ISSN 2618-1584 Vol. 7, Issue 1: 70-78, DOI: 10.25236/FMSR.2025.070111

Advances in the Treatment of Osteoarthritis with Stem Cells from Human Exfoliated Deciduous Teeth Exosomes

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Abstract: *Osteoarthritis (OA) is a chronic degenerative disease marked by the deterioration of articular cartilage and the proliferation of marginal bone, significantly impacting the quality of life and life expectancy of elderly patients. Due to the limitations of current treatment options for OA, mesenchymal stem cells (MSCs) and their exosomes have emerged as promising therapeutic strategies. Among these, stem cells from human exfoliated deciduous teeth (SHEDs) and their exosomes have gained notable attention because of their easy accessibility, low immunogenicity, and fewer ethical concerns. Numerous studies have highlighted their significant advantages in immune regulation, cartilage repair, and osteogenesis promotion. This paper summarizes the biological characteristics of SHEDs and their exosomes, along with their potential mechanisms in treating osteoarthritis, aiming to provide a reference for their clinical application and treatment of OA.*

Keywords: *Osteoarthritis; Mesenchymal stem cells; Stem cells from human exfoliated deciduous teeth; Human deciduous tooth pulp stem cells; Exosomes; Cell-free therapy*

1. Introduction

Osteoarthritis (OA) is a chronic, progressive arthritic disease characterized by degenerative changes in articular cartilage and the formation of osteophytes at the joint margins. It is the most common arthritic condition globally. From a global epidemiological perspective, the incidence of OA increased by approximately 113.25% from 1990 to 2019, with the highest percentage of cases reported in China[1]. As patients age and are exposed to risk factors such as obesity and systemic inflammation, they experience a gradual decline in joint function and the ability to perform activities of daily living, eventually leading to disability or death. Existing treatment strategies, including conservative treatments like oral cartilage supplements, non-steroidal drugs, intra-articular injections of hyaluronan or platelet-rich plasma, and surgical interventions such as arthroscopic debridement and high tibial osteotomy, can alleviate pain and improve some joint function but cannot repair the damaged joint. In recent years, advances in our understanding of OA and developments in bioengineering have highlighted the significant advantages of stem cells and their exosomes in treating musculoskeletal diseases.

Stem cells are derived from early embryonic or adult tissues with the ability to divide[2]. Mesenchymal stem cells (MSCs), the most commonly used adult stem cells, are widely distributed in adult tissues or organs. They mediate tissue repair and immune response regulation through endocrine or paracrine mechanism[3]. Among these mechanisms, exosomes play a crucial role. Exosomes contain substances such as messenger RNA (mRNA), microRNA (miRNA), and functional proteins[4]. Exosomes can regulate receptor cell function by binding directly to their membranes and releasing substances, or by activating signaling pathways via receptor pathways on the cell membrane[5].

ISSN 2618-1584 Vol. 7, Issue 1: 70-78, DOI: 10.25236/FMSR.2025.070111

Exosomes from different cellular sources exhibit distinct physicochemical properties and biological functions.

Dental pulp stem cells (DPSCs) were first successfully isolated by S. Gronthos et al. in the early 21st century[6]. Compared to other sources of MSCs, DPSCs exhibit superior proliferation, directed differentiation, and neural stem cell properties[7]. Recently, stem cells from human exfoliated deciduous teeth (SHEDs) have gained significant attention due to their easy accessibility, minimal ethical concerns, and excellent biological functions, making them a hot topic in stem cell therapy research[8]. This article provides an overview of the function of MSCs and their application in cartilage repair, the biological properties and potential therapeutic mechanisms of MSCs exosomes, and the role and therapeutic potential of SHEDs exosomes in OA, with the aim of providing new ideas for the clinical treatment of OA.

