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Potential and Mechanisms of Mesenchymal Stem Cell-Derived Extracellular Vesicles in the Treatment of Osteoarthritis

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Abstract: Osteoarthritis (OA) is a common degenerative joint disease. Current therapeutic strategies mainly focus on symptom relief and are still unable to effectively halt disease progression. Mesenchymal stem cells (MSCs) possess immunomodulatory, anti-inflammatory, and tissue-repair capacities; however, direct cell transplantation remains limited by insufficient stability during in vitro expansion, potential safety risks, and difficulties in quality control. Recent studies have shown that MSC-derived extracellular vesicles (MSC-EVs) can carry bioactive components, including proteins, lipids, mRNA, and miRNA, participate in intercellular communication, and exhibit promising therapeutic potential in OA. Compared with MSCs, MSC-EVs have advantages such as lower immunogenicity, easier storage, and greater suitability for engineering modification. This review summarizes the major mechanisms by which MSC-EVs may contribute to OA treatment, including regulation of inflammation and the synovial microenvironment, promotion of cartilage repair, modulation of immune responses, delay of chondrocyte senescence, and alleviation of pain. In addition, strategies such as surface-targeting modification, miRNA overexpression, hypoxic preconditioning, and low-intensity pulsed ultrasound are discussed for their potential to enhance the therapeutic efficacy of MSC-EVs. Although MSC-EVs show favorable prospects in OA treatment, their key bioactive components, quality standards, large-scale production, and clinical safety require further clarification.

Keywords: Osteoarthritis; Mesenchymal Stem Cells; Extracellular Vesicles; Inflammatory Regulation; Cell-free Therapy.

1. Introduction

Osteoarthritis (OA) is a highly prevalent chronic degenerative joint disease worldwide. Its major pathological features include articular cartilage degeneration, synovial inflammation, subchondral bone remodeling, and osteophyte formation [1]. As of 2020, nearly 600 million people worldwide were affected by OA [2]. Current OA treatments mainly include non-surgical and surgical approaches. Non-surgical treatments primarily aim to relieve pain, reduce inflammation, and improve joint function, but they cannot reverse cartilage degeneration. Although surgical treatment can improve joint function in end-stage disease, it is associated with high costs, considerable trauma, and postoperative complications [3]. Therefore, exploring novel therapeutic strategies that can delay OA progression and improve the joint microenvironment remains of great significance.

In recent years, MSCs have become a research focus in OA treatment because of their immunomodulatory, anti-inflammatory, and cartilage-repair-promoting properties. MSCs can be derived from multiple tissues, including bone marrow, adipose tissue, placenta, and umbilical cord, and they participate in tissue homeostasis and injury repair. However, the direct application of MSCs still has several limitations, such as reduced genetic stability after long-term in vitro culture and the susceptibility of cell proliferation, differentiation, and therapeutic effects to changes in the microenvironment [4]. Therefore, identifying an alternative strategy that preserves the therapeutic effects of MSCs while reducing the risks associated with cell transplantation has become an important research direction.

MSC-EVs are important mediators through which MSCs exert their paracrine effects. Studies have shown that the therapeutic effects of MSCs largely depend on the EVs they secrete [5]. MSC-EVs can carry proteins, lipids, mRNA, miRNA, and other non-coding RNAs, participate in intercellular communication, and play roles in immunomodulation, anti-inflammatory responses, and tissue repair [6,7]. Compared with direct MSC transplantation, MSC-EVs can avoid some risks associated with cell-based therapy and are easier to store, transport, prepare, and administer [8]. Moreover, MSC-EVs can be engineered through surface modification, nucleic acid loading, and preconditioning, thereby enhancing their targeting ability and therapeutic efficacy. Thus, MSC-EVs are considered a promising alternative to MSC-based therapy for OA.

2. Definition and Classification of Extracellular Vesicles

Extracellular vesicles (EVs) are lipid bilayer membrane structures secreted by cells. They can encapsulate bioactive substances such as DNA, RNA, proteins, and lipids, and are widely involved in intercellular communication and signal regulation [9]. According to their biogenesis and diameter, EVs are generally classified into exosomes (Exos), microvesicles (MVs), and apoptotic bodies (ApoBd). Among these, exosomes are the most extensively studied type in MSC-EV research.

