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Therapeutic Potential of Human Mesenchymal Stem Cells in Osteoarthritis

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Abstract

Osteoarthritis (OA) is a degenerative joint disease characterized by progressive cartilage breakdown, inflammation, and loss of joint function. While current treatments primarily target symptom relief, they fail to halt or reverse disease progression. Human mesenchymal stem cells (hMSCs) have emerged as promising regenerative agents due to their dual capacity for chondrogenic differentiation and immunomodulation. This review examines the therapeutic potential of hMSCs in OA treatment, emphasizing their biological mechanisms, clinical relevance, and translational barriers. Preclinical evidence highlights that in addition to their differentiation into cartilage-forming cells, hMSCs exert potent paracrine effects through the secretion of cytokines, growth factors, and extracellular vesicles such as exosomes. Studies demonstrate that these vesicles play a central role in reducing inflammation, protecting cartilage matrix integrity, and promoting tissue repair. Adjunctive interventions like low-intensity pulsed ultrasound (LIPUS) further enhance the chondrogenic efficacy of hMSCs, offering combinatorial strategies for improving therapeutic outcomes. Nevertheless, translational challenges persist, including donor variability, inconsistent manufacturing protocols, and the absence of standardized potency assays. As research advances, exosome-based therapies are gaining traction

as safer, cell-free alternatives that preserve the functional benefits of hMSCs while addressing many logistical and regulatory concerns. Collectively, these findings suggest that hMSCs—particularly through paracrine and exosome-mediated mechanisms—represent a promising avenue in the development of disease-modifying treatments for osteoarthritis.

Keywords: osteoarthritis, mesenchymal stem cells, exosome, cartilage regeneration

Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disease marked by the progressive deterioration of articular cartilage, changes in subchondral bone, and inflammation of the synovial membrane (Arthritis Foundation, 2018; WHO, 2023). As the most prevalent form of arthritis, OA primarily affects weight-bearing joints such as the knees, hips, and spine, causing pain, stiffness, and reduced mobility—symptoms that significantly impair quality of life (Arthritis Foundation, 2018; CDC, 2024).

Globally, OA has become a leading musculoskeletal condition, with approximately 528 million individuals affected as of 2019, resulting in 19 million years lived with disability (YLDs) and ranking among the top contributors to disability worldwide (WHO, 2023; Vos et al., 2020). More recent data from the GBD 2020 study report an estimated 595 million cases—a nearly 132% increase since 1990—with projections indicating this number could approach 1 billion by 2050 due to demographic changes and rising obesity rates (Cieza et al., 2023).

Current standard treatments for OA—including NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), physical therapy, and joint replacement surgery—are primarily aimed at symptom management and do not reverse underlying joint degeneration (CDC, 2024). In response to the limitations of conventional therapies, regenerative medicine has emerged as a potential solution to restore damaged joint structures. Among the various cellular approaches,

human mesenchymal stem cells (hMSCs) have garnered attention due to their capacity to differentiate into cartilage-forming chondrocytes and their secretion of bioactive factors involved in tissue repair and immunomodulation (Pittenger et al., 1999; Barry & Murphy, 2013). These multipotent stromal cells, originally characterized from adult bone marrow, have since been isolated from adipose tissue, synovium, and umbilical cord sources, making them accessible and adaptable for clinical use (Barry & Murphy, 2013). In OA models, hMSCs have shown the potential to both regenerate cartilage and influence the joint's inflammatory environment, offering a dual mechanism of action (Barry & Murphy, 2013).

This shift in understanding highlights the need to critically evaluate both the direct regenerative and paracrine-mediated mechanisms of hMSCs in OA treatment. As research advances, attention is increasingly directed toward the therapeutic potential of MSC-derived exosomes as cell-free alternatives to traditional stem cell transplantation (Zhou et al., 2024; Sun et al., 2024).

