International Journal of Nanomedicine

Dovepress
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REVIEW

The Interaction Between Microbiota and Stem Cells on Progression of Osteoarthritis and Engineered Stem Cell for Enhancing Osteoarthritis Treatment

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Abstract: Osteoarthritis (OA) is characterized by the degeneration of articular cartilage caused by several factors of which novel most trends include microbiota. Specific microbiota and the role in the development of OA is less clear. The microbiota is presumed to influence OA occurrence and progression mainly via immune modulation. In recent years, bone marrow mesenchymal stem cells (MSCs) have shown great potential for the treatment of OA, however, the therapeutic efficiency has been seriously affected by the harsh microenvironment in the joint cavity. At present, many strategies have been used to enhance the function of MSCs, among them, engineering are a promising method. Therefore, this review mainly focuses on the latest research on how the microbiota affects the development of OA, stem cell repair, and the use of engineered MSCs in the treatment of OA. In addition, engineered MSCs can enhance the therapeutic potential of exosomes as a novel strategy for treating OA. Our review provides a comprehensive perspective on the role of microbiota in OA and the influence of MSCs therapy and engineered MSCs on the treatment of OA.

Keywords: microbiota, microenvironment, engineering bone marrow mesenchymal stem cell, osteoarthritis, repair

Introduction

Osteoarthritis (OA), one of the most common degenerative diseases with changing of subchondral bone and degeneration of articular cartilage, affects more than 500 million people worldwide and causes significant pain and disability worldwide.[1,2] Despite causing a serious social burden, there are limited treatment options available to effectively prevent disease progression. OA is characterized by the destruction of articular cartilage, subchondral bone changes, and synovitis, eventually leading to limited joint movement and pain.[3,4] Therefore, it is important to analyze the pathological mechanisms underlying OA. Currently, research has found that biomechanical factors such as aging play an important role,[5–7] however, a deeper understanding of the pathological mechanism of OA is beneficial for treatment. In recent years, a large number of studies have shown that microbiota plays an important role in OA.[8,9] These include gut microbiota as well as those in joints.[10,11] Gut microbiota is a group of organisms that live in the gut, and over 1014 microorganisms have been recognized, including eukaryotes, bacteria, and archaea.[12,13] Bacteria constitute the largest proportion of microorganisms.[14] Recent research has found that OA is closely related to the gut microbiota.[15] The dysbiosis can destroy the gut barrier and change innate immunity and adaptive immunity to activate the "gut–joint axis." Among them, modification of fatty acids, LPS release, and activation of macrophages can regulate T and B cell responses and differentiation.[16–18] Moreover, Gut microbiota can interact with other OA risk factors such as sex, age, obesity, inflammation, and mechanical load to influence OA progression.[18] In contrast, the microbiota in the synovial joint is an area of active research. The joints were considered to be sterile under normal physiological conditions. However, growing evidence suggests that complex synovial microbiota is present in both joint health and disease. The balance

Received: 15 December 2024
Accepted: 27 February 2025
Published: 13 March 2025

of the microbial community is important for host health, including the protection of the immune system and absorption of minerals and dietary fiber, and its ecological imbalance is related to OA.

Traditional treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and hyaluronic acid injections, provide symptomatic relief. NSAIDs are commonly used for pain management, long-term use is associated with gastrointestinal and cardiovascular side effects. Corticosteroids provide short-term pain relief but may accelerate cartilage degeneration with repeated use. Hyaluronic acid injections improve synovial fluid viscosity and provide moderate pain relief, but their effects are temporary.[19,20] MSCs represent a fascinating therapeutic approach for OA, unlike traditional therapies that primarily provide symptomatic relief, MSCs have the potential to promote cartilage repair and modulate the inflammatory environment within the joint including the release of growth factors, exosomes, and other molecules to repair OA.[21,22] In addition, MSCs can derived from different sources, like bone marrow and adipose tissue, which have shown favorable preclinical therapeutic efficacy including OA and others due to their immunomodulatory and regenerative properties.[23,24] Therefore, it is promising to engineer MSCs to improve their therapeutic abilities.

In this review, we first provide an overview of osteoarthritis, and then discuss the latest research on how the microbiota influences the progression of OA, the interaction between microbiota and stem cells, and the advancement of engineering MSCs to repair OA.

Overview of Osteoarthritis

Osteoarthritis affects approximately 650 million people worldwide as of 2020,[25] and more than 22% of adults over 40 years of age will encounter OA, making it the fourth major cause of disability globally. Currently, the main treatment involves lifestyle modifications, including weight loss, exercise, injection of hyaluronic acid or PRP into the knee, and non-steroidal anti-inflammatory drugs. With age patients undergo total joint replacement rather that elderly patients are candidates for receiving a total joint compared to younger ones.[26] However, total joint replacement has a limited lifespan and poor prognosis, resulting in significant social costs.[27,28] Therefore, new therapeutic methods are urgently needed owing to the lack of effective treatments.

The main pathological features of patients with OA include synovial inflammation, and instability of ligaments and tendons.[29] Cartilage, the main part of a joint, is an avascular tissue, and chondrocytes are the most important cells in cartilage to maintain cartilage homeostasis through secretion of the extracellular matrix, which is the direct cause of OA.[30] The main clinical symptoms of OA include knee pain and limited knee movement.[31] Magnetic Resonance Imaging (MRI) can be used to observe the degeneration of the articular cartilage and narrowing of the joint space. However, the MRI is not the single imaging method in OA and not the golden standard as well and the potential pathogenesis of OA is still poorly understood.[27] Although OA occurs in many joints, the knee joint is particularly susceptible to OA and has been the most studied joint.[32] Knee OA leads to substantial economic losses through direct and indirect means, including reduced work-related productivity and therapeutic costs.[33] Total knee replacement surgeries are expected to increase significantly as age increases, and the annual rate of joint replacement in the USA is expected to reach one million by 2023.[34]

The Major Risk Factors of OA

OA is more frequently associated with advancing age; in this process, there are many predisposing risk factors.[35] Primary risk factors, including obesity, aging, sex, overweight, and knee injuries, among them, obesity and aging are major risk factors for OA.[27] On the one hand, obesity is widely recognized as a risk factor, beyond the mechanical overload of BMI. It also showed its effects through various risk factors.[36] Dysfunction of adipose tissue is involved in OA through inflammation of local and systemic immune dysfunction and pro-inflammatory cytokines and adipokines, which have independent effects on OA. In recent years, many studies have emphasized the importance of adipose tissue as a risk factor for inflammation. Collins et al used a mouse model of lipodystrophy to study the direct impact of adipose tissue on OA, and they found that fat-free mice were protected from cartilage damage, whether fed a chow or high-fat diet[37] (Figure 1A). In addition, obesity is closely correlated with OA-relative pain, pain is the main symptom of OA, in the past decade, joint overload of obesity was believed to be the main factor associated with pain; however, the effect of mechanical overloading of obesity on OA pain has been extended to other factors. Obesity is believed to be strongly

