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Review Article

Stem Cells Therapy for Chondral Repair and Orthopedic Regeneration: Advances, Challenges, and Future Directions

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Abstract

Cartilage and orthopedic tissue degeneration represent a leading cause of chronic pain, reduced mobility, and disability worldwide. Cartilage, bone, and joint conditions are frequently related to osteoarthritic (OA) trauma and congenital abnormalities. Central to the tissue degeneration is damage to articular cartilage, which has limited intrinsic repair capacity due to its avascular, aneural, and alymphatic nature. Furthermore, hyaline cartilage in human joints has a limited regeneration capacity, and as such, the treatment of articular cartilage lesions can be challenging. Current therapeutic regenerative (i.e., microfracture, autografts, or joint replacement) have limited long-term success. As such, stem cell–based therapies, particularly mesenchymal stem cells (MSCs), have emerged as promising candidates for cartilage and orthopedic repair. The capacity for chondrogenic differentiation, immunomodulation, and paracrine signaling of MSCs, provides opportunities to treat cartilage and orthopedic tissue degeneration. This review comprehensively examines the biology of cartilage and chondrocytes, the therapeutic potential of MSCs and other stem cell types (e.g., induced pluripotent stem cells [iPSCs], embryonic stem cells [ESCs]), and the strategies employed for in vitro chondrogenesis. To date, preclinical studies in small and large animal models have provided robust histological and biomechanical evidence of tissue regeneration. While clinical trials predominantly focused on safety and preliminary efficacy results mainly in knee OA and focal chondral lesions showed promise, bioengineering approaches, including genetic modifications, co-culture systems, biomaterial scaffolds, and extracellular vesicle delivery continue to evolve and enhance MSC performance and specificity. Despite these advances, challenges persist, including donor heterogeneity, standardization of protocols, regulatory complexities, and risks of hypertrophy or ossification. Future directions include organoid-based modeling, AI-driven patient stratification, and precision orthobiologics to enable personalized, scalable therapies. Ultimately, collaborative efforts across disciplines are essential to translate stem cell therapies into standardized, effective clinical solutions for cartilage regeneration.

Keywords: Chondrocyte, Orthopedics, MSCs, Regenerative Medicine, Cartilage Repair, Transplantation, iPSCs, Biomaterials, Polymers, Stem Cells

Introduction

Orthopedic and cartilage disorders, including osteoarthritis (OA) and traumatic chondral injuries, represent leading causes of chronic pain, disability, and reduced quality of life worldwide. An estimated 32 million adults in the US have some degree of OA, accounting for more than $100 billion annually in direct and indirect healthcare costs [1]. Traumatic joint injuries are also prevalent among younger, active populations (e.g., athletes, military personnel) [2]. For example, damage within the acetabulum of the hip, from various conditions, often manifest in post-traumatic OA wetherinadequately treated or even when adequately treated [3]. Despite the high burden of disease, current therapeutic strategies remain largely palliative or limited in capacity to address bone and joint infrastructural damage [4].

Traditional treatment strategies have long included microfracture, autologous chondrocyte implantation (ACI), and osteochondral grafting [5]. The limited regeneration capacity of hyaline cartilage within the joints makes treatment of articular cartilage lesions challenging [6]. Microfracture stimulates fibrocartilage formation but lacks the biomechanical integrity of native hyaline cartilage and often deteriorates within 5–10 years. On the other hand, ACI is technically complex, involves multiple surgeries, and is restricted by donor cell availability and chondrocyte de-differentiation [7]. Further, the surgical technique for osteochondral grafting requires precision to obtain predictable and reliable results [8]. While there have been advances in approaches to traditional treatments, limited long-term success persists. Thus, there is an urgent need for innovative biologic therapies capable of restoring true cartilage architecture and function.

Regenerative medicine approaches, including stem cell therapies, have emerged as promising alternatives to the traditional options. In particular, mesenchymal stromal cells (MSCs), derived from bone marrow (BM-MSCs), adipose tissue (AD-MSCs), synovial membrane (SM-MSCs) and umbilical cord (UC-MSCs), have demonstrated potential for inducing chondrogenic differentiation, immunomodulation, and paracrine signaling that promotes tissue repair [9,10]. In addition other human pluripotent cell types, such as induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), offer additional regenerative capacity, though their clinical translation is hindered by safety and ethical considerations [11,12]. The objective of this review is to examine the current landscape of stem cell-based strategies for cartilage and orthopedic repair, with a focus on MSCs, and to highlight recent advancements in cell sourcing, delivery methods, and translational challenges, with the aim of identifying key knowledge gaps and informing the development of next-generation regenerative therapies for musculoskeletal disorders.

