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REVIEW

Roles of Microenvironment on Mesenchymal Stem Cells Therapy for Osteoarthritis

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Abstract: Osteoarthritis (OA) induced microenvironmental alterations are a common and unavoidable phenomenon that greatly exacerbate the pathologic process of OA. Imbalances in the synthesis and degradation of cartilage extracellular matrix (ECM) have been reported to be associated with an adverse microenvironment. Stem cell therapy is a promising treatment for OA, and mesenchymal stem cells (MSCs) are the main cell sources for this therapy. With multispectral differentiation and immunomodulation, MSCs can effectively regulate the microenvironment of articular cartilage, ameliorate inflammation, promote regeneration of damaged cartilage, and ultimately alleviate OA symptoms. However, the efficacy of MSCs in the treatment of OA is greatly influenced by articular cavity microenvironments. This article reviews the five microenvironments of OA articular cavity, including inflammatory microenvironment, senescence microenvironment, hypoxic microenvironment, high glucose microenvironment and high lipid environment, focus on the positive and negative effects of OA microenvironments on the fate of MSCs. In this regard, we emphasize the mechanisms of the current use of MSCs in OA treatment, as well as its limitations and challenges.

Keywords: microenvironment, mesenchymal stem cells, osteoarthritis

Introduction

Articular cartilage contains a variety of cell types, consisting of chondrocytes, synoviocytes, endothelial cells, mesenchymal stem cells (MSCs), and immune cells.[1,2] These cellular components form a normal articular cavity microenvironment and maintain articular cartilage homeostasis.[2] In pathological states, unfavorable transformation undergoes in the articular microenvironment. The oxidative stress balance in chondrocytes and subchondral bone is destroyed, and the synthesis and degradation of extracellular matrix (ECM) are disrupted, leading to the occurrence of osteoarthritis (OA).[3,4]

OA is the leading cause of disability in the older people without radical treatments.[5,6] In recent years, MSCs therapy is proved to be a promising therapy for OA treatment. MSCs can effectively regulate the microenvironment of articular cavity, ameliorate inflammation, promote cartilage regeneration and repair, and ultimately alleviate the symptoms of OA.[7,8]

MSCs are a class of pluripotent stem cells, which originate in the mesoderm and have the capacity for self-renewal and multilineage differentiation, including chondrogenic, osteogenic, and adipogenic potential.[9] Besides, MSCs also have immunomodulatory, homing, and anti-inflammatory properties,[10] which support their versatility as bone tissue therapeutic agents.[11] The efficacy, safety and reliability of MSCs therapy in OA treatment has been demonstrated in numerous clinical trials and preclinical studies.[12–14] However, the efficacy of MSCs is affected by the microenvironment of the articular cavity, and hostile articular microenvironment can impair the bioactivity of MSCs.[15] Therefore, altering the adverse articular cavity microenvironment may be an effective strategy for OA treatment.[16]

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The microenvironment in which stem cells live is also called as the stem cell niche. It maintains critical stem cell properties. This microenvironment contains a variety of elements from systemic and localized sources, including cellular and ECM components.[17] Within the ecological niche, stem cells can interact with other cells as well as the ECM, releasing soluble signals that regulate stem cells function, thereby maintaining tissue homeostasis and promoting damage repair.[18] In brief, the stem cell niche provides a special microenvironment for stem cells, enabling them to remain in an undifferentiated state. Factors released by cells in the stem cell niche direct the stem cells fate by activating relevant intracellular signaling pathways.[19] However, the microenvironment of OA lesions deviates greatly from the stem cell niche under physiological conditions, exerting considerable impacts on the local therapeutic effects of stem cells. Therefore, research on such impact is also an important basis for us to improve stem cell treatment methods.

This paper reviews the properties and roles of MSCs and the relationship between MSCs and the microenvironment of OA, focusing on the positive and negative effects of the five microenvironments of the OA articular cavity (inflammatory microenvironment, senescence microenvironment, hypoxic microenvironment, high glucose microenvironment and high lipid microenvironment) on MSCs fate. The mechanisms of MSCs as a treatment for OA and their interactions and challenges are highlighted (Figure 1).