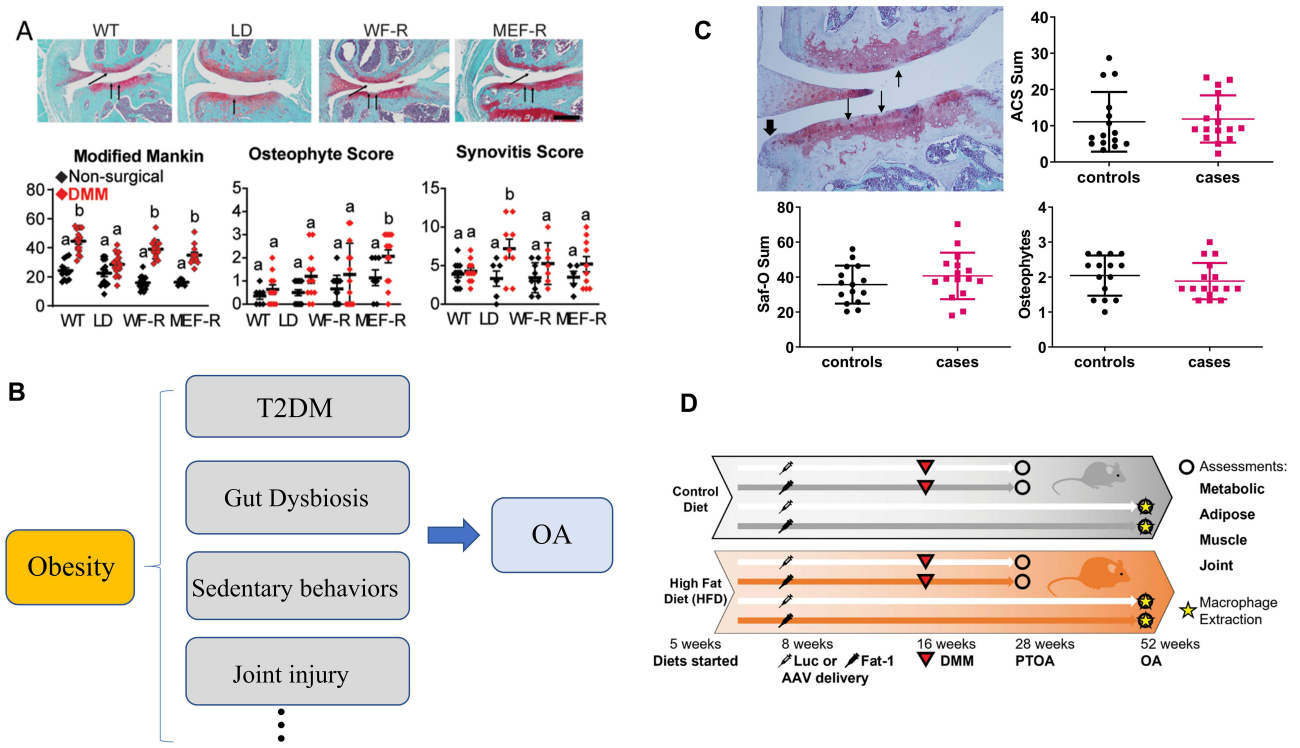

Figure 1 (A) Transplantation of fat restores susceptibility to OA damage. Reproduced from Collins KH, Lenz KL, Pollitt EN, et al. Adipose tissue is a critical regulator of osteoarthritis. Proc Natl Acad Sci U S A. 2021;118(1):e2021096118.[37] Black arrows indicate areas of cartilage damage and proteoglycan loss. $P < 0.05$ between groups is indicated by the letters "a and b". (**B**) Several OA-related risk factors are associated with obesity. (**C**) Histological analysis of knee joints from mice fed a high-fat, high-sucrose diet and transplanted with osteoarthritis or control fecal pools for 40 weeks, black arrows indicate areas of cartilage damage. Reproduced from Loeser RF, Arbeeva L, Kelley K, et al. Association of increased serum lipopolysaccharide, but not microbial dysbiosis, with obesity-related osteoarthritis. Arthritis Rheumatol. 2022;74(2):227–236. Copyright 2022, John Wiely and Sons.[42] (**D**) Experimental timeline of systemic obesity characteristics at 28 and 52 weeks of age after HFD and medial meniscus. Reproduced from Tang R, Harasymowicz NS, Wu CL, et al. Gene therapy for fat-1 prevents obesity-induced metabolic dysfunction, cellular senescence, and osteoarthritis. Proc Natl Acad Sci U S A. 2024;121(43):e2402954121.CCBY-NC-ND.[43]

associated with T2DM, gut dysbiosis, sedentary behaviors, etc., and these factors are closely associated with pain.[38] Therefore, the intricate interplay between obesity and OA factors emphasizes the importance of obesity in OA[39–41] (Figure 1B). Loeser et al found that obesity may contribute to OA through facilitated absorption of LPS by intestinal permeability, and a mouse model showed that a Western diet-induced the development of OA by cartilage degradation[42] (Figure 1C). Tang et al hypothesized that obesity leads to cellular senescence, which is associated with an increased severity of OA. They also demonstrated that systemic AAV8-fat1 gene therapy significantly reduced HFD-associated inflammation and cellular senescence[43] (Figure 1D). On the other hand, aging is another major risk factor that has been recognized for OA. Disorder in the aging-related signaling pathway significantly induced joint destruction. There have been some excellent reviews discussing the relationship between aging and OA.[44,45] Recently, Swahn et al used single-cell sequencing analyses of articular cartilage and meniscus tissues from patients with healthy and knee OA; senescence-related genes were significantly upregulated in the OA group, and FAP and ZEB1 were the main regulators and new therapeutic targets for OA treatment.[46] Chondrocytes are the main cell type in cartilage tissue. During aging, chondrocytes undergo senescence and induce dysregulation of cartilage tissue, thereby inducing the development of OA.[47] Recently, some studies have demonstrated that the elimination of senescent chondrocytes reduces OA progression by decreasing SASP secretion, indicating that targeting senescent chondrocytes could be a promising strategy for OA treatment.[48] However, the mechanisms underlying the aging of the articular cartilage are not fully understood. Recently, Cao et al found that endocytosis mediated by clathrin and activation of Notch signaling induced chondrocyte senescence and promoted the development of osteoarthritis, which could be negatively regulated by MYL3, further research found that MYL3 was reduced sharply in senescent chondrocytes in a mouse model and OA patients.[49] Therefore, chondrocyte senescence is an important risk factor for OA.

https://doi.org/10.2147/IJN.S511884

Growing evidence has shown a close relationship between the gut microbes and OA. Moreover, in addition to the gut microbes, recent studies have found that the microbiota can be identified in the joint. Therefore, we discussed the effects of intestinal microbes (Gut–Joint Axis) and joint microbes (Joint Microbiome–Joint Axis) on OA respectively.