Anatomical and Physiological Aspects of Cartilage and Chondrocytes

Structurally, cartilage is composed of four zones: 1) superficial, 2) middle; 3) deep; and 4) calcified. Each zone is distinguished by a unique extracellular matrix (ECM) with unique composition and chondrocyte morphology [13]. In general, the ECM is primarily composed of type II collagen and aggrecan, which provide tensile strength and compressive resistance, respectively [14]. Articular cartilage, specialized connective tissue that covers the ends of long bones within synovial joints, provides a smooth, lubricated surface for articulation and distributes mechanical loads to the underlying subchondral bone. Articular cartilage is avascular, aneural, and alymphatic, limiting its intrinsic regenerative capacity and contributing to poor healing after injury [15].

Chondrocytes, the sole resident cell type in cartilage, are responsible for maintaining ECM homeostasis [16]. In healthy adult cartilage, chondrocytes exist in a quiescent, low-proliferative state and vary in phenotype depending on their zonal location [17]. Chondrocytes exhibit distinct metabolic and gene expression profiles across zones, with surface zone cells expressing lubricin (PRG4) and deeper zone cells expressing hypertrophic markers such as collagen X under pathological conditions [18]. With aging and mechanical stress, chondrocytes can undergo phenotypic drift, including dedifferentiation and senescence, leading to an imbalance in anabolic and catabolic activities [19]. This disruption promotes matrix degradation and cartilage breakdown. The repair of age-related breakdown is hindered by the tissue's lack of vascularity and low mitotic activity of chondrocytes. Lesions in the superficial zones often fail to heal, while deeper injuries that breach the subchondral bone can initiate a repair response involving MSCs from the bone marrow. However, this typically results in the formation of fibrocartilage, a mechanically inferior substitute composed largely of type I collagen [20]. Microfracture, osteochondral autografts, and autologous chondrocyte implantation offer limited durability and cannot replicate the structural and functional properties of the native hyaline cartilage [21]. In OA and traumatic injuries there is greater complexity in the interplay of mechanical, biochemical, and inflammatory factors. The sustained biomechanical stress and low-grade inflammation of OA drive chondrocyte activation, leading to overexpression of matrix metalloproteinases (MMPs) and aggrecans (ADAMTS) [22]. This response leads to the degradation of collagen and proteoglycans which cannot be replaced endogenously [23]. On the other and, traumatic injuries cause localized matrix disruption and cellular apoptosis, initiating a catabolic cascade that can evolve into post-traumatic OA [24]. Additionally, the altered fuel delivery due to the injury induces a cascade of pathophysiological feedback [25]. Mitochondrial dysfunction, oxidative stress, and the production of inflammatory mediators such as IL-1β and TNF-α exacerbate ECM degradation and chondrocyte dysfunction [26]. Understanding these biological processes is essential for the development of regenerative strategies that not only restore cartilage structure but also modulate the cellular microenvironment to support long-term tissue integration and durability. In this context MSCs have emerged as the most extensively studied and clinically utilized stem cell type in orthopedic applications. Their multipotency, immunomodulatory properties, and relative ease of isolation

position them as ideal candidates for tissue engineering. MSCs not only differentiate into chondrocytes to facilitate matrix regeneration but also secrete a diverse array of cytokines and growth factors that orchestrate the repair process and promote a supportive microenvironment. Consequently, harnessing the full potential of MSCs represents a promising avenue for addressing the complex challenges of cartilage repair and ensuring the durability of regenerated tissue.

Stem Cell Types in Orthopedic Regeneration

MSCs. MSCs are the most extensively studied and clinically utilized stem cell type in orthopedic applications due to their multipotency, immunomodulatory properties, and relative ease of isolation [27]. BM-MSCs remain the gold standard due to their well-characterized chondrogenic capacity, but AD-MSCs and SM-MSCs have gained attention for their higher yield and proliferative potential [28]. MSCs are typically characterized by their adherence to plastic in standard culture, expression of surface markers ($CD73^+$, $CD90^+$, $CD105^+$, and negative for hematopoietic markers CD34, CD45, CD14/CD11b, CD79α/CD19, and HLA-DR), and their ability to differentiate into osteogenic, adipogenic, and chondrogenic lineages under defined *in vitro* conditions [29]). Importantly, MSCs' chondrogenic differentiation is enhanced in three-dimensional (3D) culture systems using chondrogenic media supplemented with TGF-*β* isoforms [30]. However, hypertrophic differentiation and the expression of collagen X remain challenges, especially for BM-MSCs, which tend to favor an endochondral ossification trajectory [31].

