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Mesenchymal stromal cells in Rheumathology: Recent findings

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Abstract

Mesenchymal stromal cells (MSCs) have emerged as promising therapeutic candidates for osteoarticular diseases because of their combined immunomodulatory, trophic, and regenerative properties. Although initially studied for their multipotent differentiation capacity, MSCs are now understood to act predominantly through context-dependent paracrine mechanisms, including secretion of soluble mediators and extracellular vesicles, as well as through interactions with innate and adaptive immune cells. These mechanisms enable MSCs to modulate inflammatory responses, suppress T- and B-cell activation, inhibit dendritic cell maturation, and promote anti-inflammatory macrophage polarization, thereby reshaping the joint microenvironment toward resolution and tissue repair.

In rheumatoid arthritis, MSC therapy is supported by strong biological plausibility, with preclinical studies demonstrating reduction of Th1/Th17 responses and enhancement of regulatory T-cell activity. Early clinical trials suggest a favorable safety profile, although evidence for sustained clinical remission remains limited. In focal cartilage defects, MSC-based strategies—particularly when combined with biomaterial scaffolds—have shown potential to enhance cartilage repair and improve functional outcomes. In osteoarthritis and degenerative disc disease, therapeutic effects appear to rely mainly on trophic and immunoregulatory signaling rather than durable cellular engraftment.

Despite encouraging progress, major translational challenges remain, including variability in cell sources, manufacturing protocols, dosing strategies, and patient selection. Future advances will likely depend on standardized cell products, robust potency assays, precision-medicine trial design, and emerging cell-free approaches such as MSC-derived extracellular vesicles.

Keywords: Mesencymal stem cells; Rheumatic arthritis; Osteoarthritis; Cartilage defect; Degenerative disk disease

1. Introduction

Mesenchymal stromal cells (MSCs), historically referred to as mesenchymal stem cells, were first described by Friedenstein and colleagues as plastic-adherent, colony-forming fibroblast-like precursors within the bone marrow stroma capable of generating osteogenic progenitors [1], [2]. Subsequent work established their multipotent differentiation capacity toward osteogenic, chondrogenic, and adipogenic lineages, notably demonstrated by Pittenger et al. [3]. To standardize their definition, the International Society for Cellular Therapy (ISCT) proposed minimal criteria including plastic adherence, expression of CD73, CD90, and CD105, absence of hematopoietic markers (CD34, CD45, CD14/CD11b, CD79α/CD19, HLA-DR), and trilineage differentiation potential in vitro [4].

Although initially valued for their differentiation capacity, MSCs are now primarily recognized for their potent paracrine and immunomodulatory properties [5], [6]. They regulate innate and adaptive immune responses through a combination of soluble mediators and vesicle-associated signals, including IDO, PGE2, TGF-β-related pathways, HGF, nitric oxide in some experimental systems, and extracellular vesicles [6], [7], [8], [9], [10]. MSCs suppress T-cell

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proliferation, promote regulatory T-cell (Treg) expansion, inhibit B-cell activation, modulate dendritic cell maturation, and induce macrophage polarization toward an anti-inflammatory M2 phenotype [6], [8], [11], [12], [13]. These properties have positioned MSCs as promising advanced therapy medicinal products (ATMPs) in immune-mediated and degenerative musculoskeletal diseases.

Osteoarticular pathologies—including rheumatoid arthritis (RA), focal cartilage defects, and osteoarthritis (OA)—represent leading causes of chronic disability worldwide. In RA, a systemic autoimmune disorder characterized by synovial hyperplasia, persistent inflammation, and progressive joint destruction, MSC therapy aims to restore immune tolerance and attenuate inflammatory cascades. Preclinical studies have demonstrated that MSC administration reduces Th17 responses, increases Treg populations, and decreases synovial inflammatory infiltration [10], [14].

In focal cartilage defects, the intrinsic avascular and aneural nature of articular cartilage severely limits spontaneous repair. Conventional surgical approaches, including microfracture and osteochondral grafting, frequently result in fibrocartilaginous repair tissue with inferior biomechanical characteristics. MSC-based strategies—either via direct intra-articular delivery or in combination with biomaterial scaffolds—have demonstrated enhanced chondrogenesis and improved cartilage regeneration in preclinical and clinical settings [15], [16]. Tissue engineering approaches integrating MSCs with three-dimensional matrices and bioactive factors aim to recapitulate hyaline cartilage architecture and restore long-term joint function.

Osteoarthritis, once considered purely degenerative, is now understood as a whole-joint disease involving low-grade inflammation, synovial activation, subchondral bone remodeling, and progressive cartilage breakdown. In this context, MSCs appear to exert predominantly trophic and immunomodulatory effects rather than durable structural engraftment [5], [17]. Preclinical models have shown that MSCs reduce catabolic mediators such as IL-1β, TNF-α, and matrix metalloproteinases while enhancing extracellular matrix synthesis and chondrocyte survival [17], [18], [19]. Clinical studies of intra-articular MSC injection report improvements in pain and function, with emerging evidence suggesting possible disease-modifying potential [20], [21].

Despite encouraging progress, several translational challenges remain, including donor-related variability, replicative senescence during ex vivo expansion, heterogeneity between tissue sources, standardization of potency assays, and regulatory harmonization under Good Manufacturing Practice (GMP) frameworks [22], [23], [24]. A deeper understanding of MSC mechanisms of action within distinct osteoarticular microenvironments will be essential to optimize patient stratification, dosing strategies, and therapeutic durability.