The Gut–Joint Axis: How Gut Microbiota Influence OA

Research has shown that gut microbes, their metabolites, and secreted components exacerbate OA by triggering systemic and local immune responses.[50] Huang et al demonstrated that transplantation of fecal microbiota in mice would accelerate osteoarthritis in metabolically compromised human donors. They showed that compared with the control group, mice with higher systemic concentrations of inflammatory factors had higher gut permeability and severe OA. A large number of *Fusobacterium* and *Faecalibacterium* and fewer *Ruminococcaceae* in the transplanted gut were consistently correlated with OA severity.[51] Schlupp et al showed that sex differences in the mice were associated with gut microbiome differences, which were associated with OA, the analysis of the gut microbiome showed 44 differences, in addition, serum cytokine analysis showed three different cytokines including IL-12, eotaxin, and TNFα, all highest in male and female-into-male transplanted animals, they provided the explicit evidence that the gut microbiome is related to sex difference and result in different OA severity.[52] The current view is that gut microbes affect OA mainly by regulating the immune system. Recent research has shown that gut microbes regulate OA through the innate and adaptive immune systems. The gut microbe product, PAMP, activates pattern-recognition receptors that are present in macrophages and other immune cells;[53] then, the inflammatory signaling pathway is activated.[54] Deng et al demonstrated that AuNPs can delay progression in a gut microbiota-dependent manner, gold nanoparticles could change the diversity of gut microbes, and increase the abundance of *Akkermansia* and *Lactobacillus*.[55] When the intestinal barrier is damaged, microbial products enter the bloodstream, leading to an inflammatory response.[56] Researchers have shown that gut microbes can also regulate T-cell responses through segmented filamentous bacteria, which induce Th17 cells in the knee. This was achieved by stimulating DCs by increasing amyloid A, which in turn induced the appearance of Th17 cells.[57] Recent studies have also shown that using *Lactobacillus paracasei* or prebiotics to treat OA has great potential in reducing obesity-related OA risks. O-Sullivan et al tested probiotic therapy for OA through oral administration of *Lactobacillus acidophilus* after induction of OA by PMM surgery and found that *Lactobacillus acidophilus* significantly reduced inflammation in the knee joint and prevented the development of OA. Their findings suggest a likely effect of *Lactobacillus acidophilus* on OA therapy.[58] As discussed above, obesity is an important risk factor for OA, and recent research indicates that the effect of obesity on OA is induced by inflammation, which is believed to be derived from gut microbiome dysbiosis Schott et al compared the lean and obese murine gut and found that beneficial *Bifidobacteria* were reduced in the obese group, while pro-inflammatory gut microbes were increased, and the supplementation of oligofructose restored the gut microbiome in the obesity group, particularly *Bifidobacterium pseudopodium*. Their results indicated that the gut-joint axis is important in the administration of special microbial species to inhibit OA.[59] In another study, to demonstrate the effects of *Lactobacillus rhamnosus* in OA, they induced OA through monosodium iodoacetate injection and orally administered *Lactobacillus rhamnosus*, and the effect was examined in an OA model. The results demonstrated that pain severity and pro-inflammatory factors were significantly decreased. In addition, intestinal damage was ameliorated by *Lactobacillus rhamnosus* extract. These findings demonstrated the therapeutic potential of *Lactobacillus rhamnosus* in OA.[60] To examine the influence of gut microbes in patients with knee OA, Huang et al collected plasma and fecal samples from patients undergoing total knee replacement, and 16S rRNA sequencing was conducted on fecal samples to determine the gut microbial composition, indicating that gut microbes play an important role in OA development with sustained pain in patients after TKR, which may be through their activation of inflammatory responses, lipid metabolism pathways, and central sensitization.[61] Therefore, the above studies indicate that the gut-joint axis plays an important role in the development of OA, and further studies should be conducted on the gut–joint axis to explore the specific mechanism.

The Joint Microbiome–Joint Axis and OA

The joints were considered sterile under normal physiological conditions. However, growing evidence suggests that complex synovial microbiota is present in both joint health and disease,[62–64] and the synovial joint microbiota is relatively sparse compared to other tissues, such as the skin and gut. They are mainly composed of bacteria, although viruses, fungi, and archaea may also be present. The predominant bacterial phyla identified in the healthy synovial fluid included Actinobacteria, Firmicutes, Bacteroidetes, and Proteobacteria.[10] Zhao et al used 16S rRNA gene amplicon sequencing to analyze bacterial

nucleic acid among OA patients and found abundant differences in bacterial RNA and that *Bacteroides caccae* was present in the synovial fluid of OA patients.[65] Another study conducted by Rodríguez et al found a large number of *Proteobacteria* in patients with OA compared with normal knee when collecting synovial fluid for next-generation sequencing analysis.[66] In addition, research identified that more than 30% of bacteria were found in patients before knee arthroplasty using RNA sequencing, and *Staphylococcus, Streptococcus*, and *Cutibacterium species* were also found.[67]

The presence of microbiota in the synovial joint raises questions regarding its role in joint health and disease.[68] Dysbiosis of the knee microbiome may also lead to higher permeability and allow other microbiota to thrive, ultimately leading to infection.[68] Borsinger et al obtained a sample from joint fluid from non-operative knees for NGS analysis, and multiple microorganisms were identified in several patients; among them, *Cutibacterium acnes* was identified as the most common organism.[69] Siala et al demonstrated that bacterial DNA was present in 50% of synovial fluid samples from patients with OA using broad-range rDNA PCR and found that *Stenotrophomonas maltophilia* and *Shigella species* were the most common species, as well as the rarely occurring pathogens in humans, such as *Arenicola species* and *Pantoea ananatis*.[70] Tsai et al aimed to analyze the intra-articular microbiome and to find the relationship between it and OA in OA progression, the data from RNA-sequencing deriving from OA patient synovial tissue showed that a large number of differentially abundant microbes were identified, which participated in inflammation-induced extracellular matrix remodeling and decreased cell signaling pathways, and those were important for OA process. They demonstrated significant associations between intra-articular microbes and the OA process[64] (Figure 2A). Therefore, the above research demonstrates that the microbiota is also present in the knee; however, its role in OA is not well understood. Wang et al used the microbiome as a biomarker to determine the risk of overweight people with OA and collected feces from overweight OA and normal people using 16S RNA sequencing to identify bacteria, and the results indicated that the diversity and richness of the microbiome were significantly reduced in overweight patients with OA. Finally, they identified seven optimal biomarkers for microbial identification, including *Gemmiger, Akkermansia, Klebsiella, Prevotella, Alistipes, Bacteroides*, and *Parabacteroides*, and used a random forest model[71] (Figure 2B).

