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Engineering Strategies for Biomaterial–Mesenchymal Stem Cell Synergy in Cartilage Defect Repair

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Abstract. Managing articular cartilage defects remains hard in clinic because this tissue barely has any endogenous repair ability, so MSC-based approaches have drawn interest but their use is limited by poor retention, early apoptosis, and differentiation that is difficult to control. Biomaterials can give structural, mechanical, and biochemical signals that improve MSC behavior. This paper sorts out the engineering strategies that combine biomaterials with MSCs for cartilage repair and compares how well they perform. Three issues stood out. Carrier-based delivery consistently increased matrix synthesis when compared with free cells or extracellular vesicles, but only a minority of studies had carrier-only or vesicle-only controls, and fibrosis and hypertrophy were seldom measured while follow-up was generally too short to catch late degeneration. MSC source heterogeneity was mostly treated as a fixed condition, with donor variability not reported. These limitations mean that durable translation will need standardized outcome measures, controlled comparisons across multiple donors using the same carrier, and longer observation windows.

Keywords: Cartilage tissue engineering, mesenchymal stem cells, biomaterials, extracellular vesicles, osteoarthritis

1. Introduction

Osteoarthritis (OA) is the most common adult joint disorder, and it adds a lot to chronic pain and disability, the 2021 Global Burden of Disease Study reported that 595 million people had OA in 2020, around 7.6% of the world population, with a 132.2% rise since 1990 and more growth expected in the knee, hip, hand, and other sites by 2050 [1]. Articular cartilage, which is the main tissue affected by OA, is avascular, aneural, and hypocellular, so after structural injury it has almost no ability to regenerate [2]. The clinical options available now, including conservative medication and standard surgical repair, mostly just relieve pain and inflammation without rebuilding functional, load-bearing hyaline cartilage, and degeneration often comes back while OA keeps progressing. Data from large arthroscopic studies also show the complexity of clinical cartilage injury; most lesions appear together with other intra-articular injuries, meaning only a small part of patients can meet the criteria for standard cartilage repair, and early defects are widely undertreated [3].

MSC-based therapy has been seen as a possible way to repair cartilage because MSCs have chondrogenic potential, immunomodulatory activity, and paracrine trophic effects, but direct

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injection of free MSCs has given inconsistent benefits, mostly because the cells die quickly in vivo, stay poorly at the defect, and show uncontrolled hypertrophic differentiation inside the inflamed joint [4]. It has become clear that biomaterials are not just passive carriers, they can act as functional regulators through scaffold physicochemical properties, spatiotemporal release of bioactive factors, and material-based cell manipulation, and by doing so they can redirect MSC fate, change the local inflammatory environment, and limit fibrocartilage formation [4]. Although many biomaterial–MSC combinations have already been made, systematic head-to-head comparisons of their therapeutic effects are still rare, and translational barriers have not been described in detail.

Against this background, the present review outlines how biomaterials and MSCs can work together during functional cartilage regeneration, and the content is arranged around three main engineering approaches: modulation of scaffold physicochemical properties, spatiotemporal delivery of bioactive factors or genes, and biomaterial-mediated MSC preconditioning or exosome-based treatment. Key therapeutic outcomes such as cell retention, survival, ECM synthesis, and inhibition of fibrosis and hypertrophy are compared in a quantitative way where possible, and the influence of MSC source heterogeneity is also examined. Unresolved technical and methodological obstacles to clinical use are pointed out, and directions for future investigation are suggested to support more standardized optimization and translation of advanced cartilage regenerative materials.

2. Principles and core elements of biomaterial–MSC synergy in cartilage regeneration

2.1. Self-healing difficulty of articular cartilage defects

Articular cartilage is a specialized connective tissue that is hypocellular, avascular, and aneural, chondrocytes make up only 1–10% of the tissue volume and the surrounding matrix is mostly water (60–80% of wet weight), type II collagen, and aggrecan [2]. Chondrocyte nutrition depends completely on passive diffusion from synovial fluid, which severely limits the intrinsic repair capacity of damaged cartilage.

Data from a large clinical sample of 25,124 knee arthroscopies also point to the complexity of cartilage injury patterns [3]. Cartilage lesions showed up in 60% of the examined knees, but only 67% of these were isolated focal defects, while the rest were linked to progressive OA or osteochondritis dissecans, and meniscal tears or cruciate ligament injury appeared together with 70% of cartilage lesions, with only 7% of patients meeting the standard criteria for clinical cartilage repair surgery. These epidemiologic findings mean that most cartilage injuries cannot qualify for conventional surgical treatment, so many defects stay undertreated and degeneration keeps going.