In this literature review, we critically analyze the biological characteristics of MSCs, their immunomodulatory and regenerative mechanisms, and the current preclinical and clinical evidence supporting their application in RA, focal cartilage repair, and osteoarthritis. We further discuss translational barriers and future perspectives for the integration of MSC-based therapies into rheumatologic practice.

2. Mechanisms of Action of Stromal Mesenchymal Cells (MSCs)

The therapeutic efficacy of mesenchymal stromal cells (MSCs) in osteoarticular diseases relies predominantly on context-dependent immunomodulatory and trophic mechanisms rather than durable structural engraftment. MSCs integrate inflammatory signals, interact with innate and adaptive immune cells, and modulate tissue microenvironments through coordinated paracrine, juxtacrine, and vesicular pathways [17], [19], [25].

2.1. Inflammatory Licensing and Functional Polarization

MSCs are not constitutively immunosuppressive; instead, their regulatory phenotype is induced by exposure to pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-1β—a process often termed *licensing* or *priming* [26], [27]. IFN-γ stimulation upregulates indoleamine 2,3-dioxygenase (IDO), PD-L1, HLA molecules, and adhesion proteins (e.g., ICAM-1), thereby enhancing their immunomodulatory competence [8], [26]. This cytokine-dependent activation enables MSCs to sense the inflammatory milieu typical of RA or osteoarthritis (OA) and adapt their secretome accordingly.

2.2. Modulation of Adaptive Immunity

MSCs exert profound regulatory effects on T- and B-cell compartments. They inhibit T-cell proliferation through both contact-dependent and soluble mechanisms, prominently including IDO in human systems, as well as PGE2 and other anti-inflammatory mediators; nitric oxide is an important suppressive pathway in several experimental models [6], [7], [26].

Furthermore, MSCs skew T helper polarization by suppressing Th1 and Th17 differentiation while promoting regulatory T-cell (Treg) expansion, a mechanism particularly relevant in RA pathogenesis where Th17/Treg imbalance drives synovial inflammation [14], [10].

Through PD-L1/PD-1 interactions and soluble mediators, MSCs also attenuate B-cell proliferation, plasma cell differentiation, and immunoglobulin production [28], [11]. These effects contribute to reduced autoantibody generation and dampened adaptive immune activation in autoimmune joint disease.

2.3. Regulation of Innate Immune Cells

Beyond adaptive immunity, MSCs critically regulate innate immune responses. They inhibit dendritic cell maturation and antigen-presenting capacity, leading to reduced co-stimulatory molecule expression (CD80/CD86) and decreased IL-12 production [6], [12].

A central mechanism involves reprogramming of macrophages toward anti-inflammatory or reparative phenotypes through mediators such as PGE2, TSG-6, and EV-associated signals, with increased IL-10 production as a recurrent downstream feature [13], [29]. In osteoarticular tissues, this shift contributes to resolution of synovitis and attenuation of catabolic signaling cascades.

Natural killer (NK) cell cytotoxicity is likewise suppressed via IDO, PGE2, and HLA-G expression, reducing local cytolytic activity and inflammatory amplification [6], [30].

2.4. Paracrine Signaling and Extracellular Vesicles

Increasing evidence indicates that MSC-mediated tissue repair is largely driven by their secretome rather than direct differentiation [5], [17]. MSC-derived extracellular vesicles (EVs), including exosomes and microvesicles, transfer bioactive proteins, lipids, mRNA, and microRNA to recipient cells, modulating chondrocyte survival, synoviocyte activation, and matrix synthesis [9], [19], [31].

In experimental OA models, MSC-EVs reduce expression of matrix metalloproteinases (MMPs), suppress IL-1β-induced inflammation, and promote extracellular matrix production, recapitulating many therapeutic effects of parental cells [19], [32].

2.5. Trophic Support, Angiogenesis, and Niche Modulation

MSCs secrete trophic factors such as VEGF, HGF, IGF-1, and FGF-2, which enhance angiogenesis, recruit endogenous progenitors, and support tissue remodeling [15], [25]. In focal cartilage defects, MSCs contribute to repair by stimulating resident chondroprogenitors and modulating subchondral bone remodeling [15], [33].

Additionally, MSCs express adhesion molecules and chemokines that facilitate homing to inflamed tissues, although long-term engraftment appears limited [34]. Instead, MSCs function as transient “drugstores,” reprogramming the joint microenvironment toward resolution and repair.

2.6. Organelle Transfer and Metabolic Reprogramming

Emerging evidence indicates that MSCs can transfer mitochondria to injured cells via tunneling nanotubes or extracellular vesicles, thereby restoring bioenergetic function and reducing oxidative stress [35]. Such metabolic support may be particularly relevant in degenerative cartilage where mitochondrial dysfunction contributes to chondrocyte apoptosis.

3. Clinical application using immunoregulatory potential of MSC: in rheumatoid arthritis

3.1. Physiopathology of Rheumatoid Arthritis

RA is a chronic, systemic autoimmune disease characterized by persistent synovitis, autoantibody production, pannus formation, cartilage destruction, and bone erosion. Its pathogenesis involves a complex interplay between genetic susceptibility (notably HLA-DRB1 shared epitope alleles), environmental triggers, and dysregulated adaptive and innate immune responses [36], [37].

Synovial inflammation is driven by activated dendritic cells, Th1 and Th17 lymphocytes, B cells, macrophages, and fibroblast-like synoviocytes (FLS), leading to excessive production of pro-inflammatory cytokines including TNF-α, IL-6, IL-1β, IL-17, and GM-CSF [38], [39]. This inflammatory milieu promotes osteoclastogenesis via RANKL signaling and matrix degradation through metalloproteinases, culminating in irreversible structural damage. Despite major therapeutic advances, a substantial proportion of patients fail to achieve sustained remission, and structural repair remains elusive [40].