2. Functions and application in the repair of cartilage defects of MSCs

2.1 Anti-inflammatory effects of MSCs

Although OA is defined as a group of degenerative diseases, the inflammatory microenvironment around the joints is a key causative factor in cartilage pathology. Pathologically, synovial inflammation is characterized by the pathological proliferation of blood vessels and infiltration of inflammatory factors[9,10]. The anti-inflammatory effect of stem cells is primarily realized through the regulation of the host immune response. MSCs can directly inhibit the inflammatory response by secreting anti-inflammatory cytokines such as interleukin 10 (IL-10) and tumor necrosis factor alpha-stimulated gene/inducible protein-6[11]. MSCs can also promote the transformation of T cells into regulatory T cells and enhance their inhibitory function, thereby reducing the autoimmune response and inflammation[12]. Additionally, MSCs can indirectly influence the inflammatory environment by promoting tissue repair and regeneration, thereby enhancing the anti-inflammatory capacity of tissues.

2.2 Immunomodulatory effects of MSCs

MSCs can immunomodulate the host immune environment by altering its cytokine network. For example, they can influence cytokine expression and modify the migration and infiltration patterns of immune cells, thus playing a therapeutic role in the disease microenvironment. Macrophages, present in almost all tissues, are essential for regulating body homeostasis and are divided into two subtypes: M1 (pro-inflammatory) and M2 (anti-inflammatory)[13]. In OA, M1 is activated throughout the process, while M2 polarization toward M1 is promoted, accelerating synovial inflammation and causing periarticular swelling and pain. Previous studies have found that MSCs and their derived exosomes can modulate the body's inflammatory response by inducing a shift of macrophages toward anti-inflammatory isoforms and inhibiting the release of related pro-inflammatory factors[14]. In an in vitro experiment, by measuring the expression levels of M1 and M2 markers in bone marrow-derived macrophages, it was found that pro-inflammatory factors such as IL-6 and IL-1β significantly decreased after co-culture with bone marrow mesenchymal stem cells (BMMSCs) for a certain period of time, while the expression of IL-10 was upregulated, indicating that MSCs have a potential mechanism to promote the transition from M1 to M2 phenotype and enhance M2 expression[15].

2.3 MSCs in cartilage repair and regeneration

Due to the lack of blood vessels, nerves, and lymphatic tissue, articular cartilage has a limited ability to repair itself. Additionally, the inflammatory microenvironment further aggravates cartilage damage and induces fibrocartilage differentiation from normal cartilage, making autologous cartilage repair extremely difficult[16]. Not only do MSCs possess potent immunomodulatory and anti-inflammatory activities, but their potential application in cartilage injury repair should not be overlooked.

In a human trial, four patients with moderate to severe OA showed improvement in knee flexion-extension mobility, self-rated pain, and walking distance after intra-articular injection of autologous bone marrow-derived MSCs into the knee joint cavity[17]. Kim et al. found that both human bone marrow-derived MSCs and human umbilical cord matrix-derived MSCs promoted cartilage regeneration in vitro. They observed upregulation in the expression of growth factors such as fibroblast growth factor-2, transforming growth factor-beta (TGF-β), and insulin-like growth factor-1, which act

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as stimulators of cartilage regeneration and injury repair[18]. The matrix metalloproteinases (MMPs) family is associated with early cartilage matrix degradation, particularly MMP13, which accelerates cartilage loss and surface collapse by targeting type II collagen cleavage, leading to rapid cartilage matrix degradation. Additionally, MMPs mediate downstream cartilage damage and matrix degradation through various regulatory mechanisms, such as tissue inhibitor of metalloproteinases (TIMPs), runt-related transcription factor 2 (Runx2), and TGF-β[19,20]. In contrast, MSCs inhibit the expression of MMPs in cartilage injury by secreting TIMPs, thereby protecting the cartilage matrix[21].

