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Research Progress on the Prevention and Treatment of Osteoarthritis with Mesenchymal Stem Cells

Bo Shen[1], Hua Guo[2,*], HuiLing Cao[3]

[1]The Second Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang, 712046, Shaanxi, China
[2]Department of Orthopedics, Xi'an No.5 Hospital, Xi'an, 710082, Shaanxi, China
[3]Xi'an Medical University, Xi'an 710021, Shaanxi, China
Correspondence Author

Abstract: ***Osteoarthritis (OA) is characterized by degeneration of joint cartilage and inflammation of the synovium. Current drugs or surgeries only provide symptomatic treatment and cannot reverse cartilage damage. Moreover, long-term use of these treatments carries a high risk of cardiovascular problems. Mesenchymal stem cells (MSCs) can differentiate in situ into chondrocytes and secrete bioactive factors such as exosomes. By virtue of their self-renewal, multipotent differentiation and paracrine properties, they directly promote chondrocyte proliferation, inhibits apoptosis and matrix degradation, thereby restoring cartilage homeostasis. Furthermore, exosomal delivery of miRNAs and mRNAs repairs mitochondrial damage, induces M2 macrophage polarization, balances pro- and anti-inflammatory cytokines, and modulates autophagy, thereby reshaping the immune microenvironment. This review summarizes recent advances in the use of MSCs to retard osteoarthritis progression and mitigate pain, providing new insights for the development of safe, effective, and non-invasive cell-based and cell-free therapeutic strategies.***

Keywords: Mesenchymal stem cells, Osteoarthritis, Exosomes.

1. Introduction

Osteoarthritis (OA) is a common chronic degenerative joint disease. Its pathological manifestations are dominated by progressive cartilage degeneration and eventual loss, coupled with reactive osteophyte formation at sites of ligamentous attachment along the articular margins and within the subchondral bone, culminating in joint pain, stiffness, deformity, and functional impairment [1]. High-resolution magnetic resonance imaging enables clear visualization of joint space narrowing, osteophyte formation, and structural alterations in the articular cartilage. According to recent reports, China had the highest number of individuals with osteoarthritis in 2019 (132.81 million), followed by India (62.36 million) and the United States (51.87 million). Between 1990 and 2019, the age-standardized prevalence of osteoarthritis rose by 156.58% in China, 165.75% in India, and 79.63% in the United States; by 2019, global osteoarthritis affected 317.44 million women—substantially exceeding the 210.37 million men—and its prevalence rose steeply with age, peaking in the 60–64-year-old age cohort [2]. Currently, clinical management continues to rely predominantly on nonsteroidal anti-inflammatory drugs (NSAIDs), physiotherapy, and surgical intervention. However, these modalities afford only symptomatic pain relief and improved mobility without the capacity to reverse established cartilage damage. In the prolonged absence of effective disease-modifying intervention, end-stage patients inevitably require joint arthroplasty—an option constrained by the finite longevity of prosthetic implants—thereby further escalating the overall healthcare expenditure for degenerative joint diseases such as osteoarthritis. Accumulated evidence has demonstrated that mesenchymal stem cells (MSCs) possess potent immunomodulatory, anti-inflammatory, and regenerative properties, rendering them a promising therapeutic option for immune-mediated disorders. Continued theoretical refinement and technological advances in mesenchymal stem cell–based therapeutics have recently opened a novel avenue for the clinical management of osteoarthritis. This review consolidates current findings on mesenchymal stem cell-based interventions for osteoarthritis, aiming to inform future fundamental investigations and thereby accelerate their clinical translation.