The inflammatory environment adds another barrier to endogenous repair, pro-inflammatory cytokines such as IL-1β and TNF-α trigger NF-κB and MAPK signaling, and this upregulates matrix metalloproteinases (MMPs) and ADAMTS enzymes that degrade cartilage ECM while also suppressing chondrogenic matrix synthesis [4]. Persistent M1 macrophage polarization keeps chronic intra-articular inflammation going, but the dynamic reversibility of this catabolic environment is not well described because most studies measure molecular markers only at endpoint time points instead of tracking continuous changes across repair.

Repair capacity also changes with defect depth, partial-thickness defects stay avascular and have no fibrin clot or progenitor recruitment, so chondrocytes cannot bridge the gap, while full-thickness defects open the subchondral bone and let marrow MSCs in, but the repair tissue that forms is mostly fibrocartilage rich in type I collagen, which is mechanically weak and tends to degenerate. Osteochondral defects also disrupt the calcified cartilage–tidemark–subchondral plate interface, causing subchondral sclerosis and osteophyte formation [4], and overall endogenous cartilage self-

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repair tends to produce pathological hypertrophic fibrocartilage rather than functional hyaline cartilage, pushing the progression from focal lesions to diffuse OA.

2.2. Roles and limitations of MSC in cartilage repair

MSCs help cartilage repair mainly via chondrogenic differentiation, paracrine secretion of trophic factors, and intra-articular immunomodulation, while MSC-derived small extracellular vesicles (MSC-sEVs) have attracted special interest as minimally invasive agents because they promote chondrocyte proliferation and improve ECM composition [4]. But moving MSC-sEV therapy into the clinic is held back by inconsistent isolation methods, variable dosing, and unstable in vivo delivery.

MSC source heterogeneity is a main confounding factor for repair outcome, bone marrow-derived MSCs (BM-MSCs) have strong chondrogenic capacity but tend toward hypertrophic differentiation, while adipose-derived MSCs (AD-MSCs) make less matrix, and synovial or umbilical cord-derived MSCs add more variability in therapeutic behavior [4]. Free MSCs injected into the joint also cannot fill the defect, bear mechanical load, or integrate stably with host cartilage, and the inflamed joint environment triggers extensive MSC apoptosis, giving highly variable and short-lived repair results.

In a 2025 rat OA study, a single intra-articular injection of adipose-derived MSC EVs raised the pain threshold, improved gait, and shifted macrophages toward an M2 phenotype according to scRNA-seq, but that study did not use a scaffold delivery vehicle, so the residence time of EVs within the joint and the possible benefit of a retentive carrier remain unknown [5]. More generally, MSC EV studies have not shown that the delivery vehicle itself adds biological activity, because observing reduced inflammation after MSC EV injection does not make clear whether hydrogels, cryogels, or bilayer scaffolds would change that response, and delivering a single MSC type in suspension is unlikely to create durable hyaline cartilage.

2.3. Synergistic functions of biomaterials

Structural support is fundamental, a 3D porous scaffold prevents defect collapse, allows cell spreading, reduces cell loss, and controls nutrient diffusion, and in osteochondral defects graded porosity can match the cartilage and bone layers at the same time. But a scaffold that is optimized for cell retention may not do well under load, since MSCs need a microenvironment with different mechanical properties from the joint, which requires a stiff, load-distributing implant, and most studies have not found a scaffold stiffness that works best for both at once.

Mechanical signals also shape MSC fate, softer matrices generally favor chondrogenesis and stiffer substrates promote osteogenesis, although 3D conditions can change these responses, while stress relaxation, surface topography, and dynamic loading all affect cytoskeletal tension. The stiffness optimum for early chondrogenic commitment may still differ from the optimum for long-term maintenance, a matrix that induces SOX9 at week 1 may later induce RUNX2 and COL10A1 at week 6 because the cells have changed, and few studies follow this temporal drift.

Chemical cues also regulate chondrogenesis, scaffolds can release TGF-β3 to promote chondrogenesis or BMP-2 to stimulate osteogenesis, and degradation products such as Ca^{2+} and Mg^{2+} can stimulate matrix synthesis, while surface functional groups matter a lot because –COOH/–OH groups tend to favor chondrogenesis, $–NH_2$ favors osteogenesis, and RGD sequences improve retention, and layered scaffolds can be designed to copy zonal cues inside native cartilage.

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The 2025 MSC-EV study achieved M2 polarization after a single bolus injection, but the core limitation of sEV therapy is still variable dosing and rapid clearance in vivo, a bolus dose cannot supply the sustained, localized, carrier-mediated release that chondrogenic commitment needs over several weeks, and no single-factor system has solved this problem yet [4, 5]. The functions of biomaterials affect cell survival, differentiation pathways, and final tissue quality, but a central problem is that existing evidence does not support a comparative ranking of strategies because outcome measures vary across studies, carrier effects are not separated from cell source effects, and donor-to-donor heterogeneity is generally not reported.