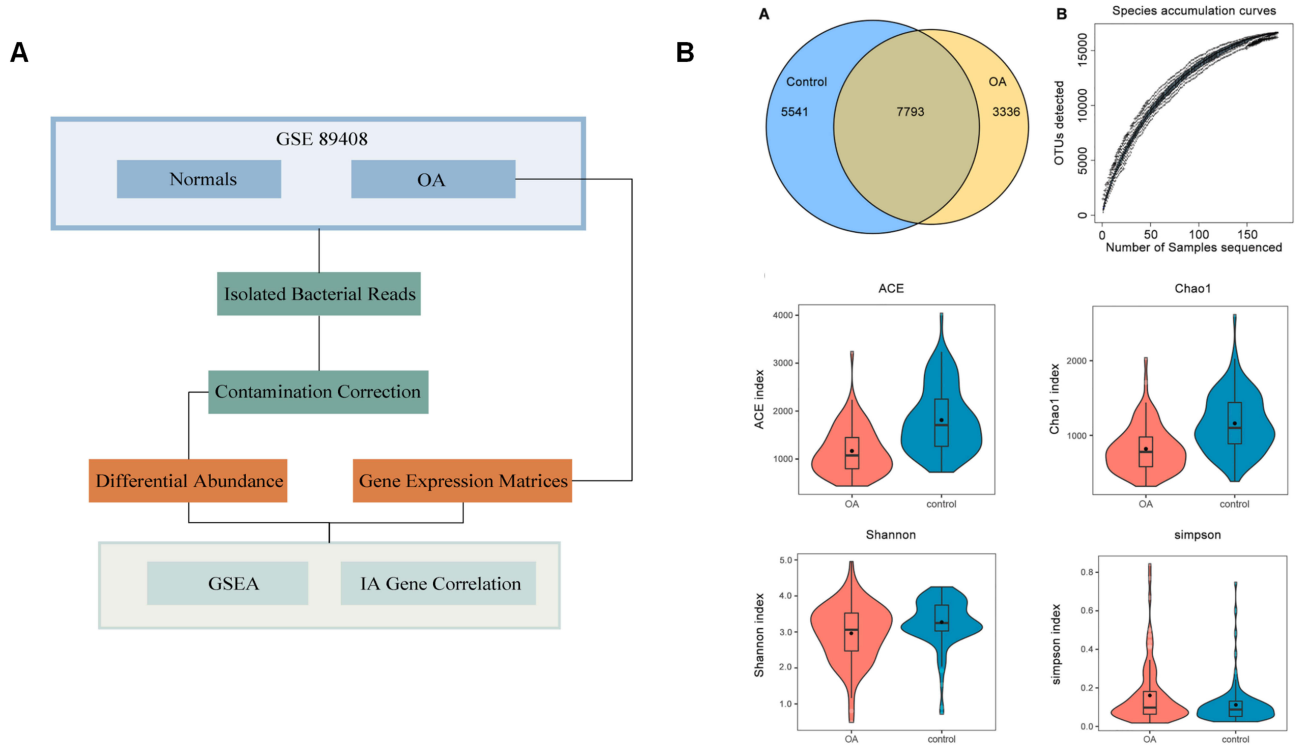

Figure 2 (**A**) Schematic diagram of the analysis and workflow for the analysis of the intra-articular microbiome between normal and OA. Reproduced from Tsai JC, Casteneda G, Lee A, et al. Identification and characterization of the intra-articular microbiome in the osteoarthritic knee. Int J mol Sci. 2020;21:22. © 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.[64] (**B**) Comparison of OTUs between OA and control groups. Reproduced from Wang Z, Zhu H, Jiang Q, Zhu YZ. The gut microbiome as non-invasive biomarkers for identifying overweight people at risk for osteoarthritis. Microb Pathog. 2021;157:104976. Cooyright 2021, Elsevier.[71]

https://doi.org/10.2147/IJN.S511884

The microbiota plays a critical role in regulating the environment in the knees through immune modulation, inflammatory response regulation, metabolic interactions, and pain perception. Understanding these mechanisms provides valuable insights into the pathophysiology of osteoarthritis and highlights potential therapeutic strategies aimed at modulating the microbiota to improve joint health. Continued research in this area is essential to further elucidate these complex interactions and develop effective microbiota-targeted therapies for OA. Therefore, joint microbiomes in the knee are important to explore the potential role of joint microbiomes in OA disease development.

The Impact of Microbiota on MSCs

Stem cell therapies are highly beneficial to patients. Research on MSC therapy has increased dramatically owing to its advantages including the relatively small number of cells required, immunomodulatory effects, and easy accessibility to patients.[72] Stem cells from autologous or allogeneic cells and different tissues have different effects in the treatment of OA. Currently, in vitro and vivo animal model, the main repair mechanism involves the differentiation of stem cells into chondrocytes under specific conditions and promotes cartilage regeneration.[73] In addition, stem cells could also act as paracrine molecules by secreting bioactive molecules that act on chondrocytes to promote proliferation and inhibit apoptosis. However, the mechanism by which the microenvironment of the joint affects the therapeutic efficiency of stem cells is not yet fully understood. The joint microenvironment includes both the physical and biological microenvironments.

The microbiota can influence stem cell repair ability through the following aspects.

1. Promotion of regenerative potential: certain metabolites such as SCFAs can improve the regenerative effort of MSCs by promoting their proliferation and differentiation into tissue-specific lineages.
2. Modulation of the immune response: by altering the joint microenvironment to affect the immune environment, the microbiota can either exacerbate or mitigate inflammation, ultimately impacting the inflammatory signals encountered by stem cells. Macrophages can polarize from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes. In addition, M1 macrophages can inhibit MSC proliferation, weaken their ability to suppress the immunosuppressive environment and prevent cartilage repair.
3. Alteration of ECM Dynamics: changes to the ECM structure and composition due to microbial activity can affect the availability of adhesion sites and growth factors necessary for stem cell function.

In addition, microbiota influences stem cell repair mechanisms by producing a range of bioactive compounds.

1. Short-chain fatty acids (SCFAs): SCFAs regulate immune responses and influence MSC differentiation and function with self-renewal and chondrogenic abilities, regulatory factors can be secreted in the body.[74]
2. Amino acid derivatives: microbes can convert amino acids into derivatives such as tryptophan metabolites, which have been shown to regulate T-cell function and potentially affect stem cell behavior. Activation of the kynurenine pathway plays an important role in the transformation of hMSCs into osteoblasts in vitro.[75]
3. Enzymes: microbial enzymes can alter the composition of the extracellular matrix (ECM) within a joint, affecting stem cell adhesion and migration. Proteases produced by bacteria can degrade ECM components, thereby affecting the stem cell niche. Inflammation accompanying the development of OA can also affect MSCs by inhibiting proliferation and cartilage differentiation by reducing the production of extracellular matrix (ECM).
4. Signaling molecules – Quorum Sensing Molecules: bacteria communicate via quorum sensing to coordinate their behaviors. These molecules indirectly affect the stem cell function by altering the local inflammatory milieu. Different concentrations of specific toll-like receptor ligands can significantly influence the immunomodulatory properties of MSCs.[76]
5. Cytokines and chemokines: while directly synthesized by microbes, microbiota can stimulate the secretion of different cytokines and chemokines by host cells. Inflammatory cytokines enhance the migration ability of synovial MSCs,[77] then recruit stem cells to sites of inflammation and influence their reparative actions. Inflammatory cytokines such as TNF-α, IL-1 β, and IL-6 can inhibit osteogenic differentiation.[78] (Figure 3)