3.2. Disease-Modifying Anti-Rheumatic Drugs (DMARD) Therapy and Persistent Unmet Needs

Current RA management relies on conventional synthetic DMARDs (csDMARDs, e.g., methotrexate), biologic DMARDs (bDMARDs, targeting TNF, IL-6R, CTLA4, CD20), and targeted synthetic DMARDs (tsDMARDs, JAK inhibitors). Treat-to-target strategies have significantly improved outcomes; however, a substantial minority of patients exhibit inadequate response or intolerance to multiple DMARD classes [40], [41].

Moreover, even in patients achieving clinical remission, subclinical inflammation and progressive bone erosion may persist. Refractory RA—defined by failure of ≥2 biologic agents—remains difficult to treat and represents a critical unmet need [41]. Importantly, no current therapy restores immune tolerance or promotes structural regeneration.

3.3. Mechanistic Rationale for MSC Therapy in RA

Given their immunomodulatory properties, MSCs provide a biologically coherent therapeutic strategy in RA. In the inflammatory synovial environment, cytokine licensing (IFN-γ, TNF-α) enhances MSC expression of IDO, PD-L1, HLA-G, and secretion of PGE2, TGF-β, IL-10, and TSG-6 [26], [42], [29].

In experimental arthritis models, MSCs reduce Th1/Th17 responses, promote Treg expansion, inhibit B-cell maturation and autoantibody production, suppress dendritic cell activation, and induce M2 macrophage polarization [14], [10], [13]. These mechanisms collectively rebalance immune tolerance and attenuate synovial inflammation.

Additionally, MSC-derived trophic factors may limit osteoclast activation and support tissue repair, although durable regeneration of erosive lesions in humans has not yet been conclusively demonstrated.

3.4. Clinical Evidence in Human RA

In a randomized, double-blind, placebo-controlled phase Ib/IIa trial, Álvaro-Gracia et al. evaluated intravenous allogeneic adipose-derived MSCs in refractory RA patients (failure of ≥2 bDMARDs) [43]. Dose-escalation cohorts (1–4 × 10^6 cells/kg at days 1, 8, and 15) demonstrated a favorable safety profile with no dose-limiting toxicity. While exploratory efficacy endpoints suggested clinical improvement in some patients, the study was not powered for definitive efficacy conclusions.

Shadmanfar et al. investigated autologous bone marrow–derived MSCs in refractory RA. The study reported acceptable safety and signals of reduced disease activity scores over short-term follow-up [44]. However, small sample size and absence of robust blinding limited interpretability.

Wang et al. evaluated intravenous umbilical cord–derived MSCs in 172 patients with active RA receiving background DMARD therapy. UC-MSC administration was well tolerated, with no serious infusion-related adverse events. Treatment was associated with reductions in serum TNF-α and IL-6, increased peripheral $CD4^+CD25^+Foxp3^+$ regulatory T cells, and improvements in DAS28, HAQ, and ACR responses. However, because the study lacked rigorous randomized blinding and patients continued concomitant DMARD therapy, the magnitude of MSC-specific efficacy remains difficult to determine. [45].

3.5. Critical Appraisal of the Evidence

A systematic appraisal by Pers and colleagues highlighted that, to date, fewer than ten clinical studies have evaluated MSC therapy in RA, only a minority being randomized and placebo-controlled [46]. Considerable heterogeneity exists regarding cell source (adipose, bone marrow, umbilical cord), autologous versus allogeneic products, dosing regimens, infusion frequency, and patient selection.

No phase III trial has yet been completed. Follow-up duration is typically short (3–12 months), structural outcomes are rarely assessed, and primary endpoints frequently emphasize safety rather than robust efficacy measures. Sample sizes remain small, and methodological limitations—including potential bias and insufficient power—preclude definitive conclusions regarding disease-modifying effects.

Importantly, while safety profiles across studies appear reassuring, evidence for sustained remission, structural repair, or superiority over optimized biologic therapy remains insufficient.

3.6. Integrative Perspective

MSC therapy in RA is supported by strong biological plausibility and consistent preclinical evidence of immune recalibration. Early-phase clinical trials confirm safety and suggest potential immunological and clinical benefit in refractory populations. However, current evidence remains exploratory. Rigorous, adequately powered, randomized phase III trials with standardized cell products, biomarker-driven stratification, and structural imaging endpoints are required before MSC therapy can be positioned within the therapeutic algorithm of RA.

4. Clinical application using differentiation potential of MSC: cartilage defect

4.1. Different types of cartilage defects: focal defects vs wide zones

Articular cartilage has limited intrinsic repair capacity because it is avascular, aneural, and alymphatic; consequently, defects frequently persist, propagate, and predispose to degenerative joint changes. Lesions can be broadly categorized into:

- Focal, well-demarcated chondral/osteochondral defects, often post-traumatic in otherwise non-arthritic joints;
- Wide-zone (diffuse) cartilage loss, typically occurring in the context of oa or inflammatory arthritides, where catabolic cytokine networks and altered joint mechanics drive progressive matrix failure and subchondral remodeling.

This dichotomy is clinically relevant because focal defects are amenable to reparative/restorative surgery, whereas wide-zone disease requires microenvironmental modulation and long-term joint preservation strategies [15], [47], [48], [49].