Given this growing interest in hMSCs for osteoarthritis therapy, this review critically evaluates the biological mechanisms, therapeutic efficacy, and translational challenges of hMSC-based interventions in OA**.** Emphasis is placed on dissecting findings from both preclinical studies and early-stage clinical trials, with a focus on clarifying how hMSCs function within the joint environment and the obstacles that must be addressed before they can become a reliable disease-modifying treatment.

Discussion

hMSC-Based Cartilage Regeneration and the Role of LIPUS Stimulation

Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) have demonstrated a capacity for articular cartilage regeneration through both chondrogenic differentiation and immunomodulatory activity. Recent findings by Chen et al. (2023) provide compelling in vitro and in vivo evidence that low-intensity pulsed ultrasound (LIPUS) significantly enhances the differentiation of hUC-MSCs into chondrocytes, as measured by upregulated expression of key cartilage markers such as SOX-9, collagen type II (COL-II), and aggrecan (ACAN). The study confirmed that LIPUS exposure at 70 mW/cm² for 20 minutes daily over seven days led to statistically significant increases in proteoglycan production, Alcian blue staining intensity, and gene expression levels associated with chondrogenesis (Chen et al., 2023, pp. 6–8).

A central mechanism underlying this enhanced differentiation is the suppression of the tumor necrosis factor alpha (TNF-α) signaling pathway. Transcriptomic analysis and quantitative polymerase chain reaction (qPCR) results from the same study showed that LIPUS treatment reduced the expression of TNF-α, interleukin-1 beta (IL-1β), and C-X-C motif chemokine ligand 8 (CXCL8) in hUC-MSCs. Notably, cells pre-treated with exogenous TNF-α exhibited inhibited differentiation, which was reversed upon subsequent LIPUS application, restoring SOX-9 and COL-II expression and proteoglycan production (Chen et al., 2023, pp. 10–12). This evidence highlights the dual benefit of LIPUS in both promoting chondrogenesis and mitigating inflammatory inhibition.

The therapeutic relevance of these findings was further validated through a rat cartilage defect model. Rats treated with both hUC-MSCs and LIPUS displayed significantly more mature cartilage regeneration by week six, as indicated by Safranin-O staining and COL-II

immunostaining, compared to control or single-treatment groups. CD44-positive cells—used to track human MSCs—were retained in the joint environment post-transplantation, confirming in vivo survival and integration (Chen et al., 2023, pp. 13–15).

This combinatorial approach addresses the twofold challenge of cartilage repair: insufficient endogenous regeneration and inflammation-induced degeneration. By downregulating pro-inflammatory cytokines and enhancing chondrogenic gene expression, LIPUS offers a non-invasive, bio-safe adjunct to MSC transplantation. These findings establish a mechanistic basis for future clinical translation, particularly in cases where osteoarthritis pathology involves heightened inflammatory responses.

Paracrine Signaling and Immunomodulatory Mechanisms of MSCs

Beyond direct differentiation, human mesenchymal stem cells (hMSCs) exert substantial therapeutic effects via paracrine signaling and immune modulation. As shown by Zhang et al. (2024), hMSCs secrete a wide array of cytokines, chemokines, and growth factors that act on surrounding tissue to reduce inflammation, protect cartilage matrix integrity, and promote tissue repair. These secreted factors include interleukin-10 (IL-10), transforming growth factor beta (TGF-β), prostaglandin E2 (PGE2), and hepatocyte growth factor (HGF), which act synergistically to shift macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, inhibit effector T-cell activation, and support regulatory T-cell function (Zhang et al., 2024, p. 2–4).

Emerging consensus suggests that the therapeutic efficacy of mesenchymal stem cells (MSCs) is primarily mediated by paracrine signaling rather than long-term engraftment or survival in host tissues. As Galipeau and Sensebé (2018) explain, MSCs exert their effects by

secreting cytokines, morphogens, and exosomes that modulate the behavior of surrounding immune and structural cells. Notably, their immunomodulatory functions are highly context-dependent—shaped by inflammatory cues in the host environment—and can vary significantly based on donor variability and manufacturing processes (Galipeau & Sensebé, 2018, pp. 825–826).