Exosomes are mainly generated through endocytosis, which first forms early endosomes that subsequently mature into multivesicular bodies (MVBs). MVBs then fuse with the plasma membrane and release vesicles into the extracellular space. The bilayer membrane structure of exosomes helps protect their contents and allows relatively stable transport

within tissues. Their biological functions are closely related to the status of the parent cells and the proteins, nucleic acids, and lipids they carry [10]. In particular, non-coding RNAs such as miRNAs, lncRNAs, and circRNAs can be taken up by recipient cells and subsequently regulate inflammatory responses, chondrocyte survival, and extracellular matrix metabolism [11]. MVs are mainly formed by direct budding from the plasma membrane, whereas ApoBd are primarily generated during apoptosis. Different subtypes of EVs vary in origin, size, and composition, but they can all serve as important carriers for intercellular information exchange. Because vesicle populations obtained using different isolation methods may be heterogeneous, the evaluation of MSC-EVs in OA treatment should consider not only their source but also their isolation and purification methods, particle size distribution, surface markers, and functional components.

3. Therapeutic Potential of MSC-EVs in OA

3.1. Regulation of Inflammation and the Synovial Microenvironment

OA is not simply a disease of cartilage wear. Inflammatory responses play an important role in its onset and progression. Pro-inflammatory cytokines can enhance catabolic activity in chondrocytes, promote matrix degradation, and aggravate synovial inflammation and joint pain. Synovitis may occur at different stages of OA and can further accelerate cartilage damage by releasing inflammatory factors, proteases, and other destructive mediators [12]. Therefore, regulating inflammation and improving the synovial microenvironment are important approaches for delaying OA progression.

MSC-EVs can exert anti-inflammatory effects by inhibiting the release of pro-inflammatory factors, increasing the levels of anti-inflammatory factors, and modulating related signaling pathways [13]. Studies have shown that bone marrow mesenchymal stem cell-derived EVs (BMMSC-EVs) can reduce the expression of COX2 and pro-inflammatory mediators such as IL-1α, IL-1β, IL-6, IL-8, and IL-17 in TNF-α-stimulated OA chondrocyte models. They can also block NF-κB signaling activation by inhibiting IκBα phosphorylation and p65 nuclear translocation [14]. In addition, SNHG7 enriched in BMMSC-EVs can be taken up by chondrocytes and suppress IL-1β-induced inflammatory responses through the miR-485-5p/FSP1 axis [15]. In animal models, BMMSC-EVs can alleviate synovitis in destabilization of the medial meniscus (DMM)-induced OA mice, and EVs derived from young donors show better therapeutic effects than those from aged donors [16]. EVs derived from synovial MSCs can also deliver miR-26a-5p into chondrocytes, reduce TNF-α levels and increase IL-10 levels by inhibiting PTEN, thereby attenuating OA-related inflammatory progression [17]. These findings indicate that MSC-EVs can regulate OA inflammation at multiple levels, including cytokines, non-coding RNAs, and classical inflammatory signaling pathways, and may help improve the abnormal inflammatory feedback between synovium and cartilage.

3.2. Promotion of Cartilage Repair and Inhibition of Chondrocyte Apoptosis

Articular cartilage is a load-bearing tissue that provides a low-friction surface and buffers mechanical stress. However, because it lacks blood vessels and nerves and has a low cell density, its intrinsic repair capacity is limited [18]. During OA progression, enhanced chondrocyte catabolism, extracellular matrix (ECM) loss, abnormal chondrocyte hypertrophy, and apoptosis jointly drive cartilage degeneration. Therefore, maintaining the chondrocyte phenotype, promoting ECM synthesis, and inhibiting matrix degradation are key aspects of OA treatment.