2. Overview of Mesenchymal Stem Cells

MSCs are self-renewing, multipotent progenitors endowed with the capacity for multilineage differentiation, immunomodulation, and potent anti-inflammatory activity. They contribute to articular cartilage repair both through direct chondrogenic differentiation and through coordinated regulation of extracellular matrix (ECM) synthesis and the inflammatory milieu. In addition, MSCs exert paracrine actions—most notably via extracellular vesicles such as exosomes—that further modulate immune responses and suppress inflammation. Owing to their autologous origin, immune-privileged status, and minimal ethical or regulatory constraints, MSCs have been extensively employed in both preclinical investigation and clinical therapy for a broad spectrum of disorders, including diabetes mellitus, neural injury, and heart failure. Their diverse subtypes and high clinical compatibility make MSCs an ideal choice for osteoarthritic cartilage regeneration. Among the various sources, bone marrow-derived, adipose-derived, umbilical-cord-blood and Wharton's-jelly-derived, and synovial membrane-derived MSCs are the most extensively investigated; each subset offers distinct advantages for cartilage regeneration [3].

3. Mechanisms Underlying MSCs-Mediated Articular Cartilage Repair

3.1 Chondrogenic Differentiation of MSCs

MSCs primarily repair damaged articular cartilage by differentiating into chondrocytes. The chondrogenic potential of MSCs is underpinned by the expression of a characteristic array of surface markers—CD90 (which governs differentiation), stromal antigen-1 (mediating MSC trafficking), CD44 (a hyaluronate receptor critical for migration), and CD49b (integrin α2 facilitating adhesion and osteochondral lineage specification) —that collectively prime these cells for chondrocyte commitment [4]. Studies indicate that the reparative effects of MSCs on articular cartilage are mediated primarily through two complementary routes: first, MSCs stimulate resident chondrocytes to augment their metabolic activity or secrete bioactive factors that trigger the chondrogenic differentiation of the MSCs themselves [4]; second, MSC-derived exosomes (MSC-Exos) potently promote chondrocyte proliferation while simultaneously inhibiting apoptosis, thereby opening a novel, cell-free therapeutic avenue for cartilage regeneration. Investigations [4-6] have demonstrated that growth factors—including insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) —potently stimulate the chondrogenic differentiation of MSCs. Bone morphogenetic protein-6 (BMP-6), a member of the BMP family, has likewise been shown to potentiate the chondrogenic capacity of MSCs. Concurrently, co-culture of MSCs with articular chondrocytes simultaneously enhances the proliferative activity of the latter while suppressing their apoptotic response. Moreover, a growing body of evidence consistently demonstrates that MSC-derived exosomes (MSC-Exos) effectively attenuate cartilage degeneration: Jin [7] and Liu [8] reported that bone marrow MSC-derived exosomes (BMSC-Exos) suppress Interleukin 1β (IL-1β) – induced chondrocyte senescence and apoptosis by down regulating A Disintegrin and Metalloproteinase with Thrombospondin Motifs 5 (ADAMTS-5), the hypertrophic marker matrix metalloproteinase-13 (MMP-13), and runt-related transcription factor 2 (Runx2), while concurrently up-regulating type II collagen (Collagen II), the cartilage-specific gene collagen type II alpha 1 (Col2α1), and Aggrecan. It concurrently suppresses aberrant subchondral-bone remodeling and significantly increases trabecular bone volume fraction, trabecular number, and connectivity density. He et al. [9] demonstrated that BMSC-Exos counteracted IL-1β–induced down-regulation of transforming growth factor-β (TGF-β) and proliferating cell nuclear antigen expression, while also attenuating the up-regulation of the apoptotic marker caspase-3, thereby mitigating IL-1β–mediated suppression of chondrocyte proliferation and migration. An additional study [10] revealed that Wnt5a/b proteins carried by synovial membrane-derived MSC exosomes (SMSC-Exos) activate YAP (Yes-associated protein) via a non-canonical Wnt signaling axis, thereby enhancing chondrocyte proliferation and migration while simultaneously promoting extracellular-matrix secretion. Therefore, MSCs endowed with chondrogenic potential can exploit relevant factors to promote and accelerate their differentiation into chondrocytes, thereby repairing cartilage damage.

