Mechanism of osteoarthritis treatment by exosomes

Xiaofei Wang[1,2], Jihang Dai[2], Lei Xu[2], Zhimin Wu[1,2], Linbing Lou[1,2], Cunyi Xia[2], Haixiang Miao[2], Wenyong Fei[2], Jingcheng Wang[2]

[1]The Yangzhou School of Clinical Medicine of Dalian Medical University, Dalian Medical University, Dalian, Liaoning 116044, China;
[2]Department of Orthopedics, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, Jiangsu 225001, China.

To the Editor: As population aging accelerates, osteoarthritis (OA) has emerged as a major cause of disability among the elderly, significantly increasing the social burden.[1] OA is recognized as a chronic, progressive joint disease resulting from the wear and tear of articular cartilage. This degeneration can lead to histological and structural changes in the joints, ultimately causing comprehensive impairment of joint function.[2]

OA features a complex pathological mechanism, making a thorough understanding of its pathogenesis or key signaling pathway molecules essential for effective treatment. The etiology and progression of OA involve pathological changes in multiple tissues surrounding the joints, including the subchondral bone, synovium, joint capsule, periarticular muscles, sensory nerve endings, and meniscus.[3]

Exosomes are vesicles with a bilayer lipid membrane structure that are widely distributed in body fluids. They are capable of transmitting genetic information from donor cells and facilitating intercellular communication. Characterized by their low immunogenicity and high transport efficiency, exosomes play a role in modulating inflammatory responses and transporting signaling molecules. These vesicles, released by various cell types, carry functional signaling molecules, including proteins and RNA. They play a crucial role in numerous biological processes, such as cellular signaling, immune responses, and other biological activities.[4] Exosomes mediate communication between different cell types *in vivo* by translocating biologically active lipids, proteins, and RNAs, including messenger RNAs and non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs).[5,6] Some scholars identified nine differentially expressed miRNAs from synovial fluid-derived exosomes from healthy and OA patients based on miRNA expression profiles in the Gene Expression Omnibus database. They used reverse transcription-quantitative real-time polymerase chain reaction to verify that miR-130 b-3 p and miR-1271-5 p were significantly upregulated. Therefore, these two miRNAs may play a key role in the communication among chondrocytes in OA.[7] In addition, exosomes can regulate various cellular activities involved in the pathological process of OA through their autocrine and paracrine functions. However, the exact mechanism by which exosomes influence OA treatment is not yet fully understood. Increasing evidence suggests that exosomes may play a significant role in the pathogenesis and treatment of OA [Figure 1].

Current studies mainly focus on the effects of exosomes on OA-related inflammation, cartilage degeneration or excessive cell death, extracellular matrix degradation, and intra-articular neovascularization.[8,9] Furthermore, several scholars have concentrated on the epigenetic regulation of OA, examining the specific roles of exosomes in OA and identifying potential molecular targets for its treatment.[10] Scholars have suggested that exosomes derived from stem cells can contribute to chondrocyte proliferation and migration while inhibiting cell apoptosis and the production of pro-inflammatory markers.[11] Exosomes derived from stem cells and other sources not only serve as drug carriers but also have an intrinsic role in reducing local inflammation in OA. Researchers have demonstrated that exosomes derived from stem cells can reduce M1 macrophage infiltration by promoting the recruitment of M2 macrophages to cartilage defects and the synovium in OA. This process aids in downregulating interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) expression, ultimately alleviating the progression of OA.[12]

Some researchers have also discovered that bone marrow mesenchymal stem cell-derived exosomes regulate

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Xiaofei Wang and Jihang Dai contributed equally to this work.

Correspondence to: Wenyong Fei, Department of Orthopedics, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, Jiangsu 225001, China
E-Mail: sbydyx105@126.com;
Jingcheng Wang, Department of Orthopedics, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, Jiangsu 225001, China
E-Mail: yzwangjingcheng@163.com