Multiple studies have shown that MSC-EVs can promote chondrocyte proliferation, migration, and matrix synthesis while inhibiting apoptosis and cartilage degradation. Human adipose-derived MSC-EVs can promote chondrocyte proliferation and migration and regulate the balance between anabolic and catabolic metabolism [19]. MSC-EVs can also promote chondrocyte proliferation and migration, inhibit apoptosis, upregulate cartilage-related genes such as COL2A1 and Aggrecan, and reduce the expression of degradation-related factors such as MMP-13 through the circHIPK3/miR-124-3p/MYH9 axis [20]. In animal experiments, exosomes derived from synovial MSCs can alleviate cartilage injury in traumatic OA models, and overexpression of miR-140-5p can further enhance their cartilage-protective effects [21]. MSC-EVs overexpressing miR-92a-3p can promote chondrocyte proliferation and migration by targeting WNT5A, improve ECM homeostasis, and delay OA progression [22].

The cartilage-repair-promoting effects of MSC-EVs are closely related to their uptake by joint cells and the miRNAs they carry. Surface molecules on EVs, such as CD44, may interact with hyaluronic acid in synovial cells or the cartilage matrix, thereby facilitating EV binding and internalization. miRNAs can mediate the effects of EVs on chondrocyte proliferation, differentiation, apoptosis, and matrix metabolism. For example, hUC-MSC-sEVs can transfer miR-23a-3p, inhibit PTEN, and activate AKT signaling, thereby promoting cartilage regeneration [23]. hUC-EVs overexpressing miR-223 can target the 3′ untranslated region of NLRP3 mRNA, inhibit NLRP3 expression, and enhance the protective effect on chondrocytes [24]. miR-100-5p, enriched in exosomes derived from infrapatellar fat pad MSCs, can enhance chondrocyte autophagy by suppressing mTOR signaling and reduce articular cartilage injury [25]. Overall, MSC-EVs may improve the OA cartilage microenvironment through the synergistic effects of multiple active components that simultaneously influence chondrocyte anabolism, catabolism, apoptosis, and autophagy.

3.3. Immunomodulatory Effects

Various immune cells, including macrophages, T cells, and B cells, are present in the synovium of OA joints, where they participate in local inflammation and cartilage destruction. Macrophages are important immune cells in the synovium, and their M1/M2 polarization status is closely associated with inflammation and tissue repair. M1 macrophages mainly mediate pro-inflammatory responses and secrete factors such as IL-1β and TNF-α, inducing cartilage matrix degradation. In contrast, M2 macrophages have anti-inflammatory and reparative functions and secrete factors such as ARG1 and IL-10, which contribute to inflammation resolution and cartilage protection. Therefore, restoring the balance of M1/M2 polarization may be an important therapeutic strategy for OA.

MSC-EVs can exert immunomodulatory effects by regulating macrophage phenotypes. Studies have shown that MSC-EV treatment can increase the infiltration of CD163+ M2 macrophages in injured regions and reduce the number of

CD86+ M1 macrophages, thereby promoting osteochondral defect repair [26]. Zhang S et al. reported that MSC-EVs promote the migration of M2 macrophages toward OA lesions, inhibit local infiltration of M1 macrophages, and reduce the expression of IL-1β and TNF-α, thereby alleviating OA inflammation [26]. In addition, human umbilical cord MSC-EVs may activate the PI3K-Akt signaling pathway by delivering specific proteins and miRNAs, promote M2 polarization, and participate in immune homeostasis regulation in OA [27].

An imbalance in T-cell subsets is also involved in the inflammatory cascade of OA. The balance between pro-inflammatory Th1/Th17 cells and anti-inflammatory regulatory T cells (Tregs) is associated with synovial inflammation and cartilage destruction. Cosenza et al. found that MSC-derived exosomes can inhibit T lymphocyte proliferation, reduce the proportions of CD4+ and CD8+ T-cell subsets, and induce Treg expansion. They also exert anti-inflammatory effects by carrying bioactive molecules such as TGF-β1 and PGE2 [28]. Another study showed that EVs released by adipose-derived MSCs after exposure to OA synovial fluid contain miRNAs such as miR-24-3p and miR-21-5p, which can inhibit T-cell activation and proliferation and promote Treg expansion [29]. Although the regulatory effects of MSC-EVs on B cells remain insufficiently studied, their effects on macrophages and T cells indicate important immunomodulatory potential.