3. Biological characterization and potential therapeutic mechanisms of exosomes

3.1 Biological characterization of exosomes

Extracellular vesicles are nanoscale lipid bilayer membrane vesicles released by various cells in the human body and are classified into exosomes, microvesicles, and apoptotic vesicles based on different physicochemical properties and functions. Exosomes, a special form of extracellular vesicles, have an average diameter of 30-100 nm and are widely present in all cell lineages. Exosomes contain numerous nucleic acids and functional proteins. These biologically active substances act on target cells through a series of delivery and release processes, exerting corresponding biological functions[22]. The formation of exosomes can be divided into the following stages: (1) invagination of the cell membrane to form early endosomes; (2) invagination of the endosomal membrane, aggregation, and encapsulation of various biologically active proteins, nucleic acids, etc., to form multivesicular bodies; and (3) fusion of mature multivesicular bodies with receptor cell membranes after delivery, releasing exosomes and triggering downstream signaling and cascade reactions[23].

3.2 Anti-inflammatory and immunomodulatory effects of exosomes

In an in vitro study, pre-treated exosomes transformed macrophages into specific anti-inflammatory phenotypes (CD206, Arg-1, B7H4, and CD138), and miRNA-16 and miRNA-21 enriched in exosomes could target and regulate macrophage polarization to anti-inflammatory M2 subtypes[24]. In addition, exosomes significantly downregulate IL-1β-induced cartilage matrix degradation and chondrocyte apoptosis, protecting cartilage by ameliorating the early inflammatory microenvironment in the joints[25]. When vascular endothelial cells are damaged, low-density lipoprotein deposited in the vascular endothelium recruits numerous monocytes, which gradually differentiate into macrophages and produce various pro-inflammatory factors (TGF-α, IL-1β), contributing to the emergence of endothelial inflammation and ultimately leading to atherosclerosis. Comparison of the expression levels of relevant pro-inflammatory factors in bone marrow macrophage exosomes with and without IL-4 pretreatment revealed that pretreated exosomes were able to control vascular inflammation by significantly enhancing macrophage polarization toward the M2 phenotype, down-regulating IL-1β expression, and targeting the inhibition of the nuclear factor kappa-B (NF-κB) pathway, providing new insights into the treatment of atherosclerosis[26].

The role of exosomes in immunomodulation is widely recognized, so can exosomes loaded with bioactive materials achieve the same effect? In a mouse spinal cord injury model, exosome-loaded electroconductive hydrogel promotes M1 to M2 macrophage polarization through targeted modulation of the NF-κB pathway, inhibiting the early inflammatory response to spinal cord injury and promoting neuronal and associated axon regeneration, thereby aiding in recovery from early spinal cord injury[27]. In the field of osteoarthritis treatment, a bilayer hydrogel loaded with diclofenac sodium and bone marrow MSC exosomes has been shown to alleviate the inflammatory microenvironment at the site of cartilage defects caused by the overexpression of reactive oxygen species[28]. This provides favorable conditions for cartilage regeneration and repair. Overall, both the use of single exosomes and exosomes loaded with other bioactive materials exhibit favorable anti-inflammatory and immunomodulatory activities.

3.3 Cartilage repair by exosomes

One of the most critical topics in current osteoarthritis treatment research is how to effectively repairing cartilage damage and slowing cartilage degeneration. Pro-inflammatory factors such as IL-1β, tumor necrosis factor-α (TNF-α), and IL-6 play a crucial role in osteoarthritis progression[29]. He et al. demonstrated that exosomes reversed IL-1β-induced inhibition of chondrocyte proliferation and migration, confirmed by further migration experiments[30]. In a mouse OA model, exosome injections

ISSN 2618-1584 Vol. 7, Issue 1: 70-78, DOI: 10.25236/FMSR.2025.070111

via the articular cavity down-regulated MMP13 and up-regulated COL2A1 in the articular cartilage compared to control and OA groups, suggesting that exosomes mediate cartilage repair. Further studies indicated that miRNAs enriched in exosomes are involved in intercellular communication and signaling, down-regulating downstream pathways to mediate cartilage injury progression or repair. Different miRNAs from various exosome sources are involved in cartilage repair through specific mechanisms.