4.2. Conventional treatment options, their challenges, and MSC-based innovation

Current surgical options for focal defects include marrow stimulation (microfracture/drilling), osteochondral autograft/allograft transfer, and autologous chondrocyte implantation (ACI/MACI) [48]. ACI is an established restorative strategy with cultured autologous chondrocytes [50]. However, the broader literature shows that while many techniques improve patient-reported outcomes (PROs), durability and tissue quality vary substantially. Microfracture tends to yield fibrocartilage, which is biomechanically inferior to hyaline cartilage and may compromise long-term durability—particularly in larger lesions [51]. In a randomized multicenter trial with 14–15 years follow-up, ACI and microfracture showed no significant long-term differences in clinical scores, with notable rates of failure and radiographic OA, underscoring that existing reparative procedures do not reliably prevent OA progression [47]. Systematic review evidence similarly highlights heterogeneity across studies and suggests lesion-size dependence and tissue-quality tradeoffs between microfracture and ACI [48].

Challenges of conventional surgery include: (i) prolonged rehabilitation (often months before return to high-impact activity), (ii) variable quality of repair tissue (fibrocartilage vs hyaline-like), (iii) graft hypertrophy and reoperation risk (notably with early ACI generations), (iv) donor-site morbidity for osteochondral grafting, and (v) limited effectiveness when cartilage loss is diffuse (OA-wide zones) [47], [48], [49], [50].

MSC-based innovation aims to address these constraints by combining (a) trophic/immunoregulatory effects (modulating synovial inflammation and catabolic signaling) with (b) pro-chondrogenic support (paracrine cues and, in some constructs, chondrogenic differentiation) and (c) one-step strategies (implantation at index surgery) potentially reducing the logistical complexity of chondrocyte expansion [15], [25], [52].

4.3. MSC implant vs chondrocyte implant: comparative rationale and advantages

ACI has strong clinical heritage and can generate hyaline-like repair, but it typically requires two stages (harvest then implantation), has higher manufacturing/logistical burden, and risks phenotypic drift during expansion [48], [50].

MSC implantation is positioned as an alternative or complement because MSCs can:

- Provide immunoregulatory/trophic signals that may improve the intra-articular environment beyond the defect itself [15], [25].

- Be integrated into single-stage protocols (depending on the product/strategy); and
- Support cartilage repair via paracrine-driven recruitment/activation of endogenous repair programs, potentially reducing reliance on expanded chondrocytes [25], [33].

A frequently cited clinical comparator is the observational cohort by Nejadnik et al., where 72 matched patients underwent cartilage repair using ACI (n=36) versus autologous bone marrow–derived MSCs (n=36); outcomes were reported as comparable overall, supporting feasibility of MSC-based cellular repair in focal lesions (Level III evidence; observational design) [52]. Importantly, this study supports *non-inferiority signals* in selected settings but does not replace the need for adequately powered randomized trials.

4.4. Experiences of MSC implantation in early OA and their relevance to cartilage repair

Large real-world cohorts suggest that MSC implantation can improve symptoms in early OA, but the evidence base remains dominated by case series and heterogeneous protocols.

A key example is the large retrospective series by Kim et al. (2020) evaluating 467 patients (483 knees) treated with MSC implantation on a fibrin glue scaffold, with ≥5-year follow-up. IKDC and Tegner scores improved significantly up to ~3 years and then gradually declined by 9 years; radiographic OA progression continued over time. Importantly, reported survival rates (based on clinical decline or radiographic progression criteria) were 99.8% at 5 years, 94.5% at 7 years, and 74.5% at 9 years, identifying age, bipolar kissing lesions, and MSC dose as prognostic factors [53]. These data support a symptom-modifying effect with midterm durability in selected early OA, but they also demonstrate that MSC implantation does not fully arrest radiographic progression.

A 2023 systematic review concluded that MSC implantation in mild-to-moderate knee OA appears safe and provides short-term clinical improvement with "satisfactory" cartilage restoration, but emphasized high heterogeneity, limited controls, and paucity of midterm/long-term comparative evidence [54]. Taken together, the OA implantation literature supports feasibility and signals of benefit, yet remains insufficient to claim robust disease-modifying efficacy across OA phenotypes.

4.5. MSC implants with scaffold: benefits vs MSC implants alone; scaffold choice criteria; scaffold types; natural vs synthetic scaffolds

Why add a scaffold? A scaffold can improve cell retention, spatial organization, and mechanical stability at the lesion site, potentially enhancing integration and matrix deposition. In OA knees, Kim et al. directly compared MSC implantation using fibrin glue as a scaffold versus MSC implantation without scaffold and reported superior cartilage regeneration/clinical associations with scaffold-based delivery, supporting the principle that delivery strategy materially affects outcomes [55]. (These are comparative cohort data, not definitive randomized evidence.)

Criteria for scaffold selection :

- Biocompatibility and low immunogenicity;
- Controlled biodegradation aligned with tissue formation;
- Mechanical competence (load-sharing, maintaining defect fill);
- Porosity/interconnectivity enabling nutrient diffusion and cell migration;
- Chondro-inductive microenvironment (supporting chondrogenesis/osteochondral integration when relevant);
- Manufacturability/sterilizability and regulatory feasibility [56], [57].

Scaffold types (representative, non-exhaustive):

- Natural biomaterials: collagen (type I/II), hyaluronic acid, fibrin, alginate, chitosan, decellularized cartilage-derived matrices. They provide inherent bioactivity and cell-adhesive cues but can have batch variability and weaker mechanical properties.
- Synthetic polymers: PLA, PGA, PLGA, PCL, polyurethane-based constructs, and synthetic hydrogels. They offer tunable mechanics/degradation and manufacturing consistency, but may require functionalization to optimize bioactivity and integration [56], [57].