3.2 Modulation of the Extracellular Matrix

The capacity of MSCs to orchestrate ECM component synthesis while precisely balancing its anabolism and catabolism constitutes a critical determinant of successful cartilage repair. Tissue inhibitors of metalloproteinases (TIMPs) are pivotal regulators of ECM turnover, tissue remodeling, and cellular behavior, functioning to suppress the proteolytic activity of matrix metalloproteinases (MMPs) within the ECM [11]. MSCs restore cartilage homeostasis by rebalancing the matrix metalloproteinase-13/tissue inhibitor of metalloproteinases-1 (MMP-13/TIMP-1) ratio and attenuating the expression of hypertrophic chondrocyte markers. Furthermore, MSCs markedly down regulate the expression of MMP-13 and ADAMTS-5, thereby preventing cartilage degradation while concurrently enhancing type II collagen expression [12]. Concomitantly, MSCs diminish the transcription of matrix metalloproteinase-1 (MMP-1) and MMP-13 while up regulating suppressor of cytokine signaling (SOCS) [13] and hyaluronan synthase-1 mRNA, and down regulating hyaluronidase-1 (HYAL-1), thereby augmenting hyaluronic acid production and accelerating extracellular-matrix deposition [14]. SRY-box transcription factor 9 (SOX9) is the master transcriptional regulator of chondrogenesis. Its expression in chondrocytes activates ECM-specific genes and thereby promotes synthesis of matrix components such as type II collagen [15]. A substantial body of evidence demonstrates that MSC-Exos restore cartilage extracellular-matrix homeostasis by repressing v-ral simian leukemia viral oncogene homolog A [10], miR-29b-3p [16,17], and Wnt5a [18], while concurrently elevating the expression of type II collagen, aggrecan (ACAN), and the master chondrogenic transcription factor SOX9. Accordingly, MSCs safeguard articular cartilage by curbing extracellular matrix degradation and simultaneously promoting its de novo synthesis, thereby achieving reparative restoration of damaged cartilage.

3.2.1 Modulation of the Inflammatory Microenvironment

MSCs facilitate their own chondrogenic differentiation and thereby remediate injured articular cartilage through precise modulation of the inflammatory microenvironment. MSCs prevent apoptosis by suppressing the release of pro-inflammatory cytokines [19] and modulate immune cells through both direct cell–cell contact and paracrine secretion. MSCS up regulate the recruitment of monocytes toward an M2-like phenotype while curtailing M1-like infiltration [20], and can reprogram macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. MSCs polarize macrophages toward an anti-inflammatory phenotype, evidenced by elevated interleukin 10 (IL-10), diminished tumor necrosis factor-alpha (TNF-α) and interleukin 12 (IL-12), and reduced co-stimulatory CD86 [21]; concomitantly, they lower IL-1β and TNF-α while up regulating interleukin-1 receptor antagonist (IL-1Ra) [12]. Furthermore, elevated interleukin 6 (IL-6) levels activate IL-6/IL-6R signaling, thereby inducing the expression of chondrogenic genes in MSCs and driving their differentiation into chondrocytes [22]. MSCs attenuate cartilage damage by suppressing the release of pro-inflammatory mediators and, conversely, exploit selected inflammatory cues to transactivate chondrogenic genes within MSCs, thereby directing their differentiation into chondrocytes that restore the injured articular surface. A substantial and consistent body of evidence further demonstrates that MSC-Exos potently suppress the expression of pro-inflammatory cytokines. Work