3. The classification and significant studies of engineering strategies for biomaterial MSC synergy

3.1. Strategies for modulating physicochemical properties of biomaterials

Scaffold design has moved past simple mechanical matching toward active control of cell fate through physical and chemical cues, and for osteochondral repair graded multiphasic constructs are now common, 3D-printed bilayer scaffolds can combine a cartilage-like collagen upper layer with a bone-like hydroxyapatite composite lower layer to give zone-specific stiffness and porosity that support simultaneous chondrogenesis and osteogenesis [6]. Most validations, however, still depend on small animal models, with little large-animal or long-term data to back clinical translation.

The YAP/TAZ axis works as a central mechanotransduction mediator, soft microenvironments reduce YAP/TAZ activation and thereby suppress hypertrophic markers and stabilize the chondrocyte phenotype, while excessive mechanical stress can drive aberrant YAP/TAZ-dependent terminal differentiation [6]. Current bioreactors do not reproduce physiological multi-axial joint loading, which limits how accurate mechanical regulation can be, and ROS-responsive smart hydrogels can adapt to inflammatory conditions through phenylboronic acid crosslinking to provide on-demand degradation and drug release, but most studies use acute traumatic defect models instead of chronic degenerative OA conditions, so long-term scaffold stability remains uncertain [6].

Surface chemistry also directs MSC lineage commitment, the type and nanoscale arrangement of functional groups influence integrin clustering and focal adhesion assembly, which then shape differentiation, decellularized ECM scaffolds have strong chondroinductive potential but are limited by batch-to-batch variability and a composition that is not fully defined [6]. Isolated bioactive motifs simplify fabrication but may lose the full synergistic effects of native matrix, and heparin-mediated immobilization of TGF-β3 and BMP-2 can sustain local bioactivity, although protease activity and scaffold degradation in vivo will change release kinetics in ways that static in vitro optimization cannot capture [6].

Scaffold degradation should be matched to the progression of tissue remodeling, a fixed degradation rate cannot adapt to early inflammation and later matrix maturation, surface-eroding polymers tend to preserve morphology and pH while bulk-eroding PLGA can undergo abrupt mechanical failure and produce acidic byproducts. Most studies measure only mass loss instead of changes in compressive modulus over time, so mechanical compatibility is often assessed imprecisely, enzyme-responsive crosslinks allow adaptive degradation, but how degradation products feed back into joint inflammation remains a largely unexplored gap.

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3.2. Spatiotemporal biofactor and gene delivery strategies

Because soluble cytokines are cleared rapidly in vivo, sustained delivery needs a carrier, and multi-stage tunable systems provide more precise regulation, kartogenin (KGN)-conjugated chitosan particles can sustain release for up to seven weeks to enhance chondrogenesis, while embedding these particles in silk fibroin hydrogels further stabilizes local concentrations [7]. Varying the silk β-sheet content modulates the release rate and allows delivery to be matched to different repair stages, but most release profiles are verified in buffered solutions while the stability of bioactive factors in inflammatory joint environments is rarely measured.

Integrated spatiotemporal delivery may improve signaling coordination, sequential release systems mimic the natural repair sequence by delivering anti-inflammatory factors first and chondrogenic cues after that, while biphasic spatial scaffolds keep chondrogenic and osteogenic signals separate to avoid contradictory lineage instructions [7]. Existing designs usually treat temporal and spatial control separately, and only a few systems optimize both dimensions together.

Gene-activated scaffolds shift the approach from exogenous factor supplementation to in situ endogenous synthesis, scaffolds functionalized with SOX9 can upregulate chondrogenic markers and suppress endochondral ossification, and co-delivery of RUNX2-targeted shRNA/miRNA can simultaneously inhibit osteogenic differentiation while enhancing SOX9-mediated chondrogenesis [8]. Still, most studies only check short-term transfection efficiency, with little long-term quantification of in situ protein synthesis or functional tissue assessment, and this limits the clinical interpretation of gene-activation strategies.

3.3. Biomaterial-mediated MSC preconditioning, co-culture, and exosome delivery

Preconditioning MSCs with biomaterials can improve repair stability, but the approach has clear limits, Joyce et al. created SOX9 gene-activated PCL-reinforced collagen–hyaluronic acid scaffolds and observed two-order SOX9 upregulation and a 17.5-fold increase in COL2 expression in hMSCs [8]. The separate contributions of scaffold mechanics and gene transfection were not isolated, and long-term transgene stability has not been checked, Wu et al. used nanoparticle–peptide dual-engineered MSCs to improve joint homing, but possible pro-inflammatory metal residues and unquantified modification efficiency raise concerns about safety and reproducibility, and layered spheroid scaffolds support spatial osteochondral regeneration although diffusion of factors across layers makes accurate assessment of outcome harder [9, 10].