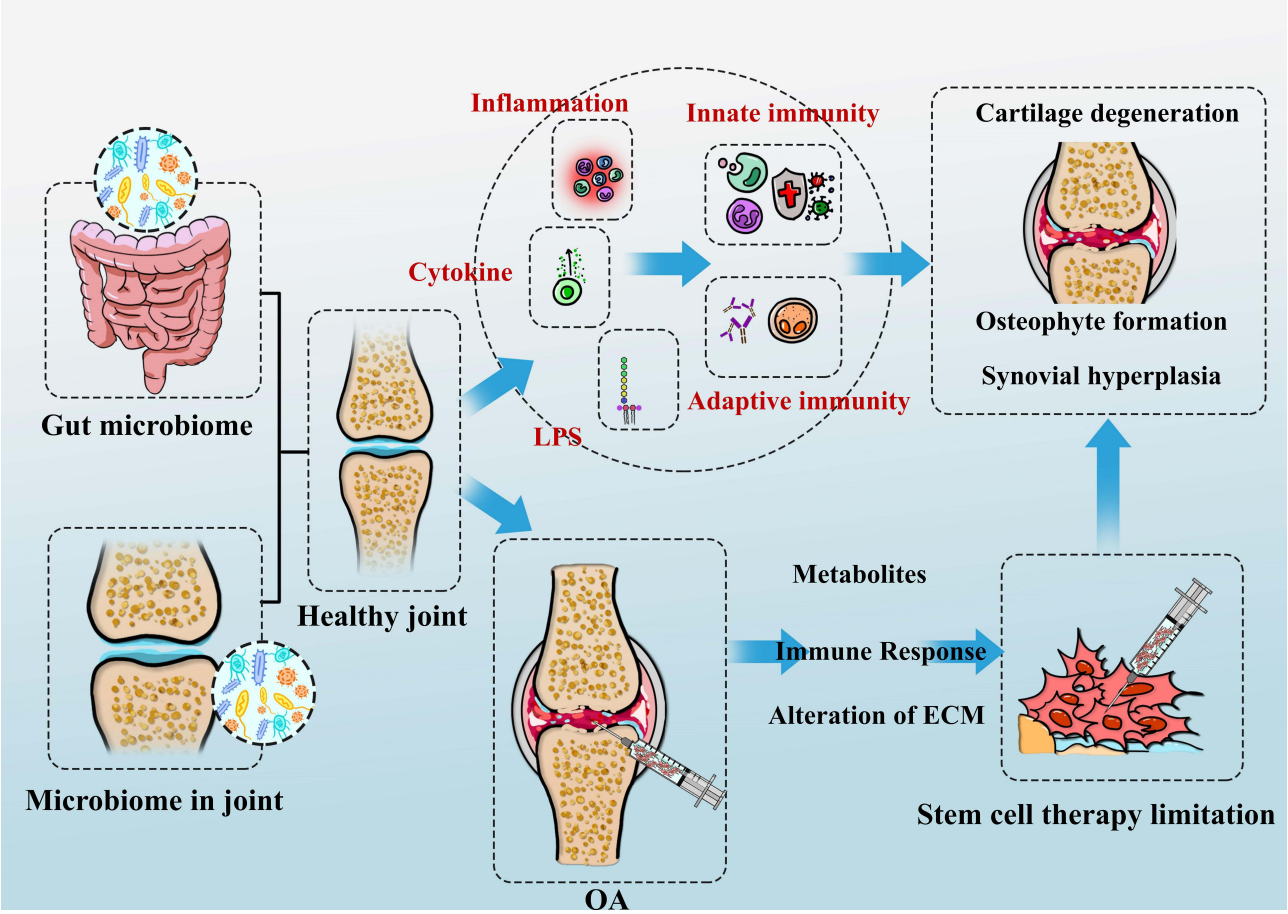

Figure 3 Relationship between microbes and OA and the impact of microbiota on MSCs for OA therapy.

Treatment of OA Through Engineering MSCs

MSCs are a promising therapeutic strategy for OA due to the action of multiple mechanisms; In addition, MSCs derived from abundant sources and have great homing and chondrogenic abilities, and they have started as potential sources for tissue repair.[79] In addition, MSCs have great immunomodulatory properties, including regulation of macrophages, T cells, B cells, and NK cells.[80] MSC exhibit regenerative capacity, mainly through the secretion of growth factors, exosomes, and other molecules that can mediate the tissue microenvironment. MSCs can be obtained from the umbilical cord, adipose tissue, and bone marrow and have shown significant therapeutic potential in different disease indications due to their immunomodulatory and other properties. Recently, the injection of MSCs into the articular cartilage has achieved significant results in OA therapy. MSCs can be regulated by different genes and proteins, including SRY-related genes, the TGF family, and FGF, during chondrogenesis.[81] SOX9 is the main transcription factor involved in the chondrogenesis process at early.[82] SOX9 binds to the COL2A1 enhancer region, and activates COL2A1 production, SOX9 also keeps chondrocyte phenotype by stimulating COL2A1 expression and suppressing COL1A2 expression.[83] Therefore, these studies indicate that SOX9 maintains the chondrocyte phenotype. MSCs undergo proliferation and condensation through the downregulation of COL1A2 and the production of cartilage matrix proteins such as COL2A1 and ACAN. However, MSCs are influenced by different factors and are prone to hypertrophy and synthesis of RUNX2 and MMP13 during development.[84] Several reviews have been published on the treatment mechanisms of MSC in OA.[85,86] Owing to the harsh microenvironment of OA, the treatment effect of stem cells is seriously affected. Therefore, improving the treatment of stem cells using engineering methods has become a research hotspot. In this study, we mainly focused on engineering MSCs for OA treatment.

Engineered MSCs by Enhancing the Targeting Ability

Although the symptoms of OA can be alleviated by injecting stem cells into the knee, however, the harsh microenvironment in the joint cavity significantly affects the efficacy of stem cells. One of the main reasons for this is that stem cells lack effective targeting ability. To recruit MSCs, injured tissues release chemokines, such as SDF-1, to bind the receptor CXCR4, which is expressed on the surface of MSC; however, When MSCs are injected into the joint cavity of the knee, they spread quickly due to systemic circulation and die quickly in the joint cavity.[87] In addition, owing to the influence of senescence by repeated proliferation in vitro, MSCs reduce CXCR4 expression and thus show a weaker homing property.[88] It has been reported that only 1% of MSCs migrate to target injury sites, and most are concentrated in the lungs after intravenous injection. In addition, the cartilage layer with an abundance of anionic proteoglycans in the tissue matrix has a negative charge, which makes it extremely challenging for MSCs to remain in joint cartilage.[89] Several strategies have been used to enhance the targeting ability of MSCs.[90]

MSCs can be genetically modified by overexpressing chemokine receptors to improve their targeting abilities.[91] In addition, MSCs can also be modified by antibodies to the cell surfaces, and after conjugation with antibodies, MSCs can bind to a specific antigen on cartilage tissue.[92] The use of a cell-targeting peptide targeting the cell surface is another unique strategy. MSCs engineered with WYRGRL peptides, which have an intrinsic affinity for collagen II in the cartilage matrix, can improve therapeutic ability.[93] In addition to improving MSC targeting through biochemical modifications, external energy such as magnetic fields can also be used to improve MSC targeting. For magnetic targeting, magnetic substances are typically loaded into cells to target interesting areas with the help of a magnetic field.[94] In a recent study, Wu et al modified MSCs by adding a cartilage-targeting peptide, which significantly increased the number of MSCs in the joints after joint injection, and the results demonstrated that MSCs showed great cartilage repair ability in an OA mouse model and cartilage samples from OA patients[95] (Figure 4A). Den et al developed a magneto-mechanical platform to control MSC to rapidly assemble MSC into highly ordered cell clusters through improved cell communication, and induced long-term MSC retention and enhanced MSC differentiation in the articular cavity of the knee, demonstrating that this strategy showed an optimal OA therapy to generate dynamic magneto-mechanical forces to induce cell clusters and long-term retention in the joint to alleviate inflammatory[96] (Figure 4B).