3.4. Inhibition of Chondrocyte Senescence

Senescent chondrocytes can accumulate in OA joints and are associated with disease severity [30]. Cellular senescence is characterized by cell-cycle arrest, enhanced resistance to apoptosis, and persistent secretion of senescence-associated secretory phenotype (SASP) factors [31]. SASP factors include various cytokines, chemokines, and matrix-degrading enzymes, such as IL-6 and MMP13, which can aggravate local inflammation and cartilage degeneration [32]. Therefore, inhibiting chondrocyte senescence is a potential therapeutic direction for OA.

MSC-EVs have shown anti-senescent effects in various tissue cells and have gradually been applied in OA-related research. Li X et al. found that synovial fluid-derived MSCs can release mitochondria-rich EVs, which are taken up by chondrocytes and reduce the expression of senescence-related markers such as SA-β-Gal, Cav1, p53, p21, and p16, while increasing SIRT1 levels. These effects inhibit chondrocyte senescence and help maintain the normal chondrocyte phenotype [33]. BM-MSC-derived exosomes can reduce the percentage of SA-β-gal-positive OA chondrocytes induced by IL-1β and downregulate the senescence marker GRP-78 [34]. In addition, miRNAs in UCMSC-Exos can regulate p53 and its downstream genes, including CDKN1A and TP53BP1, thereby reducing the production of senescence markers [35]. Engineered FTO-overexpressing EVs can also reduce oxidative stress, increase the GSH/GSSG ratio, and upregulate the Nrf2/HO-1 pathway, thereby attenuating oxidative injury-induced cellular senescence [36]. These findings suggest that MSC-EVs may delay OA progression by improving mitochondrial function, regulating the p53 pathway, and reducing oxidative stress.

3.5. Pain Management

Pain is the main reason patients with OA seek medical care and is also a major factor affecting quality of life and joint function. The mechanisms underlying OA pain are complex and involve peripheral sensitization, central sensitization, inflammatory mediator release, subchondral bone changes, and neurovascular abnormalities. Current clinical treatments mainly focus on analgesia and anti-inflammatory effects, but their long-term efficacy and safety remain limited. Therefore, identifying novel therapeutic approaches that can both improve joint pathology and relieve pain is of great importance.

MSC-EVs have shown potential in OA pain management. In a DMM-induced OA mouse model, intra-articular injection of MSC-EVs significantly improved pain-related behaviors, and the underlying mechanism may be related to the normalization of sensory neuron excitability by MSC-EVs [37]. Zhang S et al. observed in a temporomandibular joint osteoarthritis model that MSC-EV treatment increased the head withdrawal threshold and reduced the expression of pain-related genes, including Substance P, CGRP, NGF, P75NTR, and TrkA [38]. In addition, purified infrapatellar fat pad-derived MSC-EVs injected into the knee joints of ACLT-induced OA mice showed analgesic effects in gait analysis [39]. These studies suggest that MSC-EVs may not only improve cartilage and synovial microenvironments but also alleviate OA pain by influencing nerve sensitization-related pathways.

4. Engineering Modification and Other Intervention Strategies

Although MSC-EVs have multi-target advantages in OA treatment, natural MSC-EVs still face several limitations, including unstable therapeutic efficacy, insufficient targeting ability, limited yield, and short retention time in vivo. Therefore, engineering modification and culture-condition intervention are important approaches for enhancing the therapeutic effects of MSC-EVs and promoting their clinical translation.

MSC-EVs have low immunogenicity, natural tissue affinity, and relatively high tissue permeability, making them suitable nanoplatforms for delivering siRNA, miRNA, and other therapeutic molecules [7]. Feng K et al. developed a WPD-sEVs-siMDM2 system, in which siMDM2 was loaded into sEVs by electroporation and the vesicle surface was modified with a type II collagen-targeting peptide. This strategy enhanced the penetration of sEVs into cartilage and prolonged their retention time in the joint. By inhibiting MDM2 expression, this system promoted apoptosis of senescent chondrocytes and showed promising therapeutic potential [40].