by Huang [23] and Jin [24] have demonstrated that miR-206 and miR-9-5p carried in BMSC-Exos exert anti-inflammatory and chondroprotective effects through negative regulation of syndecan-1, leading to marked reductions in synovial levels of IL-1, IL-6, TNF-α, C-reactive protein, and oxidative stress indices (nitric oxide, malondialdehyde, inducible nitric oxide synthase (iNOS), cyclo oxygenase-2) while concurrently elevating superoxide dismutase activity. Dong et al. [25] further demonstrated that miR-127-3p encapsulated within BMSC-Exos selectively targets and represses CDH11 in chondrocytes, thereby interrupting Wnt/β-catenin signaling and downstream transcription of IL-6 and TNF-α, ultimately attenuating chondrocyte injury in osteoarthritis. In vitro work by Zhou [26] and Jiang [27] further indicates that BMSC-Exos suppress inflammatory responses through down regulation of TNF-α, IL-1β, IL-6, versican, MMP-13, mitogen-activated protein kinases, and nuclear factor-κB. Complementarily, studies from Luo's group [28] and Li's team [29] have respectively shown that miR-100-5p packed within stem-cell-exosomes from human exfoliated deciduous tooth pulp and miR-93-5p carried by adipose-derived MSC exosomes both effectively curtail pro-inflammatory cytokine expression.

3.2.2 Promotion of M2 Phenotype Macrophage Polarization

Studies [30,31] investigating MSC-Exos therapy for osteoarthritis have revealed that exosomes derived from human embryonic stem cell–derived MSCs significantly augment M2 macrophage infiltration while concomitantly reducing M1 macrophage accumulation at cartilage defect sites in rats. Furthermore, intra-articular injection of BMSC-Exos promotes the phenotypic transition of synovial macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 state, thereby suppressing inflammatory cytokine release and diminishing both synovial inflammatory cell infiltration and articular cartilage damage. Zavatti et al. [32] demonstrated that, when introduced during polarization toward M1 or M2 macrophage subsets, amniotic fluid MSC-derived exosomes restrained M1 polarization, as evidenced by reduced expression of CD86, iNOS, and interleukin-1 receptor 1 (IL-1R1), alongside elevated M2 macrophage markers CD163, arginase-1, and TGF-β. Concurrently, the exosomes augmented anti-inflammatory mediator release from unstimulated macrophages. Moreover, Wang's group [33] revealed that miR-135b enriched in BMSC-Exos by TGF-β1 priming down regulates MAPK6 expression, thereby diminishing the synovial M1 macrophage fraction while expanding the M2 macrophage population; this shift toward M2 macrophage polarization effectively restrains cartilage degradation.

3.2.3 Modulation of Autophagy

In vitro [34], miR-100-5p packaged within human infrapatellar fat pad MSC-derived exosomes attenuates mTOR signaling, thereby elevating the autophagosome marker lipidated form of microtubule-associated protein 1A/1B-light chain 3 (LC3-II) and accelerating degradation of the canonical autophagic substrate sequestosome 1 (SQSTM1/p62) in IL-1β-treated chondrocytes; this enhancement of protective autophagy restores catabolic–anabolic equilibrium within the chondrocytes. Additional investigations [29,35] have revealed that miR-429 and miR-93-5p carried by adipose-derived MSC-exosomes promote autophagy and ameliorate cartilage injury via targeted suppression of a disintegrin and metalloprotease-9 (ADAM9). Meanwhile, BMSC-Exos have been shown [36] to enhance autophagy in advanced glycation end-product–treated chondrocytes by down regulating dynamin related protein-1 (Drp1), thereby increasing the lipidated form of microtubule-associated protein 1A/1B-light chain 3/cytoplasmic form of microtubule-associated protein 1A/1B-light chain 3 (LC3-II/LC3-I) ratio and the expression of the autophagy regulator Beclin-1. Conversely, the long non-coding RNA KLF3-AS1 contained within BMSC-Exos suppresses autophagy in IL-1β-stimulated chondrocytes from an OA mouse model by targeting YBX1 and activating the PI3K/AKT/mTOR pathway, which lowers LC3-II/LC3-I and elevates SQSTM1/p62 expression [37].