miRNAs are endogenous non-coding nucleotides, typically 22 nucleotides long, recognized, encapsulated, and delivered by exosomes to target cells to regulate downstream gene expression. The miRNA type in exosomes depends on recognition molecules on the exosome membrane, the endosomal sorting complex, and specific miRNA binding sites[31]. Research on MSC-derived exosomes in cartilage injury repair focuses on inhibiting the inflammatory cartilage microenvironment, maintaining cartilage homeostasis, enhancing cartilage regeneration, and preventing cartilage degradation. Hu et al. found that exosomes isolated from mouse cartilage MSCs significantly increased chondrocyte viability and migration, upregulated type II collagen and glycosaminoglycan expression, and improved cartilage regeneration and repair[32]. Additionally, miR-23a-3p released from these exosomes was able to target the inhibition of PTEN expression, leading to the upregulation of AKT, which promotes chondrocyte proliferation. Maintaining the balance between extracellular matrix synthesis and degradation is crucial for cartilage homeostasis. An imbalance in cartilage homeostasis is a key factor in the pathogenesis of osteoarthritis. The mammalian target of rapamycin (mTOR) signaling pathway, which enhances cartilage autophagy and limits IL-1β expression, plays an important role in maintaining chondrocyte homeostasis[33]. Human adipose mesenchymal stem cell-derived exosomes have been shown to deliver miR-199a-3p to inhibit the downstream mTOR signaling pathway. This enhances autophagy in osteoarthritic cartilage, promotes cartilage synthesis, and protects cartilage in the osteoarthritis microenvironment, significantly slowing the progression of cartilage damage[34].

The WNT-β-catenin signaling pathway, along with its key regulatory nodes RUNX2 and Wingless-like 5A (WNT5A), plays a significant role in the pathogenesis of osteoarthritis[35]. In Li's study, human adipose MSC-derived exosomes were found to regulate chondrocyte and fibroblast functions, inhibit chondrocyte apoptosis and synovial fibrosis, and enhance cartilage synthesis and regeneration. This was achieved through the delivery of miR-376c-3p, which targets and negatively regulates downstream WNT3 or WNT9a proteins, thereby inhibiting the WNT-β-catenin signaling pathway[36]. Additionally, when mouse adipose MSC-derived exosomes were co-cultured with IL-1β-pretreated mouse chondrocytes, the expression levels of inflammatory factors were significantly altered. The exosomes delivered miR-338-3p, which targeted and inhibited the overexpression of RUNX2 in chondrocytes. This mechanism promoted chondrocyte proliferation and alleviated inflammation, demonstrating the potential of exosome-mediated miRNA delivery in modulating key signaling pathways involved in osteoarthritis progression and repair[37].

Pro-inflammatory factors such as IL-1β, IL-6, and TNF-α produced by M1-type macrophages create an inflammatory microenvironment at sites of cartilage injury or defect. This environment exacerbates cartilage degradation and chondrocyte apoptosis while also slowing the repair process of cartilage injury. Zhou et al. demonstrated that exosomes derived from human synovial fibroblasts could inhibit the expression of IL-1β, IL-6, and TNF-α in mouse OA articular cartilage, thereby alleviating cartilage inflammation, inhibiting cartilage degeneration, and stabilizing subchondral bone structure[38]. This study further suggested that miR-126-3p delivered by exosomes is a key regulator in driving the alleviation of inflammation. Similarly, Lai's study39 found that human synovial fibroblast exosomes could alleviate the inflammatory microenvironment of the synovium by delivering miR-214-3p, which offers potential for cartilage repair[39]. Moreover, exosomes and their delivered miRNAs can protect cartilage by targeting and regulating the expression of TNF receptor-associated factor 6 (TRAF6) and high mobility group protein B1 (HMGB1)[40,41].