Regulating the miRNA cargo of EVs is also an important way to enhance therapeutic efficacy. Wang Z et al. overexpressed miR-155-5p in exosomes derived from synovial MSCs using miRNA mimics or adenoviral vectors. These exosomes promoted chondrocyte proliferation, migration, and ECM secretion while inhibiting apoptosis, thereby enhancing their therapeutic effects on OA [41]. Another study increased miR-27b-3p expression in EVs through mechanical loading preconditioning and modified the EV surface with a chondrocyte-targeting peptide to construct CTP/miROE-EVs. These engineered EVs showed better therapeutic effects than conventional MSC-EVs in both in vitro and in vivo experiments [42]. In addition, IL-6-preconditioned MSCs can generate exosomes with immune-memory characteristics, which target the mt-ND3/NADH-

CoQ axis in macrophages, enhance mitochondrial oxidative phosphorylation, and promote M2 polarization, thereby alleviating OA inflammation [43].

Culture environments and physical stimulation can also affect the yield and function of MSC-EVs. Hypoxic preconditioning can alter the expression of multiple miRNAs in MSC-EVs, enhancing their ability to promote chondrocyte proliferation and migration while inhibiting apoptosis. These effects may be associated with cartilage repair through the JAK-STAT or MAPK-related pathways [44]. Low-intensity pulsed ultrasound (LIPUS) can activate autophagy and promote MSC-EV release, further enhancing cartilage repair in OA [45]. LIPUS stimulation can also enrich miR-328-5p and miR-487b-3p, thereby improving the anti-inflammatory function of EVs [46]. In addition, tropoelastin-preconditioned adipose-derived MSCs can increase ADMSC-Exos production and enhance cartilage-protective effects by increasing miR-451-5p levels [47]. Electromagnetic fields combined with ultrasmall superparamagnetic iron oxide particles can also increase EV production from BMSCs and show favorable effects in restoring chondrocyte homeostasis and inducing M2 polarization [48]. Overall, engineering modification and preconditioning strategies provide feasible approaches for improving the therapeutic efficacy of MSC-EVs. However, these methods may also introduce quality-control concerns, including loading efficiency, batch-to-batch variation, altered biodistribution, and potential immune responses. Further standardization is therefore required.

5. Discussion and Future Perspectives

Current in vitro and in vivo studies suggest that MSC-EVs have considerable potential in OA treatment. Their mechanisms involve anti-inflammatory effects, immunomodulation, cartilage repair, inhibition of chondrocyte senescence, and pain relief. Compared with conventional cell therapy, MSC-EVs have lower safety risks and greater advantages in preparation, storage, and engineering modification. They are therefore considered important candidates for cell-free regenerative medicine in OA.

However, several challenges remain in MSC-EV research. First, MSC-EVs are complex in composition. Current studies mainly focus on miRNAs, while the roles of proteins, lipids, and other non-coding RNAs in OA treatment require further investigation. Second, most existing in vivo studies are based on rodent models. Small rodents differ from humans in joint structure, mechanical loading, and disease progression. In addition, some studies have used human-derived EVs to treat mouse OA models, and the observed effects may not fully translate to patients [39]. Third, standardized methods for large-scale production, purification, quality control, and storage of MSC-EVs have not yet been established, which remains a major barrier to clinical application. Fourth, clinical studies on MSC-EVs for OA are still limited, and their long-term safety, effective dosage, administration frequency, and clinical indications require systematic validation. Fifth, EVs cannot replicate in vivo and have a relatively short half-life, which may require repeated administration to maintain therapeutic effects. Engineering strategies that prolong their retention time and half-life may represent an important direction for optimizing treatment regimens [49,50].

In summary, MSC-EVs, as a cell-free therapeutic strategy, show multi-target, modifiable, and translational advantages in OA treatment. Future studies should further clarify their key bioactive components and mechanisms of action, establish standardized production and quality-evaluation systems, and verify their safety and efficacy through large-animal experiments and high-quality clinical studies. With the development of engineering modification, targeted delivery, and preconditioning technologies, MSC-EVs may provide a promising new strategy for OA treatment.

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