Inflammatory Microenvironment

Accumulating evidence suggests that chronic low-level inflammation contributes to the accelerated the progression of OA.[20–22] Such process involves activation of the innate immune response.[23,24] In OA microenvironment, pro-inflammatory cytokines induce degradation of the ECM. The accumulated degraded products or cartilage fragments are considered to be damage-associated molecular patterns (DAMPs). DAMPs activate pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and receptor for advanced glycosylation end-products (RAGEs), the innate immune system is then activated.[25,26] PRRs stimulate fibroblast-like synoviocytes (FLS), macrophages, and chondrocytes to produce and release various pro-inflammatory factors into synovial fluid. This results in loss of chondrocyte phenotype and ECM degradation. Ultimately, an inflammatory microenvironment conducive to cartilage disease is formed.[27,28]

Immune Cells in the Inflammatory Microenvironment

Under physiological conditions, macrophages maintain microenvironmental homeostasis by phagocytosis of pathogens and debris in senescent tissues, whereas in OA articular cavity, abnormally activated macrophages may exacerbate joint

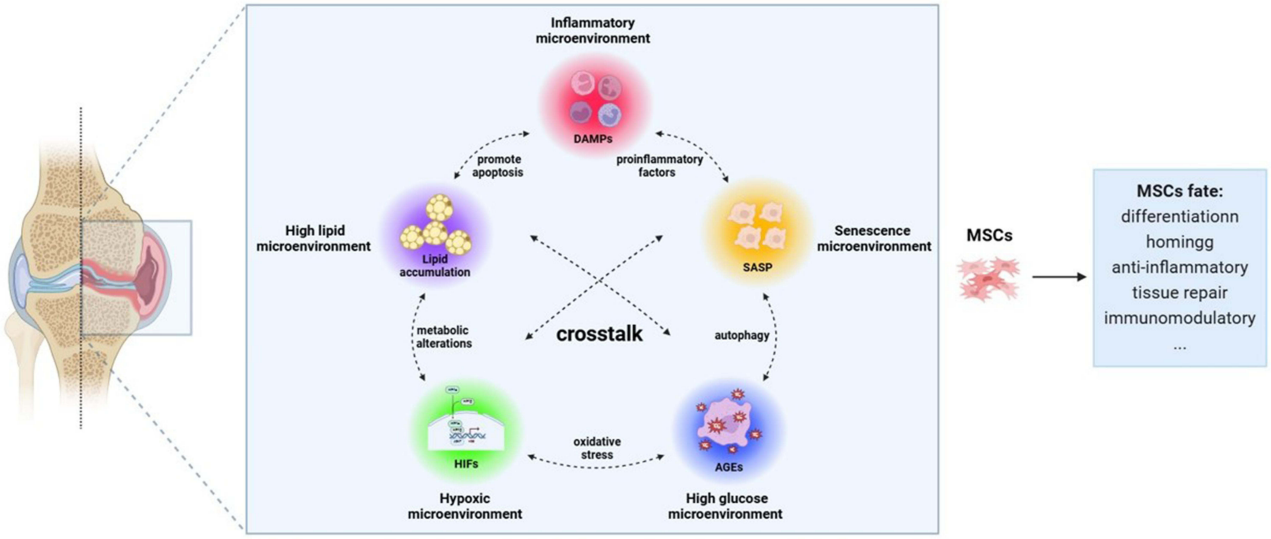

Figure 1 Regulation of MSCs fate by OA microenvironment.
Notes: Inflammatory microenvironment, senescence microenvironment, hypoxic microenvironment, high glucose microenvironment, and high lipid microenvironment in OA articular cavity alter the fate of MSCs and affect the therapeutic effect of MSCs.

destruction.[29] Macrophages have two main polarization states: M1 macrophages and M2 macrophages.[30] Macrophage polarization to phenotype-1 macrophages enhances the pathological process of OA by driving inflammation, whereas phenotype-2 macrophages are anti-inflammatory and facilitate rapid tissue repair.[31,32] It has been found that mediators released by damaged chondrocytes provide a pro-inflammatory microenvironment to promote M1 polarization.[33] M1 macrophages can produce interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), matrix metalloproteinases (MMPs), and other inflammatory cytokines, which release matrix metalloproteinases to promote the degradation of cartilage matrix.[34] Neutrophils arrive at the injury site immediately after OA injury and form a local neutrophilic infiltration in the joint.[35,36] The progression of OA is also associated with the expansion of pathogenic T lymphocytes and MSCs have been shown to successfully prevent T cells proliferation.[37,38]