A focused review of synthetic/hybrid scaffolds highlights the design tradeoffs in architecture and physicochemical properties needed for cartilage tissue engineering, and underscores why hybrid (bioactive + mechanically tunable) systems are often pursued [56].

4.6. MSC + scaffold in humans: results and limits

Human evidence indicates feasibility and clinical improvement signals, but with important caveats.

Large defects / advanced patient profiles. Song et al. (2023) reported clinical and MRI outcomes after implantation of human umbilical cord blood–derived MSCs mixed with hyaluronic acid for knee chondral defects. In 85 patients, PROs improved significantly at 1–3 years. MRI at 1 year demonstrated repaired cartilage hypertrophy of varying grades, but hypertrophy did not correlate with PROs, emphasizing that imaging morphology may not map directly to symptoms [58]. This study is informative for feasibility in older patients and larger lesions, but it is a case series (Level IV) and does not establish comparative superiority over established reconstructive options.

Overall limitations across human studies (consistent with systematic review conclusions):

- Heterogeneity in cell source (bone marrow/adipose/Umbilical cord blood), allogeneic vs autologous products, and scaffold composition;
- Variable surgical technique and concomitant procedures (e.g., alignment correction);
- Limited use of blinded, controlled designs;
- Insufficient long-term structural endpoints and standardized MRI compositional assessment;
- Uncertainty regarding the relative contribution of immunoregulation vs true hyaline cartilage restoration [54], [58].

5. Clinical application using trophic potential of MSC

5.1. Application in osteoarthritis

OA is a heterogeneous whole-joint disorder in which articular cartilage breakdown coexists with subchondral bone remodeling, osteophyte formation, synovial low-grade inflammation, and periarticular muscle changes, collectively driving pain, stiffness, and functional limitation [59], [60]. At the population level, OA represents a major and rising burden: the Global Burden of Disease (GBD) 2020 analysis estimated ~595 million people living with OA worldwide (7.6% of the global population), with large projected increases driven by ageing and obesity [61].

OA pain is weakly correlated with radiographic severity and reflects a composite of nociceptive and peripheral/central sensitization mechanisms, with inflammatory and metabolic phenotypes increasingly recognized. Current guideline-based care (education, weight loss, exercise/physiotherapy, topical/oral analgesics, intra-articular corticosteroids or hyaluronic acid in selected settings, and ultimately arthroplasty) remains predominantly symptom-modifying and does not reliably halt structural progression. In addition, drug toxicities (e.g., gastrointestinal/cardiovascular risks with NSAIDs) and incomplete analgesic efficacy contribute to a persistent unmet need for safer, more effective, and ideally disease-modifying interventions [59], [60].

Increasing evidence supports that the dominant therapeutic activity of MSCs is trophic/immunoregulatory, rather than durable engraftment and direct tissue replacement. MSCs respond to inflammatory cues and release bioactive mediators (e.g., PGE2, TGF-β-linked pathways, IDO-associated immunoregulation, pro-resolving and anti-catabolic signals) and extracellular vesicles that can (i) dampen synovitis and macrophage polarization, (ii) reduce chondrocyte catabolism and apoptosis, (iii) modulate nociceptive signaling, and (iv) support tissue homeostasis and repair programs [5], [62], [63], [64]. In preclinical OA models, intra-articular MSCs can reduce synovial inflammation and cartilage degeneration and improve pain-related behaviors, while mechanistic readouts commonly align with paracrine immunomodulation and matrix homeostasis rather than long-term donor-cell persistence [62], [63], [64].

5.1.1. ADIPOA (phase I dose-escalation; autologous adipose-derived stromal/stem cells)

The ADIPOA first-in-human program evaluated intra-articular autologous adipose-derived stromal cells in knee OA using a dose-escalation design, prioritizing safety while exploring signals of symptom improvement. The published phase I study reported feasibility and an acceptable safety profile in the studied dose range, with exploratory improvements in pain/function measures that required confirmation in controlled trials [65].

5.1.2. "More than one injection" strategies

Because MSC effects are expected to be trophic and time-limited, repeated dosing has been explored. A randomized study comparing different injection strategies (including repeat dosing) suggested that multiple administrations might

prolong symptomatic benefit in some designs, but interpretation remains constrained by small sample sizes, heterogeneous cell products (tissue source, expansion, potency), and variable comparators [66].

5.1.3. Meta-analyses of MSC results in OA

Systematic reviews and meta-analyses pooling heterogeneous cell-based interventions (expanded MSCs and/or adipose-derived cell products depending on inclusion criteria) often report improvements in pain and function and a generally favorable short-term safety signal. However, many analyses emphasize substantial heterogeneity, risk of bias, inconsistent blinding, variable control arms (saline/ Hyaluronic acid), and limited high-quality structural endpoints—factors that can inflate pooled effect sizes and reduce certainty [67], [68].

5.1.4. Randomized controlled trial-level evidence and ADIPOA2

The key maturity step is placebo-controlled, blinded RCT evidence. ADIPOA2 was designed as a phase IIb multicenter, randomized, double-blind, placebo-controlled, dose-finding trial evaluating intra-articular autologous adipose-derived ex vivo expanded MSCs in symptomatic mild-to-moderate tibiofemoral knee OA, using patient-reported outcomes (pain/function) as the clinical efficacy focus [69]. While ADIPOA2 materially strengthens the evidence base by using rigorous trial architecture (randomization, blinding, placebo comparator and prespecified dosing), interpretation should still prioritize: (i) durability beyond 12–24 months, (ii) consistency across pain/function instruments, (iii) structural outcomes (MRI-based cartilage measures) and whether they track clinical benefit, and (iv) subgroup signals that may determine who benefits [69].