Adipose Tissue-MSCs (AD-MSCs). AD-MSCs have garnered increasing attention as a promising cell source for chondral and orthopedic tissue repair due to their abundance, minimally invasive harvest procedures, and potent regenerative capabilities. Compared to bone marrow-derived MSCs, AD-MSCs yield higher initial cell counts and exhibit comparable trilineage differentiation potential, including robust chondrogenic capacity under appropriate culture conditions [32,33]. AD-MSCs express classical MSC markers (CD73, CD90, CD105) and demonstrate immunomodulatory effects through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-*β*, making them particularly advantageous for modulating the inflamed microenvironment characteristic of osteoarthritis and post-traumatic joint injuries [34]. Preclinical studies have shown that intra-articular injection or scaffold-based implantation of AD-MSCs enhances cartilage regeneration, reduces synovial inflammation, and improves biomechanical properties of the repair tissue [35]. Furthermore, AD-MSCs have demonstrated efficacy in large animal models, where they promoted hyaline-like cartilage formation and integrated well with surrounding native cartilage [36]. In clinical studies, AD-MSC-based therapies have shown encouraging results, with improvements in pain, joint function, and MRI-assessed cartilage quality in patients with knee osteoarthritis and focal chondral defects [37]. However, variability in isolation protocols, donor heterogeneity, and the need for standardized characterization and potency assays remain key challenges to widespread clinical adoption [38]. Despite these limitations, ongoing advancements in cell processing, scaffold integration, and regulatory frameworks continue to support the translational potential of AD-MSCs in orthopedic regenerative medicine.

Synovial Membrane-MSCs. SM-MSCs are a promising cell source for cartilage regeneration due to their high proliferative capacity, superior chondrogenic differentiation, and native joint-tissue origin. Compared to MSCs from bone marrow or adipose tissue, SM-MSCs demonstrate enhanced expression of chondrogenic markers such as SOX9, COL2A1, and ACAN under TGF-β3 stimulation, and generate more hyaline-like extracellular matrix *in vitro* and *in vivo* [39]. Their isolation from arthroscopic synovial biopsies offers a relatively non-invasive and joint-specific harvest method, minimizing donor-site morbidity while enabling autologous application [40]. Recent studies in animal models show that intra-articular delivery of SM-MSCs leads to superior cartilage integration and improved histologic scores compared to other MSC types [41]. In humans, clinical trials and case series report that SM-MSCs improve pain, function, and MRI-based cartilage morphology in knee osteoarthritis and focal chondral lesions, with sustained effects and favorable safety profiles over 12–24 months [42,43]. Furthermore, their immunomodulatory capacity enables anti-inflammatory crosstalk with synoviocytes and macrophages, reducing catabolic cytokine production and slowing osteoarthritic progression [44]. Nonetheless, challenges remain in standardizing GMP-compliant isolation, scaling for large joints, and ensuring reproducible cell potency across donors and disease states [44]. However, their anatomic proximity to cartilage and responsiveness to biomechanical stimuli underscore SM-MSCs as optimal candidates for precision cartilage repair strategies.

Induced Pluripotent Stem Cells (iPSCs). iPSCs also offer a promising alternative to traditional treatment strategies. iPSCs have unlimited proliferative capacity and ability to differentiate into any somatic cell type, including chondrocytes [45]. iPSCs can be generated from patient-specific somatic cells, such as fibroblasts or peripheral blood mononuclear cells (PBMCs), and reprogrammed using transcription factors (e.g., OCT4, SOX2, KLF4, c-MYC) [46,47]. Chondrogenic differentiation of iPSCs can be achieved through embryoid body formation, stepwise induction mimicking embryonic development, or direct lineage conversion using transcriptional or epigenetic modifiers [48]. Recent protocols incorporating SOX9 overexpression and biomimetic scaffolds have enhanced the generation of hyaline-like cartilage from iPSCs [49]. Despite these advances, iPSC-derived therapies are not yet widely used clinically due to concerns over tumorigenicity, including teratoma formation from residual undifferentiated cells [50]. Moreover, regulatory pathways for iPSC-derived products remain complex, given the critical need for stringent quality control, genetic stability monitoring, and good manufacturing practices (GMP) within the regulatory pathway. In parallel, other pluripotent stem cell sources such as ESCs have also demonstrated regenerative potential in orthopedic applications; however, their clinical translation has been hindered by persistent ethical concerns, limited public acceptance, and regulatory constraints related to their derivation and use.

Embryonic Stem Cells (ESCs). ESCs have shown potential in

orthopedic regeneration but remain less commonly used due to ethical and translational barriers [51]. ESCs possess robust chondrogenic capacity and have been used in preclinical models to generate articular cartilage-like tissue [52]. However, their clinical use is limited by ethical concerns surrounding embryo-derived cell sources, as well as similar risks of tumorigenicity [53]). In addition, cartilage-derived progenitor cells (CDPCs) and periosteal progenitors, offer lineage specificity with reduced risk of dedifferentiation [54]. However, low abundance and limited *in vitro* expansion capacity constrain large-scale application. UC-MSCs and amniotic-derived cells are allogenic sources, which present immunologic and logistical advantages. To date limited clinical validation has been performed with UC-MSCs [55].