MSCs in the Inflammatory Microenvironment

MSCs inhibit the inflammatory microenvironment by decreasing pro-inflammatory factors and inhibiting B cells infiltration.[39] Through influencing the interaction of B lymphocytes and T lymphocytes, MSCs influence the adaptive immune system.[30] Specifically, MSCs can directly bind to the PD-9 receptor on B cells, thereby preventing B cells from activating into plasma cells.[40] Moreover, MSCs can also upregulate PD-1 receptors on Tregs to enhance Tregs-mediated immunosuppression.[41] The anti-inflammatory cytokine IL-10 secreted by MSCs can induce the transformation of macrophages from M1 to M2, mediating anti-inflammatory effects.[42] MSCs exert immunosuppressive effects by converting pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages, thereby attenuating the macrophage-induced inflammatory microenvironment.[43] MSCs or MSCs conditioned medium significantly reduced the number of infiltrating neutrophils and alleviated the progression of OA.[44]

Inflammatory Microenvironment and MSCs Fate

The inflammatory microenvironment in which MSCs reside affects their self-renewal, multilineage differentiation and proliferation capabilities.[45] The Wnt/β-catenin pathway regulates the differentiation of MSCs.[46] In inflammatory microenvironment, mitochondrial autophagy is inhibited by activating Wnt/β-catenin pathway. Thus, damaged mitochondria accumulate continuously in MSCs and impair their differentiation.[47] Inflammatory factors in the inflammatory microenvironment activate the Wnt/β-catenin pathway, leading to decreased differentiation ability of MSCs.[48] In inflammatory microenvironment, the cartilage protective effect of human umbilical cord mesenchymal stem cells (hucMSCs) was weakened, which impaired the repair effect of hucMSCs[15] (Figure 2).

Although most of the evidence suggests the adverse effects of the inflammatory microenvironment on MSCs, the inflammatory microenvironment also enhances the anti-inflammatory effects of MSCs. MSCs exert their biological effects by releasing exosomes.[49] For example, IL-1β-induced MSCs exosomes significantly enhanced their anti-

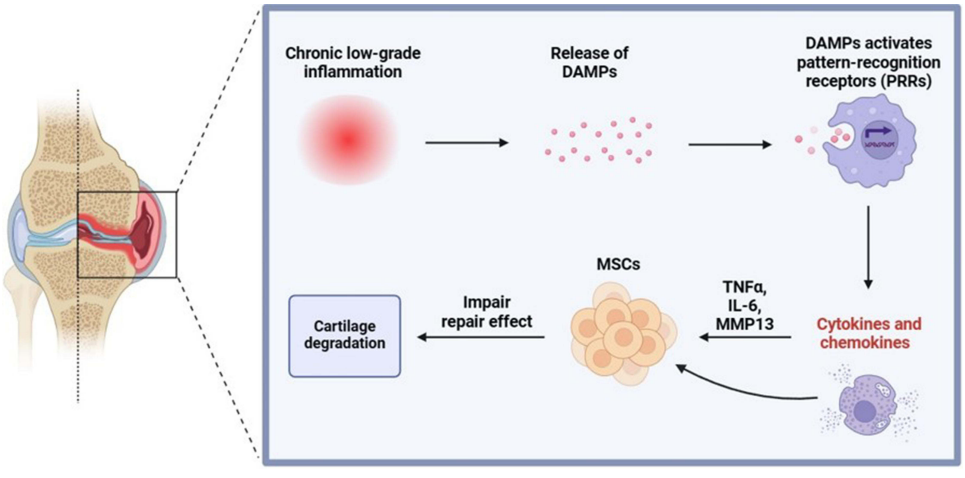

Figure 2 The inflammatory microenvironment in OA.
Notes: Chronic low-grade inflammation releases DAMPs, activates PRRs to release pro-inflammatory factors to impair the cartilage repair effect of MSCs.

inflammatory activity in osteoarthritic cells SW982 compared to MSC-Exo.[50] In a double-damage rabbit OA model, intraarticular injection of human adipose-derived stem cells (hADSCs) reduced joint effusion, which helped to attenuate the inflammatory microenvironment in the joint cavity and promote cartilage repair.[51] In vitro inflammatory exposure enhances the immunomodulatory capacity of MSCs, and the resulting secretome can protect chondrocytes from catabolism.[52] Hypoxia and inflammatory microenvironment can protect MSCs from damage in harsh microenvironments, thereby increasing the survival, homing, and paracrine capacities of MSCs in vitro and in vivo.[53] Inflammation and lesion sites trigger enhanced MSC homing for tissue remodeling and repair.[54,55]

Overall, the different fates of MSC in the inflammatory microenvironment may be related to their status.