Engineered MSCs by Enhancing the Delivery Efficiency

The rapid expansion of MSCs in joints is an urgent problem; therefore, optimizing the delivery strategies of MSCs into joints is urgently required for OA therapy. Currently, the use of hydrogels which have unique physicochemical properties like

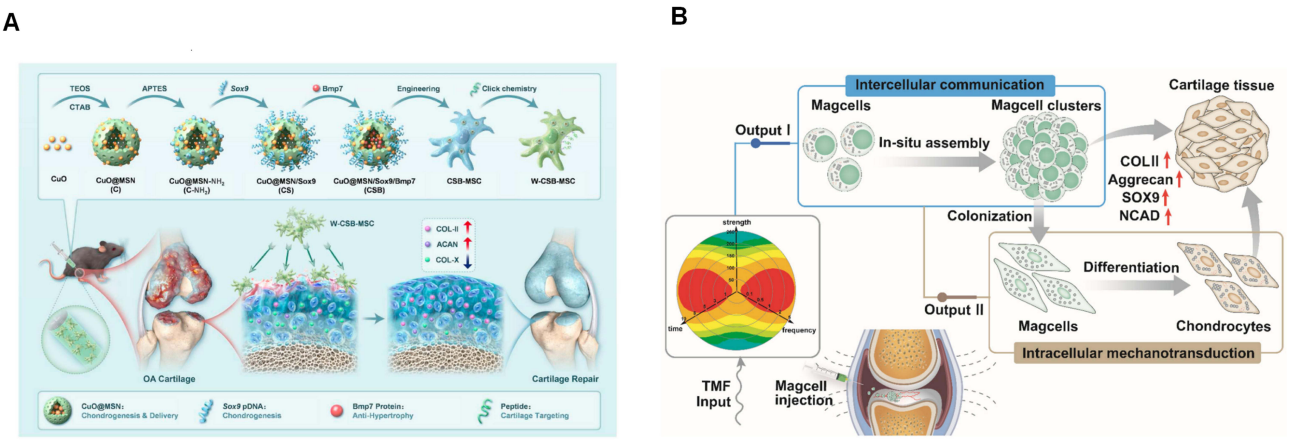

Figure 4 (**A**) Schematic illustration of the preparation of co-delivered NPs and W-CSB-MSCs and their application in OA therapy, red arrows represent up expression and blue arrows represent down expression. Reproduced from Wu C, Huang Z, Chen J, et al. Efficiently directing differentiation and homing of mesenchymal stem cells to boost cartilage repair in osteoarthritis via a nanoparticle and peptide dual-engineering strategy. Biomaterials. 2025;312:122720. Copyright, 2025, Elsevier.[95] (**B**) Schematic of sophisticated magneto-mechanical actuation for chondrogenesis of Magcells during OA treatment, red arrows represent up expression. Reproduced from Deng C, Li Z, Lu L, et al. Sophisticated magneto-mechanical actuation promotes in situ stem cell assembly and chondrogenesis for treating osteoarthritis. ACS Nano. 2023;17(21):21690–21707. Copyright © 2023 American Chemical Society.[96]

biodegradable and biocompatible ability has emerged as a suitable strategy for delivering MSCs to the joints to improve their viability.[97] First, the hydrogel with a suitable porous structure provides a favorable environment for MSCs survival, promoting cell survival and functionality. In addition, specific growth factors can be co-embedded in hydrogels to promote MSCs proliferation and differentiation.[98] Finally, embedding MSCs into hydrogels can significantly reduce shear force when injected into the joint cavity.[99] Injectable hydrogels are a promising strategy that can be injected in situ and solidified.[100] Tang et al constructed a hybrid scaffold with MSCs embedded in platelet-rich plasma hydrogels, which released growth factors to regulate proliferation and differentiation.[101] Thakur et al constructed a 2D nanosilicate reinforced hydrogels for MSCs delivery. Chemical modification of κCA with 2D nanosilicates enhances its mechanical properties and physiological stability. After delivering hMSCs, the cells showed high viability and power for cartilage tissue regeneration.[102] To increase cell retention time at the injection site, Castro et al used microfluidic generators to microencapsulate MSCs using droplets in flow-focus mode with different polymers and concentrations, prolonging the retention time of MSC after injection in rat joints and demonstrated that both the type and concentration of polymer played an important role in the retention time of MSCs when injected into the articular cavity, which could enhance the long-lasting therapeutic effects for osteoarthritis[103] (Figure 5A). McKinney et al used sodium