Figure 1

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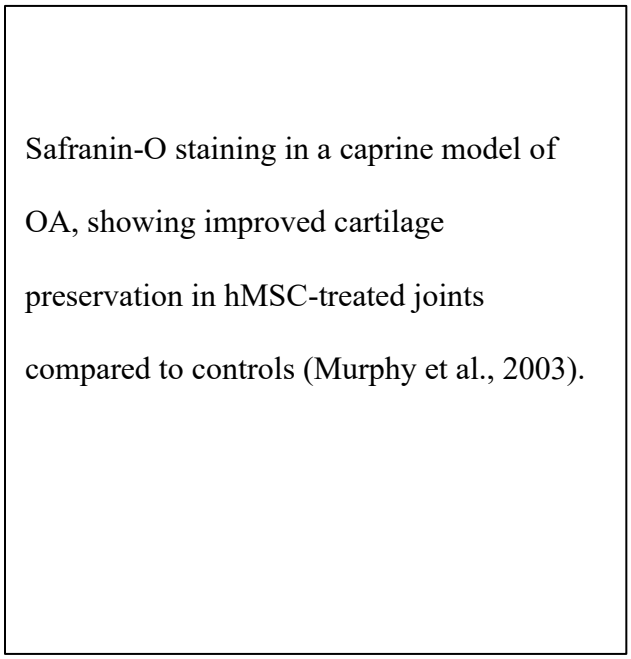

Safranin-O staining in a caprine model of OA, showing improved cartilage preservation in hMSC-treated joints compared to controls (Murphy et al., 2003).

Murphy et al. (2003) demonstrated that intra-articular injection of autologous bone marrow–derived MSCs in a caprine model led to significant improvement in cartilage repair compared to controls, as shown by Safranin-O staining in Figure 1, and gross morphological scoring (Murphy et al., 2003). Histological sections revealed that MSC-treated joints exhibited

reduced cartilage degradation and improved surface characteristics compared to controls, including “less damage to the articular surface and less evidence of osteophytic changes” (Murphy et al., 2003, p. 3470). The study also reported that MSCs were detected primarily at the surface and within neomeniscal tissue following injection, and noted that “engraftment of the transduced cells in the neomeniscus occurred without evidence of an immune response at this site or elsewhere in the joint” (p. 3472).

Exosome-Mediated Cartilage Protection

Recent studies underscore the promise of exosome-based therapies in osteoarthritis (OA). Zhou et al. (2024) conducted a meta-analysis of 20 in vivo studies and reported that stem cell-derived exosome treatment significantly reduced cartilage degeneration, as measured by OARSI (Osteoarthritis Research Society International) scores, and also improved osteophyte scores and chondrocyte counts in animal models. Their subgroup analysis showed that early-stage OA models responded more favorably, and once-weekly administration was more effective than multiple injections per week. They also found that exosomes extracted using kit-based methods showed a trend toward greater therapeutic efficacy. Sun et al. (2024) further support these findings, explaining that MSC-derived exosomes modulate inflammation by downregulating pro-inflammatory cytokines such as IL-1β and TNF-α and enhance cartilage protection through mitochondrial transfer and matrix regeneration mechanisms.

A growing body of research indicates that MSC-derived exosomes are the principal effectors of paracrine signaling in osteoarthritis treatment. Rather than relying on long-term engraftment, MSCs exert therapeutic effects by secreting extracellular vesicles enriched with bioactive molecules such as microRNAs, mRNAs, proteins, and lipids. Galipeau and Sensebé (2018) note that the functionality and potency of MSCs may be affected by factors such as

manufacturing methods, metabolic fitness, and donor-specific responsiveness to stimulation, particularly regarding expression of key effector pathways like IDO. Zhou et al. (2024) confirmed through a meta-analysis that exosome therapy led to significant reductions in OARSI scores and improved cartilage and chondrocyte outcomes. Sun et al. (2024) further elaborate that MSC-derived exosomes modulate inflammation by downregulating cytokines such as IL-1β and TNF-α and contribute to cartilage repair by delivering mitochondria and promoting extracellular matrix regeneration. These findings underscore the therapeutic potential of exosomes as cell-free agents that preserve the functional benefits of MSCs while mitigating risks associated with direct cell transplantation.