Senescence Microenvironment

The process of organismal senescence is accompanied by cellular senescence, which caused by a sustained DNA damage response, telomere dysfunction, stem cells exhaustion, and impaired intercellular communication.[56] Senescent cells accumulate in osteoarthritic joints and release factors called senescence-associated secretory phenotype (SASP), which include the pro-inflammatory cytokine IL-6 and IL-8, monocyte chemotactic protein 1 (MCP1), and ECM proteases.[57,58] The transcriptional activation of a SASP program affects the microenvironment in which senescent cells reside and reinforces cellular senescence.[59] SASP can accelerate cell senescence and deteriorate the neighboring cells function.[56]

Senescence Microenvironment and MSCs Fate

MSCs are critical cells for maintaining tissue homeostasis and organization during tissue and organ injury.[60] The exhaustion of stem cells is the marker of aging.[61] Senescent MSCs are able to function in the surrounding environment and regulate MSCs niche.[62] The functional capacity and their number of MSCs declines with age.[63,64] During aging, MSCs experience functional degeneration and gradual loss of stemness, with subsequent changes in the fate of MSCs and aberrant differentiation.[65] Accumulation of senescent MSCs in the articular cavity may aggravate the process of OA.[66] Senescence OA-MSCs cause senescence, inflammation and fibrosis in cartilage.[67] Studies have found that MSCs isolated from OA patients are influenced by aging-driven OA inflammation and nutritional microenvironment, resulting in diminished cartilage anabolism and enhanced cartilage catabolism.[68] Recent studies have shown that injection of senescent MSCs in the joint cavity of young mice drives an OA-like phenotype.[69] In the senescence microenvironment, MSCs lose stemness and inhibit chondrogenic differentiation, and the paracrine role of MSCs is also affected.[69] Compared with MSCs from young donors, senescent donor-expanded MSCs exhibit increased expression of senescence markers, elevated levels of inflammation, decreased immunoregulatory function, and reduced proliferation and differentiation.[70,71] Aging MSCs contribute to the establishment and maintenance of an inflammatory environment in stem cell niche. In senescent MSCs, SASP effect factor IL-1α and IL-8 induce early senescence of MSCs in a NF-κb dependent manner through paracrine.[72] There is a correlation between MSCs aging and the age-related disease OA, which is accelerated by enhanced m6A levels and down-regulated expression of the demethylation enzyme ALKBH5 during MSCs aging.[73]

Hypoxic Microenvironment

Due to the lack of blood supply, articular cartilage is located in a hypoxic environment throughout life.[74] Hypoxia-inducible factor (HIF) is a core factor in inducing hypoxia gene and regulating cellular oxygen environment, mediating chondrocyte adaptation to the hypoxic microenvironment.[75] HIFs are heterodimers of heterogeneous proteins polymerized from two distinct subunits, the oxygen-sensitively regulated α subunit (HIF-1α, HIF-2α & HIF-3α) and the structurally expressed HIF-1β subunit.[76] The most important members of the HIFs protein family are HIF-1α and HIF-2α. In hypoxic environment, HIF-1α undergoes activation and enters the nucleus, where it binds to the subunit to form an active HIF-1α transcription factors, which are involved in autophagy and apoptosis, promotion of chondrocyte phenotype and maintenance of chondrocyte viability.[77] Unlike HIF-1α, HIF-2α is mainly involved in promoting the expression of chondrocytes catabolic factors, up-regulates the expression of the apoptotic gene Fas, increasing chondrocyte apoptosis, and exacerbating inflammatory responses, leading to more severe articular cartilage destruction.[78]

Hypoxic Microenvironment and MSCs Fate

In the past, it was thought that hypoxia is beneficial for MSC, numerous studies have shown that cultured under hypoxic conditions would exhibit enhanced MSCs proliferative potential and stemness.[79–81] Since the oxygen concentration of tissue is less than 5%, cell culture of MSCs under hypoxic environment can mimic in vivo microenvironment and help to maintain the physiological processes of MSCs from differentiation, proliferation, and metabolic homeostasis.[82] Hypoxia can induce upregulation of pluripotent markers of MSCs, enabling MSCs to maintain their function.[83] Hypoxic microenvironment maintains the undifferentiated phenotype of MSCs.[84] In addition, HIF acts as the regulatory molecule of the hypoxic microenvironment to control the differentiation and fate of MSCs.[85] Isolation and amplification of bone marrow mesenchymal stem cells (BMSCs) under hypoxic environments can up-regulate the expression of chondrogenesis genes and enhance the chondrogenic differentiation of BMSCs.[86] Different oxygen concentrations had different effects on adipose tissue-derived MSCs (ADSCs).[87] In vitro, hypoxic preconditioning of MSCs can up-regulate the expression of MSCs chemokine receptors CXCR4, CXCR7 and CX3CR1, which contributes to the migration and tissue repair of MSCs.[88]