5.1.5. Critical reading across OA MSC trials

Evidence emerging from controlled clinical studies indicates several relatively consistent observations regarding intra-articular mesenchymal stromal cell (MSC)–based interventions. First, short-term safety profiles appear generally acceptable when these approaches are administered under controlled clinical conditions. Across published trials, most reported adverse events are mild and transient,. serious treatment-related events appear uncommon in published trials, though surveillance periods are often short [65], [67], [69]. Second, Symptom signals (pain/function) are frequently reported, but magnitude varies widely and is sensitive to trial design and comparator choice [67], [68].

Despite these encouraging signals, several methodological and biological factors currently limit confidence in the interpretation of MSC therapy as a disease-modifying strategy in osteoarthritis. A major limitation is substantial product heterogeneity across studies, including variability in tissue source (e.g., adipose tissue, bone marrow, or perinatal tissues), culture expansion protocols, passage number, cryopreservation procedures, cell viability and potency assays, and dosing strategies [67]. In addition, comparator selection and placebo effects represent important confounders in intra-articular intervention trials. Procedural interventions are associated with meaningful contextual and placebo responses, while commonly used comparators such as saline or hyaluronic acid may themselves exert biological or symptomatic effects, thereby reducing detectable between-group differences [59], [67]. Another critical issue is the frequent dissociation between structural and symptomatic outcomes: imaging endpoints such as MRI-derived cartilage measures do not consistently correlate with improvements in patient-reported symptoms, and structural signals of cartilage hypertrophy or repair may occur without proportional clinical benefit, or conversely [59], [69]. Finally, osteoarthritis is a biologically heterogeneous disease, and broad “all-comer” trial designs likely dilute treatment effects within specific biologically responsive subgroups, such as patients exhibiting inflammatory or synovitic phenotypes[60], [62].

5.2. Application in degenerative disc disease (DDD)

DDD is a major contributor to chronic low back pain (cLBP), which remains a leading global cause of disability [70], [71]. Disc degeneration reflects loss of nucleus pulposus proteoglycans and hydration, annular fissuring, endplate changes (including Modic inflammatory phenotypes in subsets), altered biomechanics, and neurovascular ingrowth that can amplify pain signaling [72], [73], [74]. Standard care (education, exercise/rehabilitation, analgesics/NSAIDs, cognitive-behavioral strategies, selected interventional procedures, and surgery in carefully defined indications) frequently yields incomplete relief in chronic discogenic pain, motivating biologic approaches aimed at modifying the disc microenvironment [70], [75].

Intradiscal MSC delivery is hypothesized to (i) reduce inflammatory/catabolic signaling (IL-1/TNF-linked cascades, matrix metalloproteinase activity), (ii) support anabolic matrix programs, and (iii) modulate nociceptive pathways—again primarily via trophic/immunoregulatory mechanisms rather than durable repopulation of the disc [63], [73]. However, the disc is avascular, hypoxic, acidic, and nutrient-limited; these features can suppress MSC survival/function and constrain efficacy [73], [74].

5.2.1. Summary and critical reading of MSC intradiscal injection experiments

Clinical studies of intradiscal MSCs include small cohorts and at least one randomized placebo-controlled design. A notable randomized trial of allogeneic bone marrow MSCs in discogenic pain has been reported with imaging-based degeneration staging and patient-reported endpoints (pain and disability), supporting feasibility and providing controlled estimates of effect sizes [76]. Systematic reviews/meta-analyses aggregating intradiscal MSC studies generally report improvements in pain Visual Analog Scale (VAS) and disability Oswestry Disability Index (ODI) in many cohorts, but repeatedly underscore high heterogeneity, small sample sizes, variable cell products/doses, and limited long-term structural validation [77].

5.2.2. Why failure (or inconsistent benefit) can occur in DDD MSC therapy

Mechanistically plausible causes of null or modest outcomes include:

- Hostile disc niche (low glucose, low oxygen, acidic pH, inflammatory cytokines) limiting MSC viability and paracrine output [73], [74].
- Advanced structural collapse (severe height loss, fibrosis, endplate sclerosis) leaving little regenerative substrate—trophic signals cannot reconstruct lost architecture [72], [74].
- Pain generator heterogeneity: not all cLBP is discogenic; facet joints, sacroiliac joint, myofascial pain, and central sensitization can dominate even when imaging shows disc degeneration, diluting treatment signal [70], [75].
- Dose/potency uncertainty: unlike hematologic cell therapies, there is no universally accepted potency assay that predicts disc response, and cell dosing is inconsistent across trials [23], [24], [77].
- Delivery/retention issues: injectate leakage through annular fissures, suboptimal intradiscal distribution, and short-lived retention can reduce effective exposure [73], [74].

6. Current limitations and future perspectives of MSC therapy in osteoarticular diseases

Across RA, focal cartilage defects, and OA, mesenchymal stromal cell (MSC)–based interventions have progressed from a "cell replacement" paradigm toward a context-dependent immunoregulatory and trophic model. The preceding chapters highlighted consistent preclinical anti-inflammatory activity and generally favorable short-term safety in early-phase trials, yet translation into reproducible, disease-modifying benefit remains inconsistent, particularly when tested in rigorous placebo-controlled designs [43], [65], [69], [75]. This gap frames the key limitations and the most credible paths forward.