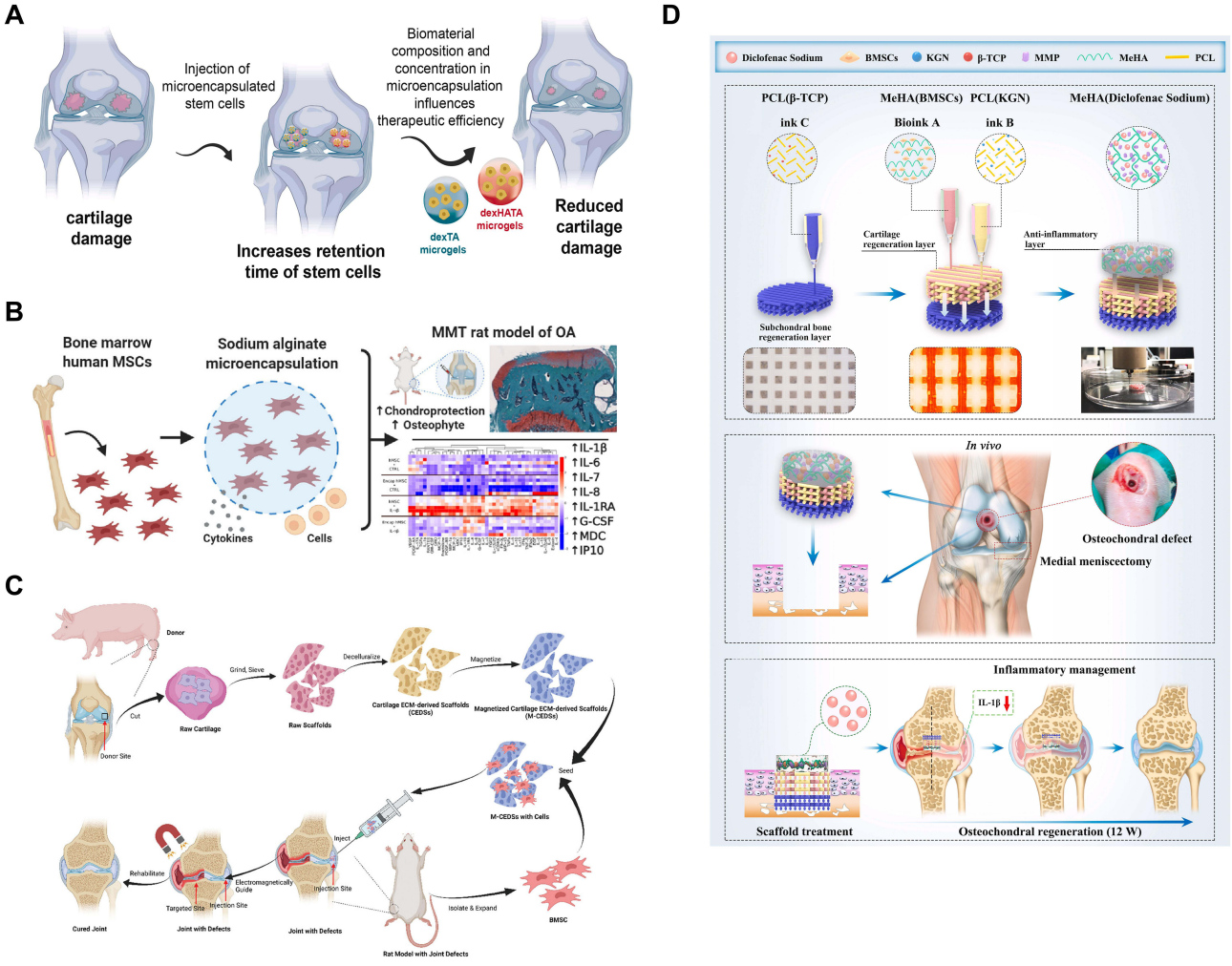

Figure 5 (**A**) Biomaterial formulation and concentration determine the retention time and therapeutic effect of injected microencapsulated stem cells in vivo. Reproduced from Johnbosco C, Karbaat L, Korthagen NM, et al. Microencapsulated stem cells reduce cartilage damage in a material dependent manner following minimally invasive intra-articular injection in an OA rat model. Mater Today Bio. 2023;22:100791. Copyright 2023, Elsevier.[103] (**B**) Sodium alginate microencapsulation of MSC for treating established OA through the secretion of immunomodulatory cytokines, black arrows represent up expression. Reproduced from McKinney JM, Pucha KA, Doan TN, et al. Sodium alginate micro-encapsulation of human mesenchymal stromal cells modulates paracrine signaling response and enhances efficacy for treatment of established osteoarthritis. N J Acta Biomaterialia. 2022;141:315–332. Copyright 2022, Elsevier.[104] (**C**) Fresh porcine articular hyaline cartilage was pulverized, sieved, decellularized, and magnetized to fabricate magnetized cartilage ECM-derived scaffolds, and carried MSCs OA cartilage regeneration was performed. Reproduced from Huang H, Li J, Wang C, et al. Using Decellularized Magnetic Microrobots to Deliver Functional Cells for Cartilage Regeneration. Small. 2024;20(11):e2304088. Copyright 2024, John Wiley and Sons.[105] (**D**) Flowchart of scaffold fabrication and treatment for osteochondral defects in OA joints, red arrows represent down expression. Reproduced from Liu Y, Peng L, Li L, et al. 3D-bioprinted BMSC-laden biomimetic multiphasic scaffolds for efficient repair of osteochondral defects in an osteoarthritic rat model. Biomaterials. 2021;279:121216. Copyright 2021, Elsevier.[106]

https://doi.org/10.2147/IJN.S511884

alginate to encapsulate MSC to analyze the therapeutic efficacy and paracrine signaling of MSCs and assessed the therapeutic potential of this strategy through a preclinical rat model of OA. They found that they enhanced the therapeutic efficacy of hMSCs in vivo to prevent the disease progression of OA by extending the residence time[104] (Figure 5B). To mimic a natural niche-like environment to support MSC survival and differentiation, Huang et al constructed a natural cartilage ECM-derived scaffold to load MSC using decellularized scaffolds and magnetic-driven MSC delivery to treat OA, which could deliver MSC to the articular cavity for cartilage regeneration and release MSCs at a target knee location for at least 20 days[105] (Figure 5C). They demonstrated the use of decellularized microrobots for MSC delivery and demonstrated their in vivo therapeutic potential in preclinical applications. In order to support the cartilage regeneration in OA, and solve the problem of lacking enough MSC seed cells in the defect articular and chronic inflammation, Liu et al developed a 3D-bio printed multilayer scaffold for MSC loading, which proliferated and differentiated well, produced many cartilage-like extracellular matrices in vitro in the scaffolds, significantly inhibited joint inflammation, the OA animal model further demonstrated 3D-bio printed BMSC-laden scaffolds for cartilage defect repair in OA[106] (Figure 5D). In conclusion, a large body of evidence demonstrates the potential advantages of hydrogels for treating OA.

Engineered MSCs Through Proper Mechanical Stimuli

Mechanical stimuli can regulate MSCs chondrogenic differentiation and homeostasis, thereby affecting the therapeutic effects of OA. Magnetic fields and mechanical forces are two mechanical stimuli that regulate the regenerative efficiency of MSCs.[107,108] MSCs are mechanosensitive; therefore, appropriate mechanical stimulation can induce their differentiation into chondrocytes. Nevertheless, the type of mechanical stimuli and their optimal durations are still not understood. Recently, researchers found that using dynamic compression improved cartilage matrix levels starting at a later time; in contrast, at an early time point, chondrocyte markers decreased.[109] A study showed that the use of static hydrostatic pressure in the range of 5–10 MPa for 2 weeks could result in a strong anabolic response. However, excessive hydrostatic pressure will ultimately lead to the development of OA.[110,111] Zhang et al fabricated three-dimensional magnetic scaffolds by incorporating magnetic nanoparticles embedded in electrospun gelatin nanofibers, and MSCs were embedded in magnetic scaffolds. This scaffold could induce mechanical stimulation of MSCs by an alternating magnetic field, which significantly enhanced chondrogenesis and stimulated MSCs under a dynamic magnetic field within the scaffolds, resulting in superior osteochondral repair in vivo.[112] Recently, a prospective, randomized, placebo-controlled, single-blind clinical trial conducted by Nasb et al showed that low-intensity pulsed ultrasound significantly improves the treatment efficiency of OA in combination with MSCs.[113] Therefore, appropriate mechanical stimuli can significantly enhance the therapeutic efficacy of MSC.