Translational Challenges in MSC-Based Therapies

Despite promising preclinical outcomes, several translational hurdles limit the clinical adoption of MSC-based therapies for osteoarthritis. As highlighted by Galipeau and Sensebé (2018), significant donor-to-donor variability, combined with differences in manufacturing processes and metabolic fitness of cultured MSCs, introduces inconsistencies in therapeutic potency (pp. 825–826). These issues are exacerbated by the use of cryopreserved MSCs, which frequently exhibit impaired viability and reduced immunomodulatory capacity post-thaw, potentially diminishing therapeutic efficacy (Galipeau & Sensebé, 2018, p. 826). Furthermore, the absence of standardized potency assays or predictive biomarkers complicates quality control and regulatory approval pathways for MSC-based products (Galipeau & Sensebé, 2018). Murphy et al. (2003) further emphasize limitations in current preclinical models. Although their caprine study demonstrated short-term cartilage repair without evidence of adverse immune response, long-term safety, engraftment durability, and scalability of MSC therapies remain uncertain (Murphy et al., 2003, p. 3472).

In parallel, regulatory and commercialization challenges arise from high production costs, strict oversight, and the complexity of ensuring consistency across large-scale cell therapy products (Galipeau & Sensebé, 2018). Together, these challenges emphasize the need for optimized manufacturing protocols, robust quality assessment tools, and long-term safety evaluations before MSC-based interventions can be widely implemented in clinical osteoarthritis management.

Conclusion

Human mesenchymal stem cells (hMSCs) hold significant promise as a disease-modifying treatment for osteoarthritis (OA), offering both regenerative and immunomodulatory benefits. While early research emphasized their direct differentiation into chondrocytes, increasing evidence now highlights the dominance of paracrine mechanisms—particularly the secretion of exosomes—as primary drivers of their therapeutic efficacy. These bioactive vesicles, enriched with anti-inflammatory and matrix-protective factors, enable hMSCs to modulate the joint environment and promote cartilage preservation without requiring long-term engraftment.

Findings from Chen et al. (2023) demonstrate that adjunctive strategies such as low-intensity pulsed ultrasound (LIPUS) can enhance hMSC chondrogenic differentiation and counteract inflammatory inhibition, supporting the potential of combination approaches to optimize cartilage repair. Moreover, studies by Zhang et al. (2024), Zhou et al. (2024), and Sun et al. (2024) reveal the immunomodulatory functions of hMSCs and the therapeutic potential of exosome-based treatments, providing robust preclinical support for transitioning toward cell-free MSC therapies.

However, significant translational challenges remain. As Galipeau and Sensebé (2018) emphasize, donor variability, inconsistent manufacturing processes, metabolic fitness of cultured

MSCs, and post-thaw viability loss create substantial barriers to standardization and scalability. The lack of validated potency assays and predictive biomarkers further complicates clinical translation and regulatory approval. Additionally, as highlighted by Murphy et al. (2003), long-term safety, sustained engraftment, and the durability of therapeutic outcomes have yet to be conclusively demonstrated in large-animal models or human trials.

To realize the clinical potential of MSC-based interventions for OA, future research must focus on overcoming these challenges by establishing standardized production protocols, refining quality control metrics, and conducting rigorous long-term safety studies. In parallel, advancing exosome-based, cell-free strategies could address many of the logistical and safety concerns inherent to live-cell therapies.

In conclusion, while hMSC therapies for OA remain at an early translational stage, the accumulating preclinical evidence positions them—especially via paracrine and exosome-mediated mechanisms—as a promising frontier in regenerative medicine. Continued multidisciplinary efforts will be essential to transform this potential into safe, standardized, and effective treatments for osteoarthritis patients.

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