4. Clinical Investigations of MSC-Based Therapy for Osteoarthritis

Recent clinical studies employing MSCs for osteoarthritis have demonstrated favorable outcomes in both inflammation control and chondrogenic differentiation, collectively suggesting that this approach represents a safe and effective therapeutic option.

4.1 Chondrogenic Changes

Extensive in vitro data demonstrate that MSC therapy attenuates cartilage degeneration. Direct intra-articular injection of adipose-derived stem cells (ADSCs), their ex vivo preconditioning, or their combination with scaffold/carrier suspensions consistently promotes ADSC chondrogenesis and ameliorates osteoarthritic symptoms. Jo et al. [38,39] and Freitag et al. [40] systematically compared the impact of ADSCs dose and injection frequency on knee osteoarthritis (KOA). At six months post-treatment, the high-dose cohort exhibited marked clinical improvement; arthroscopic and histological evaluations revealed superior cartilage regeneration relative to the medium- and low-dose groups. A two-year extension demonstrated durable efficacy in the high-dose cohort, whereas medium- and low-dose patients deteriorated after 12 months, indicating a positive dose–response relationship. A subsequent frequency trial showed that all intra-articular ADSC recipients improved at 12 months, but patients receiving two injections achieved significantly greater benefits than those given a single dose. Collectively, these data confirm that both higher cell numbers (1.0×10^8) and repeated injections enhance clinical outcomes without compromising safety. Jung [41] and Sun [42] further investigated fibrin-glue scaffolds and PLGA microsphere scaffolds loaded with human adipose-derived stem cells (hADSCs) plus TGF-β3 to promote the chondrogenic differentiation of ADSCs. Their experiments revealed that the fibrin-glue scaffold furnished a novel extracellular matrix that supported ADSCs proliferation and directed their differentiation into chondrocytes, thereby facilitating de novo cartilage formation. The concurrent delivery of hADSCs, TGF-β3, and PLGA microsphere scaffolds markedly potentiated articular cartilage regeneration and substantially diminished osteoarthritic severity. Additionally, a series of tissue-engineering investigations have demonstrated that

nanofiber scaffolds, hyaluronic acid hydrogels, and polycaprolactone/collagen nanoscaffolds all significantly enhance the chondrogenic commitment of umbilical cord–derived MSCs (UC-MSCs). Consequently, the integration of these biomaterials has further refined UC-MSC-based cartilage regeneration strategies [43,44]. Moreover, intra-articular administration of ADSCs has been shown to attenuate synovial hyperplasia, curtail cartilage destruction, and limit tendon-associated osteophyte formation, thereby retarding both the onset and progression of OA [45].

To enhance the efficiency of MSC homing to chondral lesions after transplantation, Kato et al. [46] co-implanted synovial membrane-derived MSC (SMSCs) with platelet-rich plasma (PRP) into osteoarthritic knees. The resulting SMSC–PRP suspension enabled rapid migration of cells to the defect, markedly amplifying cell-targeting efficiency; however, rapid PRP degradation limits sustained chondral repair. Alternatively, a three-dimensional tissue-engineered construct (TEC) composed exclusively of SMSCs, extracellular matrix, and autologous fibrillar collagen offers superior plasticity and cartilage adhesiveness [47], conforming precisely to the lesion. Because TEC contains only patient-derived cells and matrix, it carries a higher safety profile than approaches employing exogenous biomaterials. Arthroscopic implantation of the TEC into cartilage defects in patients with knee osteoarthritis yielded complete, stable filling at 24-month follow-up arthroscopy and MRI, with repair tissue histologically resembling hyaline cartilage.