6.1. Current limitations

6.1.1. Efficacy signals are heterogeneous and often vulnerable to bias

Most osteoarticular MSC studies remain small, underpowered, and methodologically heterogeneous (cell source, donor selection, passage, cryopreservation, viability, delivery route, concomitant procedures, rehabilitation, and endpoints). These features amplify risk of selection/performance bias and complicate between-study synthesis. In OA in particular, large placebo responses and fluctuating symptoms can obscure true treatment effects, contributing to discordance between uncontrolled series and randomized trials [65], [66], [67], [69].

6.1.2. "Tissue repair" remains insufficiently proven as a durable clinical outcome

A recurring uncertainty is whether MSCs meaningfully regenerate hyaline cartilage or primarily reduce pain and synovitis through paracrine immunomodulation. Many reports rely on conventional MRI morphology rather than compositional imaging, blinded scoring, or robust structural endpoints, and structural changes—when present—frequently show weak correlation with PROs [54], [58], [59], [69]. This creates a persistent mechanistic–clinical mismatch: symptomatic improvement may occur without demonstrable structural modification.

6.1.3. Dose, frequency, and delivery remain empiric

Several key therapeutic parameters in mesenchymal stromal cell (MSC)–based interventions remain insufficiently defined. These include the optimal dose (cells per injection, viable versus total cell counts, and potency-adjusted dosing), the frequency of administration (single versus repeated injections), the route of delivery and cellular retention—particularly given the rapid clearance of cells from the synovial space after intra-articular injection—and the formulation of the cellular product, such as fresh versus cryopreserved cells, carrier solutions, or scaffold-assisted delivery systems.

Importantly, the field still lacks validated exposure–response relationships, and available studies do not yet establish that increasing cell number or repeating administration consistently improves the magnitude or durability of benefit across indications. [66], [73].

6.1.4. Target population and disease stage are not standardized

OA is not one disease; inflammatory/synovitic phenotypes, mechanical phenotypes (malalignment, instability), metabolic phenotypes, and pain-sensitization phenotypes likely respond differently. Similarly, cartilage defects vary in size, chronicity, subchondral bone status, and alignment. Without phenotype-driven stratification, trials risk dilution of effect and false-negative conclusions [59], [60], [62], [66].

6.1.5. Manufacturing standardization and potency testing are still inadequate

Even when identity criteria are met, MSC products differ substantially in transcriptome/secretome and immunomodulatory capacity depending on donor, tissue source, culture media, oxygen tension, passage number, cryopreservation, and inflammatory priming. Critically, potency assays are not harmonized, and many clinical programs proceed without a potency metric that is mechanistically linked to the intended clinical effect (e.g., suppression of inflammatory macrophage polarization, IDO/PGE2 activity, or synoviocyte catabolic signaling). This limits batch comparability and impedes regulatory alignment [22], [23], [24].

6.1.6. Cost and scalability remain structural barriers

Good Manufacturing Practice expansion, release testing, cold chain, and clinical administration costs remain high. Without clearer efficacy and standardized potency, health-economic justification and reimbursement remain uncertain—particularly for chronic diseases like OA with very large patient populations [22], [23].

6.2. Perspectives for MSC therapy

6.2.1. Scaffold-embedded MSC and tissue-engineered repair (cartilage defects and early OA)

For focal lesions, retention and spatial organization matter. Combining MSCs with biomaterials aims to:

- Improve cell retention within the defect,
- Provide mechanical support and integration cues,
- Create a local chondro-inductive microenvironment.

This perspective aligns best with focal defects and selected early OA cases, while diffuse OA likely requires broader microenvironmental modulation plus correction of mechanical drivers (alignment, instability) to sustain any biological benefit [56], [57], [78], [79].

6.2.2. Priming/licensing to increase consistency of immunoregulation

The figures highlight “MSC priming” as a route to improve efficacy. The most defensible approaches are:

- Inflammatory licensing (e.g., IFN-γ/TNF-α exposure) to enhance immunosuppressive mediators (IDO, PD-L1, PGE2 pathways) in a controlled and product-reproducible manner [26], [10], [27].
- Microenvironmental conditioning (hypoxia, 3D culture) to shape secretome/EV output [19], [31], [64].

The key translational requirement is that priming must be coupled to potency assays and safety testing, otherwise it simply adds another uncontrolled variable.

6.2.3. Co-injection and combination strategies

Combination approaches are increasingly explored to enhance the efficacy of mesenchymal stromal cell (MSC)–based therapies in osteoarthritis. These strategies typically involve co-administration of MSCs or MSC-derived extracellular vesicles (EVs) with agents or interventions designed to improve the intra-articular environment or increase product retention. For example, MSCs may be combined with viscosupplementation agents such as hyaluronic acid or biomaterial carriers to prolong intra-articular residence and support paracrine activity within synovial tissues [55], [80]. Combining MSC therapy with anti-inflammatory strategies may be advantageous in inflammatory OA phenotypes, because synovial inflammation can impair joint homeostasis and potentially influence the effectiveness of cell-based interventions [17], [59], [63]. Mechanical interventions—including alignment correction or joint unloading—may further support regenerative processes by reducing recurrent biomechanical stress that drives cartilage degeneration

[59]. However, clinical trials must be designed to distinguish additive from synergistic effects and to minimize confounding from concomitant therapies.