In Vitro Chondrogenesis Using MSCs

The success of MSC-derived cartilage constructs is heavily influenced by the culture system, signaling environment, and biophysical cues provided during differentiation. MSCs cultured in traditional two dimensional (2D) monolayers typically lose their chondrogenic potential over successive passages due to dedifferentiation and expansion-associated senescence [56]. In contrast, 3D culture systems (e.g., pellet cultures, micromass cultures, and scaffold-embedded constructs) better recapitulate the native chondrogenic niche and enhance cell–cell and cell–matrix interactions. This enhanced recapitulation is critical for increasing the effectiveness of chondrogenesis [57]. Pellet cultures are commonly used to induce chondrogenesis through spontaneous MSC condensation and are often the gold standard for *in vitro* differentiation assays [58]. Chondrogenic induction of MSCs requires supplementation with defined growth factors, most notably members of the transforming growth factor-beta (TGF-β) superfamily. TGF-β1 and TGF-β3 are essential for initiating and maintaining chondrogenic differentiation via SMAD2/3 signaling, which promotes expression of chondrogenic transcription factors such as SOX9 [59]. Bone morphogenetic proteins (BMP-2, BMP-6, BMP-7) synergize with TGF-β to enhance ECM production and inhibit hypertrophy [60]. In contrast, Wnt signaling plays a dual role: canonical Wnt/β-catenin signaling is associated with terminal hypertrophic differentiation and ossification, while non-canonical Wnt pathways may promote stable chondrogenesis [61]. Thus, temporal and spatial modulation of these pathways is critical to engineer hyaline-like cartilage tissue.

For scaffold-embedded constructs, the choice of scaffold greatly affects MSC chondrogenesis. Via influencing cell morphology, matrix deposition, and nutrient diffusion the scaffold can mimic aspects of the native ECM. Natural polymers (e.g., collagen, alginate, hyaluronic acid, and fibrin) mimic aspects of the native ECM and support biocompatibility and cell viability [62]. On the other hand, synthetic hydrogels like polyethylene glycol (PEG) and polylactic-co-glycolic acid (PLGA) provide tunable mechanical and degradation properties. While there are benefits to synthetic polymers, they may lack intrinsic bioactivity [63]. In addition, the combination of natural and synthetic scaffolds as well as enhancement of scaffolds functionalization with adhesion peptides (e.g., RGD motifs) have been used to improve MSC attachment and chondrogenic outcomes [64]. More recent advancements, such as injectable thermo-responsive hydrogels and 3D-printed biopolymer matrices that allow for patient-specific tissue engineering continue to expand the therapeutic platform [65].

Cartilage is a load-bearing tissue, and mechanical cues are essential to recapitulate *in vivo* conditions during *in vitro* chondrogenesis [66]. Dynamic compression, hydrostatic pressure, and shear stress applied via bioreactors have been shown to upregulate chondrogenic gene expression and enhance ECM organization [67]. Cyclic loading activates integrin-mediated mechano-transduction and promotes synthesis of collagen type II and aggrecan, key components of functional cartilage [68]. Optimized bioreactor systems facilitate nutrient exchange and mechanical loading while maintaining sterile, scalable culture conditions necessary for clinical translation [69].

Successful *in vitro* chondrogenesis is characterized by the upregulation of specific molecular markers. SOX9, a master transcription factor, is essential for MSC commitment to the chondrogenic lineage [70]. ECM components such as aggrecan and collagen type II (COL2A1) indicate synthesis of cartilaginous matrix, while suppression of collagen type I (COL1A1) and type X (COL10A1) is necessary to avoid fibrocartilage and hypertrophic phenotypes, respectively [71]. Quantitative RT-PCR, immunohistochemistry, and biochemical assays (e.g., DMMB for glycosaminoglycans) are routinely used to assess differentiation status and tissue quality.

Preclinical Animal Models and Outcomes

The preclinical evaluation of stem cell–based therapies for cartilage repair has relied extensively on both small and large animal models, each offering distinct advantages and limitations in translational research. Small animal models, particularly rodents, have enabled rapid, cost-effective exploration of cell-scaffold interactions, full-thickness cartilage defect repair, and initial safety profiling. These models typically involve surgically created defects in the femoral trochlea or condyle, followed by evaluation of MSC or biomaterial-based treatments. However, rodents possess thin articular cartilage, high intrinsic regenerative potential, and quadrupedal gait, which limits the predictive value for human translation due to their enhanced capacity for spontaneous healing and biomechanical differences [72].

Large animal models such as goats, sheep, pigs, and horses better mimic human cartilage thickness, subchondral architecture, and joint loading conditions, thereby offering more rigorous assessment of safety and efficacy. Goats and sheep are commonly employed for osteochondral defect models, particularly in the medial femoral condyle and patellar groove, while equine models provide a clinically relevant system with spontaneous cartilage lesions that mirror human post-traumatic OA [73]. Although gait mechanics differ from bipedal humans, large animal models allow for longer-term evaluation, weight-bearing recovery, and integration with clinical imaging modalities such as MRI and arthroscopy.