MSC-EV therapy depends on exosomal bioactive cargo to modulate repair, exosomal CD73 converts ATP to adenosine and activates AKT/ERK signaling to promote chondrocyte proliferation, but current inhibitor experiments do not tell apart adenosine receptor subtypes, and the in vivo retention, distribution, and cell-specific uptake of EVs remain poorly defined, with most studies reporting only single-time-point efficacy without systematic mechanistic analysis or carrier-based optimization [11].

4. Comparison of strategy efficacy and analysis of problems

4.1. Quantitative comparison of core therapeutic indicators

Cell or EV retention is the most basic endpoint, but inconsistent detection standards make cross-study comparison difficult, most scaffolds improve local retention although retention half-life and long-term safety risks are seldom quantified. The evaluation of cell survival has a logical

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contradiction because some studies treat post-transplantation MSC apoptosis as beneficial since apoptotic vesicles can promote M2 polarization, while other studies define cell survival as a core therapeutic advantage, and this leaves the field with conflicting criteria.

ECM synthesis is the outcome measured most often, scaffold-based delivery consistently produces greater sGAG and type II collagen deposition than injection of cells or EVs alone, but most studies leave out blank carrier and pure EV controls, so the independent therapeutic contributions stay unclear, and conflicting effects on cell proliferation versus matrix synthesis further point to unresolved mechanistic ambiguities in current signaling models [11].

Inhibition of fibrosis and hypertrophy is one of the most clinically important long-term endpoints but is also the least evaluated, most studies use short-term histological OA scores instead of quantitative measures of COL10A1, MMP-13, or fibrotic area, and short in vivo follow-up means late hypertrophic ossification and fibrocartilage degeneration are rarely captured, which is a primary translational bottleneck for current repair strategies [4].

4.2. MSC source heterogeneity affects repair outcomes

Current studies use MSCs from multiple sources such as bone marrow, adipose tissue, umbilical cord, and infrapatellar fat pad, with inconsistent pretreatment and modification protocols, these sources differ inherently in chondrogenic potential, susceptibility to apoptosis, and paracrine profiles, donor-to-donor variability is often ignored, and cell source is treated as a fixed condition, which adds to unstable and hard-to-reproduce results [9-11].

Cell engineering and carrier delivery add further confounders, spheroid culture, peptide transfection, and scaffold encapsulation all change cellular behavior, so it is impossible to separate the effects of cell source, modification, and carrier, no standardized comparative experiment has been reported, and there are no operational criteria for evaluating MSC therapeutic efficacy, so widespread heterogeneity seriously impedes clinical standardization of biomaterial–MSC composite therapy.

5. Conclusion

This paper organized and compared three engineering strategies for biomaterial–MSC synergy in cartilage repair, that is, modulation of scaffold physicochemical properties, spatiotemporal delivery of bioactive factors or genes, and cell preconditioning through co-culture or extracellular vesicle-based approaches, scaffold design supplies structural and mechanical cues that direct MSC fate, controlled release systems prolong the availability of chondrogenic signals, gene-activated matrices support sustained endogenous protein production, and vesicle-based strategies use paracrine pathways while avoiding the viability limitations of whole-cell transplantation. Across studies, carrier-mediated delivery consistently improved matrix synthesis relative to free cells or vesicles, but the size of this advantage is unclear because most studies lacked carrier-only or vesicle-only controls, fibrosis and hypertrophy received the least attention, and follow-up was generally too short to capture late degeneration, while MSC source heterogeneity was treated as a batch constant rather than a controlled variable, leaving donor variability unquantified.

These observations lead to several conclusions, the apparent synergy between biomaterials and MSCs cannot be separated from carrier dose and local release kinetics unless experiments are designed to isolate each component, and the current reliance on histology and short-term readouts tends to overestimate early repair and underestimate late failure, which produces an incomplete evidence base. Cross-study synthesis is also difficult under existing reporting practices, because

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without standardized retention half-lives and hypertrophy markers, results from different laboratories cannot be readily compared.

The framework presented here links scaffold design, signaling strategies, and cell source to measurable repair outcomes and offers practical guidance for choosing engineering approaches according to defect type and clinical constraints, a quantitative meta-analysis was not possible because endpoints were heterogeneous and reporting was incomplete, so future studies should apply the same carrier across multiple MSC sources and donors, adopt unified outcome measures, and extend follow-up to detect fibrosis and hypertrophy, and such standardization is needed before biomaterial–MSC synergy can be translated into durable repair of articular cartilage.

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