As a biomarker	No mention	[42]

Furthermore, angiogenesis also promotes chondrocyte hypertrophy and endochondral ossification [50].

In the above description, exosomes exhibit a satisfactory effect on inflammation inhibition and protection of cartilage. Conversely, in synovial-derived exosomes, proinflammatory action is remarkable after treatment of macrophages with exosomes, and exosomes also promote the release of various chemokines and metalloproteinases (MMPs) [51]. IL-1β is a key factor in cartilage degradation and joint inflammation [52]. The precise mechanism of exosomes involved in the pathogenesis of OA remains unclear, so further elucidation of the mechanism is important for our effective monitoring and treatment of OA. Finally, we describe the function of exosomes in OA in Figure 2.

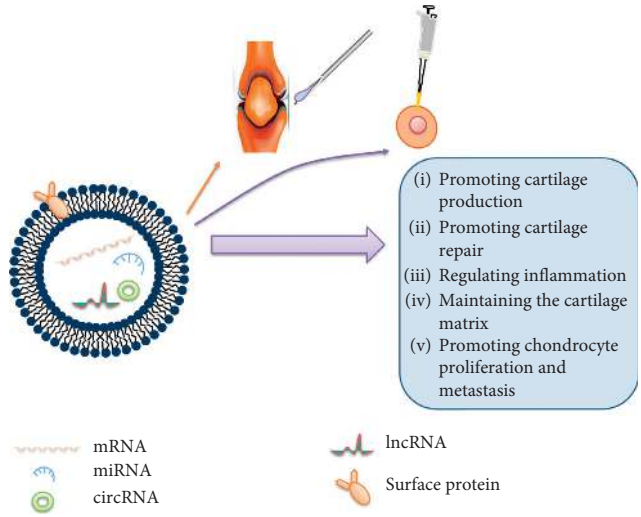

Figure 2: The function of exosomes in OA. We describe the important functions of exosomes in OA through intra-articular injection and cell transfection, including promoting cartilage production, promoting cartilage repair, regulating inflammation, maintaining the cartilage matrix, and promoting chondrocyte proliferation and metastasis. These indicate the potential clinical value of exosomes for OA treatment.

6. Prospect of Clinical Application

Cell transplantation technology has shown great clinical potential as a new treatment. Therapeutic purposes are achieved by the local transplantation of autologous or allogeneic stem cells in vivo. MSCs have great anti-inflammatory and tissue repair effects [53]. In preceding studies, MSC has an excellent effect on heart disease, kidney disease, lung disease, nervous system disease, bone injury, and OA [54–59]. In addition, in the clinical trials of osteoarthritis, joint injection therapy of mesenchymal stem cells has a better therapeutic effect [60, 61]. There are still serious problems in immune rejection and ethics when MSCs are transplanted into damaged organisms [62]. In addition, economic, regenerative, and security issues remain issues of concern [53]. Of note, it is generally believed that the paracrine function of mesenchymal stem cells plays a major role, and its secretions have strong immunoregulatory effects, such as extracellular vesicles, exosomes, and cytokines, of which exosomes is an important substance [63]. Exosomes, as a secreted extracellular vesicle, have good intercellular communication function and no cell structure, which dramatically reduce immune rejection and have good safety and efficacy. As a safe and effective treatment, exosomes can avoid the problems of transfer of infectious pathogens, genetic instability, and malignant transformation of damaged sites [64]. In previous reports, exosomes have an observable effect on cartilage repair and delayed degradation in basic research and animal experiments. Therefore, development and application of exosome therapy as a therapeutic agent in regenerative medicine have good clinical application prospects.

7. Discussion

Good effects of exosomes have been shown in many diseases. However, the problems such as how to increase the secretion of exosomes more efficiently, whether it can promote the transport of exosomes to target cells through specific conditions, whether it can fully exert its repairing effect by controlling the pH of the microenvironment of its action, and whether the exocrine secreted by the tissue has different effects on the repair effect of the damage make the exosomes actually face many difficulties in clinical application. In OA patients, surgical treatment poses a definite safety risk and causes greater pain to the patient. The treatment of drugs also has certain side effects. Therefore, safe, effective, and non-side-effect treatment modes are clinically explored. In addition, it is also essential for the prevention of OA diseases. With the deepening of research on exosome

mechanisms and the continuous maturity of technical means, it is of high clinical value to operate exosome therapy in the prevention and treatment of OA. This is beneficial for OA patients to relieve pain and improve their quality of life.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

CJ was the major contributor in writing and revising the manuscript. RFL and YZ performed the literature search and screening. FFZ and JS conceived and designed the study and critically revised the manuscript for important intellectual content. XBL and ZPZ participated in the design of the review and helped to finalize the manuscript. All authors read and approved the final manuscript.

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