4.2 Alterations in Inflammatory Cytokines

Studies have demonstrated that MSCs can lower circulating inflammatory mediators and alleviate pain in patients with OA. Hamdalla et al. [48] reported that intra-articular injection of bone marrow-derived MSC (BMSCs) markedly suppressed the expression of TNF-α, IL-1β, IL-6, NF-κB p50 within the NF-κB signalling cascade, thereby exerting a potent anti-inflammatory effect. In joints treated with BMSCs, IL-10 levels were concurrently elevated, immune responses attenuated, chondroprotection was enhanced, chondrocyte proliferation was increased and cartilage degeneration attenuated [49]. Furthermore, intra-articular administration of BMSCs in knee OA has been shown to reduce IL-12 concentrations and diminish macrophage infiltration, thereby attenuating synovial inflammation and improving passive range of motion in patients with advanced disease [50]. Conditioned medium from adipose-derived MSCs (ADSCs) has also been found to inhibit IL-1β production via the NF-κB pathway. Following intra-articular injection of icariin-primed ADSCs, significant reductions in TNF-α, IL-1 and nitric oxide were observed, accompanied by suppressed chondrocyte apoptosis [51]. Co-culture experiments revealed that ADSCs simultaneousiy to OA chondrocytes and synoviocytes down-regulated IL-1, IL-6 and TNF-α secretion [52]. Additionally, ADSCs secrete anti-inflammatory mediators such as IL-10 and IL-1Ra, and indirectly augment IL-10 production by promoting the expansion of immunosuppressive $CD4^{+}FOXP3^{+}$ T helper cells [53]. SMSC attenuate inflammation by upregulating TGF-β, IL-10 and IL-4, and by polarising T helper cells from a pro-inflammatory Th1 to an anti-inflammatory Th2 phenotype, thereby retarding knee OA progression [54]. SMSCs also release extracellular vesicles that elevate miR-26a-5p expression, resulting in decreased IL-1β, IL-6 and TNF-α levels, while concurrently activating the E2F1/PTTG1 axis to suppress inflammatory responses and mitigate cartilage damage [55].

5. Concluding Remarks

OA is among the most prevalent musculoskeletal disorders, and cartilage destruction constitutes its cardinal pathological feature. Achieving sustained and effective repair of damaged articular cartilage therefore remains the central therapeutic challenge. Continued elucidation of the molecular events that govern OA initiation and progression has propelled therapeutic strategies to the cellular level. MSCs, by virtue of their anti-inflammatory, immunomodulatory, autophagy-regulatory and apoptosis-regulatory capacities, can stimulate chondrocyte proliferation and promote cartilage matrix restoration, and are consequently regarded as a promising modality for reversing OA-associated degeneration. Both MSCs and MSC-derived extracellular vesicles (MSC-Exos) exert reparative effects by enhancing chondrocyte proliferation, promoting extracellular matrix synthesis, maintaining mitochondrial homeostasis, attenuating inflammation, polarising macrophages toward the M2 phenotype, and modulating autophagy. A more comprehensive understanding of the molecular mechanisms through which stem cells rescue chondrocytes and suppress inflammatory mediators will further refine their therapeutic efficacy against OA. Nevertheless, MSCs exhibit pronounced inter-donor and intrapopulation heterogeneity; prolonged ex vivo expansion and the catabolic, hypoxic intra-articular milieu can erode lineage fidelity, curtail extracellular matrix deposition and precipitate apoptotic or necrotic cell death. Moreover, critical procedural parameters—including isolation protocols, purification strategies, cell dosage and the optimal timing of implantation—remain unstandardised. Investigations to date are overwhelmingly preclinical, and marked disparities in the tissue origin of MSC-Exos, isolation methodologies, dosing regimens and animal models constrain cross-study comparability; consequently, the most efficacious cellular source and the definitive mechanisms of action have yet to be conclusively established. Future endeavours must therefore develop rigorously standardised operating procedures, undertake systematic head-to-head comparisons of the therapeutic profiles of MSCs and their exosomes derived from disparate anatomical origins, and elucidate their underlying molecular circuitry, thereby generating high-quality, reproducible evidence to accelerate safe and effective clinical translation.

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