The mode of stem cell delivery is a critical determinant of ther-

apeutic outcome. Intra-articular injection of MSCs offers a minimally invasive approach for widespread cartilage degeneration, yet retention and homing remain significant challenges. Conversely, scaffold-based delivery into focal chondral defects allows for localized engraftment, mechanical stabilization, and controlled trophic factor release. Biomaterial carriers such as biodegradable hydrogels, collagen sponges, and decellularized extracellular matrix composites have shown efficacy in improving cell retention, phenotypic stability, and matrix deposition [74].

Outcome measures in preclinical studies are multifaceted. Some examples are presented below:

i. Histological analysis using Safranin-O staining for glycosaminoglycans, immunohistochemistry for collagen type II, and scoring systems such as O'Driscoll or ICRS II remains the gold standard for tissue evaluation [75].

ii. MRI and micro-computed tomography (μCT) are used for longitudinal monitoring of defect fill, integration, and subchondral remodeling [76].

iii. Biomechanical assessments, such as indentation testing and compressive modulus measurements, quantify restoration of functional properties relative to native cartilage.

iv. Synovial biomarkers (e.g., COMP, MMP-13) and cytokine profiling offer insights into inflammation and joint homeostasis [77].

Key Findings and Translational Relevance

Numerous studies using large animal models have demonstrated that MSCs enhance cartilage regeneration by promoting matrix deposition, modulating inflammation, and improving mechanical properties. In a goat model, collagen scaffolds seeded with autologous MSCs implanted into full-thickness femoral condyle defects resulted in significantly improved histological repair and mechanical function compared to acellular controls [78]. Intra-articular MSC injection in an ovine OA model reduced cartilage erosion and synovial inflammation, highlighting their chondroprotective and immunomodulatory potential [79].

Additionally, preconditioning strategies have been shown to enhance chondrogenic differentiation and suppress hypertrophic markers, especially in iPSC-derived chondrocytes [80]. These advances have further refined the regenerative profile of stem cell-based constructs and extended their translational appeal.

Despite promising outcomes, translational challenges persist. These include species-specific immune responses, differences in cartilage healing kinetics, and variability in defect creation and assessment methodologies. Nonetheless, well-designed, GLP-compliant large animal studies now represent a critical component of the regulatory pathway for Investigational New Drug (IND) submissions in regenerative orthopedics. Regulatory agencies increasingly require such studies to substantiate clinical trial readiness, highlighting the need for reproducible and rigorous preclinical evidence to bridge the bench-to-bedside gap.

Clinical Applications and Trials

Therapeutic stem cell regimen for cartilage repair have progressed from preclinical promise to clinical application in select orthopedic indications. Initial trials primarily focused on OA, focal chondral lesions, and meniscal injuries, leveraging MSCs. More recently, iPSC–derived chondrocytes have been administered. While numerous early-phase studies demonstrate encouraging safety and efficacy, beyond OA of the knee, larger RCTs remain limited. Furthermore, methodological variability continues to challenge interpretation and generalizability across joints. A 2023 systematic review identified over 100 clinical trials investigating intra-articular MSC therapy for knee OA, with most using autologous BM-MSCs or AD-MSCs [81]. Phase I/II studies consistently demonstrate good tolerability and modest improvements in pain and function (e.g., WOMAC, VAS), particularly in patients with Kellgren-Lawrence grade II–III OA [82]. The landmark trial (Chondrogen, NCT01227694) compared allogeneic BM-MSCs to hyaluronic acid (HA) in knee OA and showed superior improvement in WOMAC scores at 12 months without serious adverse events [83]. For focal cartilage defects, surgical implantation of MSC-laden scaffolds has yielded promising outcomes. Gobbi *et al*., administered autologous BM-MSCs seeded on a HA scaffold showed significant defect fill and improved International Knee Documentation Committee (IKDC) scores at 2 years [84]. Similarly, a commercial allogeneic UC-MSC product (Cartistem), demonstrated improved MRI and histological scores in a phase III trial in Korea (NCT01733186) [85]. Meniscal repair studies are more limited but suggest potential for MSCs to enhance integration and prevent degenerative progression. Vangsness *et al*. reported in a phase I/II study that meniscal volume increased significantly at 12 months after allogeneic MSC injection post-partial meniscectomy [86].

The human trials have primarily employed two principal delivery strategies. Intra-articular injection of MSCs is less invasive and suitable for early to moderate OA. It permits repeated dosing and has been the predominant mode in most trials. However, concerns include poor cell retention, distribution, and potential off-target effects [87]. The other, surgical implantation involves placing MSCs, either in suspension or scaffold-bound, into focal defects. This method enables precise localization, supports chondrogenic differentiation via 3D microenvironments, and facilitates better integration with surrounding tissue [88]. While more invasive, it is preferred for isolated defects or younger active patients.