Engineered MSCs to Obtain Their Special Exosomes

Exosomes are extracellular vesicles secreted by almost all cells and have a diameter of approximately 50–250 nm. An increasing number of studies have confirmed that exosomes can not only transmit parent information but also regulate cell function.[114] They can deliver functional proteins, RNA, and lipids to regulate cellular function. Cosenza et al demonstrated that MSC-derived exosomes could reduce the production of iNOS, MMP13, and ADAMTS5 in OA chondrocytes while promoting the expression of type-II collagen and aggrecan and inhibiting cell apoptosis.[115] Therefore, using engineered MSCs to produce functional exosomes is a promising strategy. Wu et al preconditioned MSCs with TNF-α, which significantly enhanced the secretion of exosomes compared with non-preconditioned MSCs. Mechanistic research demonstrated the activation of the PI3K/AKT signaling pathway and showed that the exosomes had more LRP1, which could protect cartilage against cartilage damage caused by OA.[116] Luo et al pretreated MSC with fucoidan and found that exosomes could better protect chondrocytes from OA. miRNA sequencing of exosomes demonstrated that they could effectively inhibit inflammatory responses and extracellular matrix degradation through miR-146b-5p to inhibit TRAF6 activation.[117] FGF18 has been shown to prevent OA development and promote cartilage healing in different animal models, showing a beneficial role of FGF18 in OA therapy. However, it has a low delivery efficiency and a short half-life in vivo, which significantly reduces the therapeutic efficiency of OA treatment. Chen et al developed a hybrid exosome system containing a chondrocyte-affinity peptide and loaded an FGF18-targeted gene editing tool for OA therapy, demonstrating that this delivery system could promote cartilage repair, reduce inflammation,

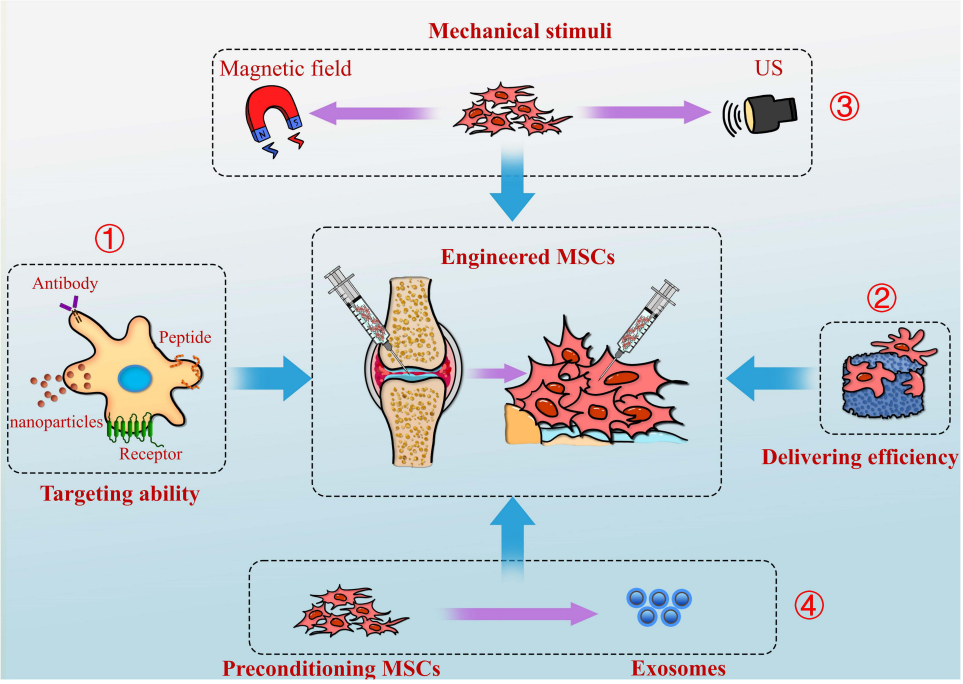

Figure 6 Engineering MSCs using different OA therapy strategies.

and prevent ECM degradation.[106] Because of the short half-life of exosomes in vivo, exosomes can be easily cleared by the body, which results in a short retention time in the articular cavity. Therefore, Yin et al developed hydrogel microparticles to encapsulate exosomes through microfluidic technology, and sustained release of exosomes could treat OA for long-term.[118] Moreover, exosome extraction from engineered MSCs can significantly enhance the therapeutic efficiency in OA. Therefore, engineering MSCs using different strategies may play a significant role in OA therapy (Figure 6). Table 1 below summaries some recent studies using engineering MSCs for OA therapy A.

Table 1 Summaries of Recent Research on Engineering MSCs for OA Therapy

Cell Sources	Product Method	Outcome	Ref
Bone marrow mesenchymal stem cells	Type II Collagen-Conjugated MSCs	Antibody-conjugated MSCs is a potential method for targeted delivery of MSCs in cartilage defects	[92]
Bone marrow mesenchymal stem cells	Magnetically Guided Delivery of Kartogenin	KGN-loaded magnetically guided nanocarrier system to promote chondrogenic differentiation by MSCs	[119]
Bone marrow mesenchymal stem cells	Hydrogel Spheres	HA-based hydrogel microspheres are beneficial as a cell delivery vehicle by supporting the high viability of MSCs, and maintaining the stemness and improving joint integrity in an OA model.	[120]
Bone marrow mesenchymal stem cells	Hyaluronan-based hydrogel	Adding a nutrient to the hydrogel could feed stem cells and promote their survival during OA regenerative therapy.	[98]
Bone marrow mesenchymal stem cells	Pulsed electric fields (PEFs)	MSCs pretreated by PEFs greatly inhibited the development of OA in vitro and in vivo.	[121]
Immortalized human mesenchymal stromal/stem cell line	Magnetic scaffolds with the embedded MSCs	MSCs seeded within the dynamic cell culture systems displayed enhanced chondrogenesis and osteogenesis due to the synergetic effects of various stimuli with alternating magnetic field	[112]

(*Continued*)

https://doi.org/10.2147/IJN.S511884

Table 1 (Continued).

Cell Sources	Product Method	Outcome	Ref
Infrapatellar fat pad (IPFP)-MSCs	Preconditioned with TNF-α	The preconditioning of TNF-α enhanced the up-regulation of low-density lipoprotein receptor-related protein 1 in Exos, and showing chondroprotective ability	[116]
Bone marrow mesenchymal stem cells	FTO-overexpressing EVs	Engineering FTO-EVs suppressed cellular senescence and apoptosis, and triggered protective autophagy to suppress OA development	[122]

Challenges and Future Directions

Research on synovial joint microbiota faces several challenges, including the difficulty in obtaining uncontaminated synovial fluid samples and interpreting the significance of low-abundance microbiota. Future directions include further characterization of the microbiota in both healthy and diseased states, investigation of its functional roles, and exploration of how the microbiota interacts with the host immune system and stem cells. In addition, the development of more effective strategies for engineering MSCs for OA treatment of OA was pressing.

Conclusion

Osteoarthritis (OA) is increasingly recognized as a multifactorial disease, rather than merely a result of wear and tear. Among these, the gut and joint microbiota have emerged as critical players in joint health and disease progression. The microbiota, a complex ecosystem of microorganisms, interacts with host cells and tissues, modulating inflammation, immune responses, and metabolic processes. These interactions are particularly relevant in OA, where dysbiosis (microbial imbalance) can exacerbate joint inflammation and cartilage degradation. Recent research has highlighted the pivotal role of microbiota in regulating mesenchymal stem cells (MSCs), which are essential for tissue repair and regeneration. The complex microenvironment of OA, characterized by chronic inflammation and altered biomechanics, often impairs the natural repair capacity of MSCs. This has led to a growing interest in engineering MSCs to overcome these limitations and enhance their therapeutic potential. Continued exploration of the interplay between microbiota, OA pathogenesis, and MSC function will likely yield novel strategies for tissue engineering and OA management, paving the way for more effective and targeted treatments.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest.

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