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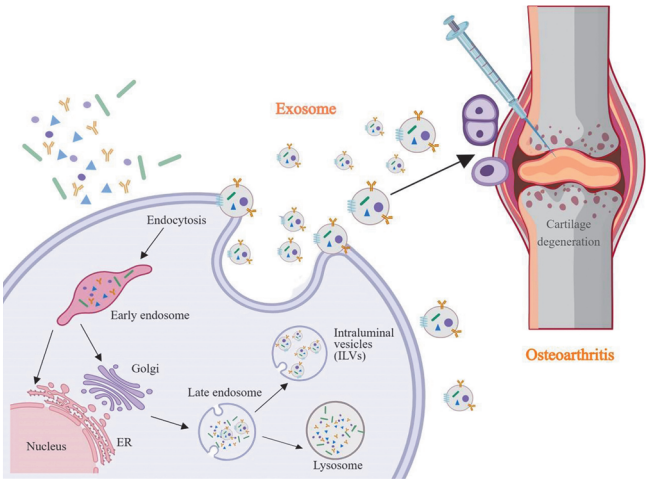

Figure 1: Schematic presentation of exosome formation, release, and intercellular transmission, as well as its application in the treatment of OA. ER: Endoplasmic reticulum; ILVs: Intraluminal vesicles; OA: Osteoarthritis.

ferroptosis by reducing inflammation, preventing ferroptosis, and enhancing the expression of glutamic oxaloacetic transaminase 1/chemokine (C-C motif) receptor 2, which improves OA in mouse models.[13] Moreover, intra-articular injection of exosomes derived from activating transcription factor 4 can partially restore autophagy and inhibit chondrocyte apoptosis, thereby protecting cartilage and suppressing the progression of OA.[14]

During the progression of OA, chondrocytes produce matrix-degrading enzymes such as matrix metalloproteinase 13 and a disintegrin and metalloproteinase with thrombospondin motifs 5, which target aggregated proteoglycans for degradation and exacerbate the destruction of articular cartilage. These biomechanical and biochemical changes disrupt cartilage homeostasis, leading to the pathological condition of OA, which includes joint space narrowing, cartilage destruction, and functional loss. Some exosomes derived from chondrocytes or stem cells can help counteract these effects by reshaping the migration and secretion of extracellular matrix. They achieve this by upregulating type II collagen, aggregating proteoglycans, and sex-determining region Y-box 9, while downregulating matrix metalloproteinase 13.[15]

Additionally, some exosomes can modulate immune responses by regulating T cell activation and differentiation while inhibiting B cell function. Simultaneously, these exosomes can also inhibit abnormal angiogenesis or normalize uncoupled bone remodeling and abnormal hypertrophic vessel formation in the subchondral bone, thereby effectively alleviating the progression of OA.[16]

Compared with traditional nanocarriers, exosomes are natural nanomaterials, and engineered exosomes have the potential to serve as efficient and safe delivery carriers for cell-free therapy of OA. However, using engineered exosomes for OA treatment faces many challenges, including technical difficulties in large-scale production, control of intra-articular stability, storage methods, and quality control. While extracellular vesicles have demonstrated significant potential in cartilage repair, further research is needed to optimize their enrichment and delivery methods. A recent study highlights that magnetic polysaccharide hydrogel particles combined with microcarriers can synergistically treat OA. Additionally, the combination of the anti-inflammatory drug diclofenac sodium, released by microcarriers, and exosomes has shown synergistic effects in relieving OA symptoms and promoting cartilage repair.[17]

What's more, with advancements in nanomedicine, research into methods such as micro- and nano-particles, as well as hydrogels for intra-articular injection of engineered drug carriers, is gradually increasing. Recent studies have revealed that engineered exosomes with surface modifications, such as genetic and chemical engineering, exhibit enhanced targeting capabilities. These modifications increase local drug concentration, reduce immunogenicity and toxicity, and improve the engineering capabilities of the exosomes. As a result, engineered exosomes are better equipped to overcome the dense type II collagen barrier and achieve more precise therapeutic effects in treating OA.[18]

Due to the availability of exosomes from a variety of sources and their widespread distribution throughout the organism, these exosomes can influence different intercellular communication pathways to alleviate OA. In recent years, engineering exosomes have emerged as a prominent and challenging research focus for accurately delivering various substrates to OA target sites and increasing their therapeutic efficacy. A thorough understanding of the specific mechanisms by which exosomes exert its effects is crucial for reversing OA. However, given the complexity of the pathogenesis and progression of OA, the therapeutic mechanism of exosomes for OA is not yet fully understood. Therefore, further researches into the specific targets of exosome therapy are needed to provide new insights and theoretical foundations for the future treatment of OA.

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Conflicts of interest

None.

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