Across completed trials, MSC therapies have demonstrated a favorable safety profile, with no reports of tumorigenesis, ectopic tissue formation, or long-term adverse events attributable to the cells [89]. Reported benefits include reductions in pain and stiffness, improved cartilage thickness by MRI (dGEMRIC, T2 mapping), and histologic evidence of hyaline-like cartilage regeneration in select biopsy studies [90]. Despite these findings, heterogeneity in MSC source, dose, expansion protocols, and outcome measures complicates cross-trial comparison. In a RCT (NCT03686196), autologous ADSCs significantly improved KOOS scores and MRI-assessed cartilage thickness over saline control at 12 months [91]. Additionally,

cartilage regeneration with BM-MSCs combined with microfracture outperformed microfracture alone in a matched cohort analysis, showing sustained benefit at 5 years [92]. In another study, post-meniscectomy injection of allogeneic MSCs (NCT01856140) showed a dose-dependent increase in meniscal volume and reduced pain scores [93]. Several critical limitations persist in clinical translation. Many trials lack standardized definitions of cell phenotype, viability, or passage number. In addition, most trials assess outcomes over 6–24 months, which may not capture durability or delayed adverse effects, and many early-phase studies are uncontrolled or open-label. Further, methodological concerns (e.g. the use of heterogeneous scoring systems and imaging modalities) hinder analytical validity. Adding complexity is the divergent regulatory classifications across countries challenge global trial harmonization and market approval [94]. To address these issues, consortia such as the International Cartilage Regeneration & Joint Preservation Society (ICRS) and FDA's Regenerative Medicine Advanced Therapy (RMAT) designation are working to establish trial standards and fast-track promising therapies [95].

Engineering Approaches and MSC Enhancement

The promise of MSCs for cartilage regeneration has been to some extent attenuated by their intrinsic chondrogenic capacity and long-term functional integration remain suboptimal. Advanced bioengineering strategies aim to enhance MSC performance by modifying their genetic, epigenetic, and microenvironmental context. These approaches seek to improve cell fate control, augment matrix synthesis, and promote durable hyaline cartilage formation. Genetic engineering of MSCs has emerged as a strategy to drive lineage-specific differentiation and mitigate hypertrophy. Transfection with chondrogenic transcription factors such as SOX9 enhances cartilage-specific matrix production and suppresses osteogenic drift [96,97]. Viral and non-viral vectors have been used to overexpress TGF-β3, BMP-2, and IGF-1, resulting in increased type II collagen and aggrecan expression [98]. However, concerns regarding insertional mutagenesis and long-term gene expression stability limit clinical application. Novel systems like dCas9-VP64 for targeted epigenetic activation offer more controlled modulation of gene networks without altering DNA sequence [99].

Co-culture with primary chondrocytes or chondrogenically primed cells enhances MSC differentiation through paracrine signaling and ECM deposition [100]. Direct contact and trans-well systems have shown that chondrocyte-derived ECM and secreted morphogens promote SOX9 activation, enhance GAG production, and delay hypertrophy [101]. Dynamic co-culture systems are now being integrated with bioreactors to mimic the zonal architecture of native cartilage [102].

Biomaterial Scaffolds with Controlled Growth Factor Delivery

The design of biomimetic scaffolds has advanced from passive structural support to active modulators of cell behavior. Natural polymers (e.g., collagen, hyaluronic acid, alginate) and synthetic hydrogels (e.g., PEG, PLGA) are functionalized with growth factor–loaded nanoparticles for spatiotemporal release of chondrogenic cues [103]. Scaffold systems delivering TGF-β3, BMP-7, or Kartogenin have been shown to enhance *in vivo* cartilage regeneration and reduce the need for repeat dosing [104]. Smart materials responsive to mechanical loading or pH further enable on-demand factor release [105].

MSCs secrete extracellular vesicles (EVs) and exosomes containing miRNAs, proteins, and lipids that mimic the regenerative functions of their parent cells. MSC-derived exosomes have demonstrated anti-inflammatory, chondroprotective, and matrix-stimulating effects in OA models [106]. Encapsulation of EVs in hydrogels or fibrin clots improves joint retention and cartilage targeting [107]. Preconditioning MSCs (e.g., hypoxia, inflammatory cytokines) enhances the bioactivity of their exosomes, suggesting a path for cell-free therapeutic development [108].

CRISPR/Cas9 gene editing enables precise activation or repression of genes involved in chondrogenesis and hypertrophy. For instance, CRISPR-mediated knockdown of RUNX2 or MMP13 in MSCs has been shown to suppress terminal differentiation and matrix degradation [109]. In parallel, microRNAs (e.g., miR-140, miR-221) regulate SOX9, ACAN, and COL2A1 expression and are being leveraged as gene therapy targets or delivered via nanoparticles [110]. Epigenetic drugs like HDAC inhibitors and DNA methylation modulators are also being explored to stabilize chondrogenic gene expression and resist dedifferentiation [111].