4. Role and therapeutic potential of SHEDs exosomes

4.1 Biological characterization of SHEDs exosomes

Since the first successful isolation of DPSCs from the pulp of human permanent teeth, MSCs from other dental tissues have also been identified. These include SHEDs[42], dental follicle stem cells[43], and periodontal ligament stem cells[44]. Among these, SHEDs have garnered significant attention due to their easy accessibility, minimal ethical concerns, and exceptional biological functions, making them a prominent focus in current stem cell therapy research.

ISSN 2618-1584 Vol. 7, Issue 1: 70-78, DOI: 10.25236/FMSR.2025.070111

As members of the MSC family, SHEDs characteristically express a range of biological phenotype markers. These include not only the MSC markers CD73, CD90, CD44, STRO-1, CD106, OCT4, and NANOG but also osteoblast markers such as Alpl, Runx2, CBFA1, and Collagen I, as well as chondrocyte markers Col10a1 and Acan[45]. SHEDs have been found to express higher levels of the early MSC marker CD146 and the endothelial progenitor cell marker CD105 compared to DPSCs, suggesting that SHEDs possess superior differentiation potential and biological properties[46]. Based on these characteristics, numerous in vivo and ex vivo studies have been conducted to explore the osteogenic properties of SHEDs and their exosomes, along with the mechanisms underlying cartilage damage repair.

4.2 Anti-inflammatory and immunomodulatory functions of SHEDs exosomes

SHEDs have demonstrated a significant advantage in regulating the dynamic balance between regulatory T cells (Treg) and helper T cells (Th17) in systemic lupus erythematosus compared to BMMSCs. Specifically, SHEDs can more significantly upregulate the Treg/Th17 ratio[47]. Tregs are known to regulate autoimmunity by suppressing the expression of related pro-inflammatory factors[48]. Previous studies have indicated that the dynamic balance between the anti-inflammatory effects of Treg and the pro-inflammatory effects of Th17 can influence the onset and progression of various inflammatory diseases, including OA[49]. In Muhammad's study, significant reductions in the levels of pro-inflammatory factors IL-6 and IL-10 expressed by chondrocytes pretreated with IL-1β were observed in SHEDs-containing conditioned medium compared to the control group. SHEDs were found to downregulate the mRNA expression of NF-κB, thereby attenuating the expression of downstream inflammatory factors and markers of cartilage degradation[50]. These findings suggest that SHEDs possess favorable anti-inflammatory activity.

Long-term chronic pain is the primary reason OA patients seek medical care, which may be closely related to central sensitization and the infiltration of peripheral inflammatory factors[51]. Upregulation of chemokine (C-C motif) ligand 2 expression leads to pain-associated neuronal excitation and macrophage activation, resulting in persistent pain or nociceptive hypersensitivity[52]. Exosomes have shown promise in promoting macrophage polarization, reducing the expression, delivery and release of relevant pro-inflammatory factors, and decreasing the expression of cytokines upregulated in response to inflammatory factor stimulation, offering new perspectives for OA pain relief[53].

4.3 Role of SHEDs exosomes in the repair of cartilage damage

In Wei's studies, bone marrow stromal cells were co-cultured with SHEDs exosomes (experimental group) and SHEDs (control group). Initially, the control group showed increased levels of Alp and Runx2-related genes, while the experimental group exhibited no significant changes. However, over time, the SHEDs exosomes demonstrated their osteogenic properties. After two weeks, the bone marrow stromal cells in the experimental group began to differentiate into osteoblasts, expressing high levels of osteoblastic markers such as Runx2 and Osx[54]. This finding further confirms the crucial role of the TGF-β signaling pathway in bone differentiation and metabolism. SHEDs exosomes can alleviate inflammation by inhibiting the release of pro-inflammatory factors IL-6 and IL-8 and suppressing the expression of catabolic markers MMP13 and ADAMTS5, which mediate cartilage damage. This helps maintain cartilage homeostasis. In-depth studies revealed that miR-100-5p, enriched in SHEDs exosomes, is a crucial mechanistic node, inhibiting cartilage inflammation through the targeted suppression of the downstream mTOR signaling pathway[55]. Furthermore, SHEDs exosomes can promote osteogenic differentiation by enhancing Wnt and bone morphogenetic protein signaling pathways, which can alleviate bone defects in periodontitis patients[56]. This suggests promising prospects for cartilage restoration therapy in OA patients.