6.2.4. Gene editing and engineered products

Engineering strategies aim to enhance the biological performance of MSC or EV therapies. Approaches under investigation include improving homing and retention within injured tissues, increasing resistance to inflammatory apoptosis, sustaining anti-catabolic and pro-regenerative signaling, and enhancing targeted immunomodulation. Preclinical engineering approaches have sought to enhance MSC or EV performance by improving retention, resistance to inflammatory stress, and sustained pro-regenerative signaling, although robust clinical translation remains limited [31], [33], [81]. Similarly, engineered EVs enriched with specific microRNAs or proteins are being investigated as next-generation cell-free therapeutics [31], [81]. Nevertheless, because osteoarthritis is a chronic non-lethal disease affecting large populations, engineered products must demonstrate clear advantages in safety, reproducibility, and efficacy over simpler cell-based or EV-based modalities.

6.2.5. "Combination of strategies" and precision trial design

Given the biological heterogeneity of osteoarthritis, the most credible future pathway is likely a **precision-medicine framework** rather than a universal MSC product. Osteoarthritis involves variable contributions from synovial inflammation, subchondral bone pathology, mechanical overload, and altered pain processing [49], [60]. Future strategies should therefore (i) phenotype the joint—particularly regarding synovitis, bone marrow lesions, alignment, and pain sensitization; (ii) match the therapeutic modality accordingly (cells versus EVs, scaffold-assisted delivery, or primed/engineered products); and (iii) align clinical endpoints with the underlying mechanism, using inflammatory imaging or biomarkers for immunomodulatory approaches and compositional MRI or biomechanical measures for structural repair. Such mechanistically informed trial design may improve identification of treatment-responsive subgroups and strengthen evidence for MSC-based interventions.

6.3. Focus on extracellular vesicles (EVs)

6.3.1. "Acellular" approaches: moving from cells to secretome/EVs

A major emerging direction in regenerative medicine is the therapeutic exploitation of mesenchymal stromal cell (MSC)–derived paracrine products, particularly extracellular vesicles (EVs). By delivering bioactive signals without the direct administration of living cells, EV-based approaches may help reduce product variability, enable more standardized dosing strategies, and simplify storage and handling. Compared with cell-based therapies, EVs may offer several practical advantages, including improved physicochemical stability, easier logistical management, and a lower theoretical risk of uncontrolled cellular persistence after administration. In addition, EV preparations can potentially be manufactured under scalable conditions compatible with batch production and release testing, while also providing a platform amenable to iterative engineering strategies, such as cargo enrichment or surface modification to enhance tissue targeting [19], [31], [81], [82].

Despite these promising attributes, significant translational challenges remain. Rigorous definition, quantification, and purity control of EV preparations are essential prerequisites for clinical development, as emphasized by international methodological guidelines and translational reviews of EV therapeutics [82], [81].

Particle counts alone are insufficient to characterize EV products, and comprehensive analytical frameworks are required to ensure reproducibility and comparability between studies. Furthermore, several non-trivial limitations must be addressed, including the intrinsic heterogeneity of EV populations (e.g., exosomes versus microvesicles and mixed particle fractions), the risk of co-isolated contaminants such as protein aggregates or lipoproteins, and the absence of a universally accepted dose metric—whether based on particle number, protein content, or functional bioactivity. These issues highlight the critical need for stringent characterization protocols and transparent reporting standards in EV-based therapeutic research [82].

6.3.2. Current clinical evidence in knee OA (early but instructive)

A randomized, triple-blind, placebo-controlled clinical trial evaluated placental MSC-derived EVs administered intra-articularly in knee OA. In that study, EV treatment was reported as safe but did not demonstrate significant superiority over placebo on key clinical outcomes, underscoring that acellular approaches remain subject to the same challenges of placebo response, patient selection, and endpoint sensitivity [83]. In parallel, first-in-human development programs have reported clinical-grade EVs derived from umbilical cord MSCs with preclinical packages and early intra-articular human validation frameworks, reflecting accelerating translational infrastructure for EV therapeutics in OA [84]. The

field is moving quickly, but definitive efficacy evidence is still emerging and must be judged by rigorous, blinded, adequately powered trials.

7. Conclusion

Mesenchymal stromal cells (MSCs) have emerged as promising therapeutic candidates for osteoarticular diseases, including RA, focal cartilage defects, and OA. Initially considered as cells capable of direct tissue regeneration, MSCs are now primarily understood as immunomodulatory and trophic mediators that regulate inflammatory responses, modulate immune cell activity, and influence tissue repair through paracrine signaling.

Preclinical studies consistently demonstrate that MSCs can attenuate synovial inflammation, inhibit cartilage degradation, and promote a regenerative joint microenvironment. Early clinical trials have confirmed the favorable safety profile of MSC therapy and have reported improvements in pain and function in several osteoarticular conditions. However, clinical efficacy remains variable, and clear evidence of durable structural cartilage regeneration is still limited. These discrepancies largely reflect heterogeneity in cell sources, manufacturing processes, dosing strategies, and patient selection.

Major challenges remain, particularly regarding standardization of MSC products, development of robust potency assays, and identification of the most responsive patient populations. In parallel, emerging strategies such as MSC priming, scaffold-assisted delivery, gene engineering, and combination therapies aim to enhance therapeutic efficacy.

Among these developments, MSC-derived extracellular vesicles (EVs) represent a promising cell-free alternative that may retain many of the immunomodulatory and regenerative properties of MSCs while offering advantages in manufacturing standardization and safety.

Overall, MSC-based therapies hold considerable potential for osteoarticular diseases, but their successful clinical translation will depend on rigorous clinical trials, standardized manufacturing protocols, and mechanism-driven therapeutic strategies to achieve consistent and reproducible outcomes.

Disclosure of conflict of interest

Author doesn't have financial or non-financial interests to disclose.

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