Immunomodulatory and Paracrine Effects of MSCs

MSCs possess potent immunomodulatory and paracrine properties that contribute significantly to their therapeutic efficacy in osteoarthritis (OA) and cartilage repair. Beyond their differentiation potential, MSCs influence the inflammatory milieu and facilitate tissue homeostasis by interacting with immune and stromal cells through secreted bioactive molecules and direct cell-cell contact.

Within the OA joint, persistent inflammation contributes to cartilage degradation, synovial hyperplasia, and pain. MSCs exert anti-inflammatory effects by secreting immunosuppressive cytokines such as interleukin-10 (IL-10), transforming growth factor-β (TGF-β), prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (IDO) [112]. These factors suppress Th1 and Th17 responses while promoting regulatory T cells (Tregs), thus rebalancing the local immune environment [113]. Intra-articular injection of MSCs has been shown to significantly reduce synovial inflammation and matrix metalloproteinase (MMP) expression, preserving cartilage integrity in both preclinical and clinical studies [83].

MSCs actively interact with synoviocytes, macrophages, T cells, and natural killer (NK) cells, modulating their activation states. In OA joints, fibroblast-like synoviocytes (FLS) contribute to chronic inflammation and cartilage breakdown. MSC-derived exosomes and

direct contact with FLS can downregulate pro-inflammatory mediators such as IL-6, TNF-α, and MMP-13, shifting FLS toward a less aggressive phenotype [114]. MSCs also polarize macrophages toward the anti-inflammatory M2 phenotype, which promotes tissue remodeling and pain relief [115]. These interactions are mediated by both soluble factors (e.g., TSG-6, HGF) and extracellular vesicles containing microRNAs (e.g., miR-21, miR-146a) [116].

Role in Modulating OA Progression

The paracrine and immunomodulatory mechanisms of MSCs contribute to delayed OA progression, reduced cartilage erosion, and symptom amelioration in both experimental and clinical settings. *In vivo* studies show that MSC-treated joints exhibit decreased synovitis, reduced osteophyte formation, and improved cartilage histology [117]. Clinical trials have reported sustained improvements in pain, function, and joint space narrowing, attributed in part to the immunosuppressive environment fostered by MSCs rather than structural regeneration alone [118]. These findings suggest that MSC-based therapy may function as a disease-modifying osteoarthritis drug (DMOAD), a designation currently unmet by conventional treatments.

Challenges and Limitations

Despite encouraging advances in MSC-based therapies for cartilage repair and OA, several challenges continue to hinder consistent clinical translation and regulatory approval. These limitations span biological variability, manufacturing complexity, safety concerns, and ethical and economic barriers. One of the most significant biological barriers to MSC therapy is donor-dependent variability, which affects proliferative capacity, differentiation potential, secretome composition, and immunomodulatory efficacy. Age, sex, comorbidities (e.g., diabetes, obesity), and tissue source (e.g., bone marrow vs. adipose) all influence MSC phenotype and function [119,120]. Additionally, MSCs represent a heterogeneous population, and culture expansion further contributes to phenotypic drift and reduced potency over time [121]. This heterogeneity complicates reproducibility and therapeutic consistency across studies and patient populations.

There is a pressing need for standardized protocols for MSC isolation, expansion, and characterization. Variables such as enzymatic digestion conditions, culture media composition, passage number, and surface marker expression thresholds (e.g., $CD73^+$, $CD90^+$, $CD105^+$, negative for CD45/CD34) are inconsistently reported [122]. The absence of uniform potency assays and reliable biomarkers to predict *in vivo* performance limits regulatory approval and clinical uptake [123]. Good Manufacturing Practice (GMP)–compliant production also requires strict control of contaminants, sterility, and batch-to-batch consistency, adding substantial complexity and cost. Cell-based therapies must comply with evolving regulatory frameworks from agencies such as the FDA and EMA, which require extensive preclinical data on biodistribution, tumorigenicity, and mechanism of action [124]. MSCs have shown a low but non-negligible risk of ectopic tissue formation, particularly hypertrophy, osteophyte formation, and ossification when used for chondrogenesis [125,126]. Some studies have also raised theoretical concerns about pro-tumorigenic behavior, particularly in immune-suppressed environments or in long-term cultures with accumulated mutations [127]. These safety considerations necessitate extensive monitoring and limit rapid clinical translation.

While MSCs derived from adult tissues (e.g., bone marrow, adipose, synovium) bypass many of the ethical challenges associated with embryonic stem cells, the use of perinatal sources (e.g., umbilical cord, placenta) still prompts debate regarding consent and commercialization. Furthermore, economic barriers remain substantial, as large-scale GMP production, cold-chain logistics, and personalized dosing models are resource-intensive [128]. Cost-effectiveness studies are needed to demonstrate long-term value in comparison to conventional surgical or pharmacological treatments for cartilage disorders.