4.4 Perspectives of SHEDs exosomes in the treatment of OA

As a cell-free therapy, SHEDs exosomes can circumvent the inherent complications associated with previous cell-based therapies, such as stem cells or MSCs, which include microvascular occlusion, pulmonary embolism, immune rejection, cardiac arrhythmias, ectopic ossification, and abnormal transformation of transplanted cells[57-60]. Exosomes, being vesicle components with a nanometer diameter, do not express major histocompatibility complexes on their surfaces. This characteristic not only reduces the risk of microvascular occlusion and prevents the formation of non-target or tumor cells through abnormal expansion in the body but also enables miRNAs, proteins, and other substances

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contained in exosomes to be directly targeted. These components can regulate downstream transcription and expression or be delivered to target cells, exerting beneficial anti-inflammatory, osteogenic, and cartilage repair effects without provoking an immune response[61].

SHEDs exosomes have the unique advantage of being derived from human deciduous teeth, a previously neglected source widely available and easily accessible, thus resolving many ethical issues. As cell-free components, exosomes exhibit a low rate of metabolism and do not pose the risk of unpredictable cellular mutations or proliferation. Their endogenous origin allows for on-demand use, with a variety of administration routes available, including local injection into the joint cavity, vascular administration, and intramuscular administration. Additionally, exosomes are easy to store, maintaining their biological activity and properties even after long-term storage or freezing, ensuring their efficacy in therapeutic applications[62].

However, in the current research on the application of SHEDs exosomes to orthopedic diseases, several urgent issues need to be addressed: (1) Simplifying and standardizing exosome separation and extraction methods to improve efficiency and purity, and effectively differentiate exosomes from other extracellular vesicles. Current extraction strategies include ultracentrifugation, ultrafiltration, polymer precipitation, immunoaffinity separation, microfluidics, and chromatography. However, the lack of uniform standards has led to inconsistencies in purity and biological properties, which affect clinical efficacy[63]. (2) Although numerous animal experiments have investigated the therapeutic mechanisms of exosomes in osteoarthritis, there is a lack of sufficient animal data and assessment of the feasibility of extending these experiments to humans[64,65]. (3) Developing methods to purify and increase the amount of miRNA in exosomes while ensuring safety, to enhance the expected therapeutic benefits. (4) Exploring the potential of using bioactive materials as carriers to deliver exosomes to articular cartilage in a targeted manner, comparing the differences with exosome-only therapy, and assessing their corresponding biological effects.

5. Future research directions and challenges

SHEDs and their derived exosomes have garnered significant attention due to their unique and potent biological properties, including immunomodulation, promotion of osteogenesis, mediation of cartilage damage repair, and inhibition of inflammatory expression. These features position them as a promising new strategy for the treatment of OA. As a cell-free therapy, their safety, efficacy, and convenience have also been confirmed. Future research should focus on unifying the isolation and extraction standards of exosomes, optimizing the miRNA content within them, and obtaining sufficient animal data to establish a solid foundation for human trials. This will help to elucidate the exact therapeutic mechanisms and evaluate their efficacy.

Acknowledgements

The Fundamental Research Funds for the Central Universities (21623311).

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ISSN 2618-1584 Vol. 7, Issue 1: 70-78, DOI: 10.25236/FMSR.2025.070111

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