Future Directions and Emerging Technologies

The field of regenerative orthopedics is rapidly evolving, propelled by innovations in bioengineering, artificial intelligence (AI), and personalized medicine. Emerging platforms seek to overcome current translational barriers by improving preclinical modeling, optimizing patient selection, and enhancing therapeutic efficacy through multimodal strategies. Organoid and microphysiological systems (MPS) such as cartilage-on-a-chip platforms have emerged as powerful tools to model cartilage physiology and drug response *in vitro* with high fidelity [129,130]. These platforms replicate zonal architecture, biomechanical loading, and synovial fluid flow, allowing precise assessment of chondrogenic differentiation, ECM production, and inflammatory responses. Compared to traditional monolayer or pellet cultures, these systems provide more predictive data for translational success and reduce the need for early animal testing. Machine learning algorithms are increasingly being integrated into clinical trial design and regenerative medicine to identify patient subgroups most likely to benefit from stem cell therapy [131,132]. AI can analyze high-dimensional datasets (i.e., imaging, genomics, and serum biomarkers), to predict treatment outcomes and optimize MSC sourcing or dosing strategies [133]. Predictive analytics may also support adaptive trial designs and real-time monitoring of joint function, aiding personalized care. Autologous iPSCs represent a promising avenue for truly personalized regenerative medicine [134]. These cells can be reprogrammed from patient-specific somatic cells and differentiated into chondrocyte-like cells with reduced immunogenicity and ethical concerns [37]. However, variability in differentiation efficiency and potential for genomic instability remain barriers that must be overcome with standardized manufacturing and quality control. The next generation of cartilage regeneration strategies involves synergistic approaches that combine MSCs with gene therapy, bioactive scaffolds, or controlled-release systems for sustained delivery of growth factors such as TGF-β3, BMP-7, and FGF-18 [135,136]. Co-delivery of chondrogenic genes via non-viral vectors is under investigation to enhance lineage commitment while minimizing safety concerns associated with viral transduction. These combination strategies aim

to more closely mimic the complex, multifactorial environment of native cartilage repair. Emerging point-of-care bioprocessing platforms now enable intraoperative isolation and delivery of autologous MSCs, potentially reducing processing time and cost [137]. Portable devices for real-time characterization of stem cells and biomaterial-enhanced injectables may allow precision orthobiologics tailored to defect geometry, local inflammation, and patient-specific biology. Integration with wearable sensors could provide closed-loop feedback on function and tissue response post-treatment.

Conclusion

Significant advances over the past two decades have established stem cell–based strategies, particularly MSCs, as promising candidates for cartilage regeneration in orthopedic medicine. Preclinical studies have demonstrated the chondrogenic capacity of MSCs in both scaffold-based and injectable systems, with supportive histologic, biomechanical, and imaging outcomes across diverse animal models. Emerging technologies, including bioprinting, extracellular vesicles, genetic modification, and immunomodulation, further enhance the therapeutic potential of these approaches. Early-phase clinical trials suggest intra-articular MSC administration is safe and associated with symptom relief and some degree of cartilage regeneration, particularly in osteoarthritis and focal chondral lesions. However, heterogeneity in patient responses, outcome measures, and manufacturing processes remains a major barrier to robust interpretation.

Despite encouraging early results, stem cell–based cartilage repair has not yet achieved widespread clinical adoption. Translation to routine care is hindered by inconsistent definitions of cell identity and potency, lack of consensus on dosing and delivery routes, and variability in trial design and endpoints. The field is also challenged by regulatory hurdles, particularly for genetically modified or allogeneic products, and by the economic burden of cell manufacturing under Good Manufacturing Practice (GMP) standards. Nevertheless, innovations in point-of-care processing, smart biomaterials, and predictive biomarkers, augmented by advances in patient stratification using AI and multi-omics, are likely to accelerate the development of next-generation orthobiologic therapies. Longitudinal registries validated surrogate endpoints, and integration with real-world data will be crucial to demonstrate durability, cost-effectiveness, and comparative efficacy.

To unlock the full clinical potential of regenerative orthopedics, the field must embrace standardized frameworks for stem cell sourcing, expansion, characterization, and delivery. Harmonization of protocols across academic, clinical, and industry stakeholders in conjunction with adherence to international guidelines is essential to ensure reproducibility and safety. Multi-center clinical trials with shared data repositories, unified outcome metrics, and longer follow-up periods are urgently needed to overcome current knowledge gaps. Collaborative efforts across disciplines will be key to developing scalable, personalized, and regulatory-compliant solutions. In this context, stem cell–based cartilage regeneration stands poised to redefine the treatment paradigm for osteoarthritis and cartilage injury, addressing an urgent and growing burden in both civilian and military populations.

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