Despite the prevailing view that hypoxia is beneficial to stem cells, it can also adversely affect MSCs. Chronic hypoxia predisposes BMSCs from patients with cyanotic congenital heart disease (CCHD) to premature senescence, possibly due to dysbiosis of the intestinal flora, which induces the accumulation of D-galactose.[89] It was shown that hypoxic microenvironment in osteonecrosis zone led to hypoxia-induced apoptosis in transplanted BMSCs. Under hypoxic condition, the expression of the pro-apoptotic gene Bax was increased, whereas down-regulation expression of apoptosis inhibitor Bcl-2, leading to apoptosis in more than 70% of BMSCs.[90] Notably, severe hypoxia inhibits the adhesion and mobility of BMSCs, which limits their use.[91] The hypoxic microenvironment also leads to increased cellular oxidative stress, leading to senescence of MSCs and affecting MSCs differentiation.[92,93]

High Glucose Microenvironment

Obesity and the related disease have been shown to be risk factors for developing OA.[94] Diabetes mellitus (DM) is an obesity-related disease, which is characterized by hyperglycemia, which chronically affects the physiological function of the cells involved and leads to their damage.[95] High blood glucose levels in patients are involved in a variety of complex pathologic events, including a rise in ROS, cellular stress, and inflammatory cytokines.[96,97] Hyperglycemia also induces the production and accumulation of advanced glycosylation end products (AGEs), which adversely affects and irreversibly alters the microenvironment in which the cells live.

High Glucose Microenvironment and MSCs Fate

MSC-based cell therapy treatments are promising for treating diabetes, but the microenvironmental stress in patients with hyperglycemia can significantly inhibit the survival time of MSCs in human bodies, which ultimately affects their therapeutic efficacy. In vitro, the high glycemic microenvironment also affected the culture efficiency of MSCs.

In diabetic patients, the number of circulating MSCs is reduced, causing an insufficient number of MSCs migrate to the injury site, and the regeneration and repair of target tissue is impaired.[98] The diabetic microenvironment impaired the therapeutic effect of MSCs infusion on bone reduction, which is attributed to the fact that the hyperglycemic condition inhibited MSC-T-cell interactions through the AMPK pathway and reduced the anti-inflammatory capacity of MSCs.[99] The high glucose microenvironment down-regulated the AKT-Sirt1-TWIST pathway and inhibited TWIST exacerbated high glucose-induced apoptosis in MSCs but promoted osteogenic differentiation of MSCs.[100] A recent study showed that hAD-MSCs cultured in high glucose had reduced immunosuppressive capacity, which was associated with significant reductions in the levels of IDO, IL-10, and complement factor levels, as well as a significant increase in immune proteasome activity.[95] Exposure of AGEs to the diabetic environment leads to stem cell dysfunction. The increase of AGEs inhibits the proliferation of MSCs, induces apoptosis of MSCs and prevents the differentiation of MSCs to adipose, cartilage, and bone.[101] AGE-BSA induces chemokine/cytokine production through activation of ROS-p38-mediated pathways. These chemokines/cytokines have inhibiting effects on the growth and migration of MSCs.[102] In most cases, the articular cavity microenvironments are crosstalk with each other. High glucose induces BMSCs to produce ROS through activating NADPH oxidase. ROS activates autophagy by upregulating ATGs expression and induces BMSCs senescence.[103] High glucose and hypoxia upregulate HIF-1α expression, which promotes inflammation and

oxidative stress.[104] In stable state, MSCs depend on glycolysis, have low ROS content, and high ROS levels can damage proteins and DNA at the telomere level, inducing replicative aging, also known as stress-induced premature aging.[105] These results suggest that the articular cavity microenvironments are much more complex than previously thought.

High Lipid Microenvironment

Excessive lipid accumulation is a hallmark of obesity-related pathologies.[106] Abnormally high lipid levels promote the release of inflammatory mediators and induce macrophage polarization toward the inflammatory M1 phenotype, causing an inflammatory response in the body.[107] Previous studies have suggested that obesity promotes excessive lipid deposition in non-adipose tissues, which leads to lipotoxicity and tissue dysfunction.[108] Recent evidence suggests that articular cartilage accumulates lipids during the aging process, and lipid accumulation in cartilage was found to be positively correlated with the severity of knee OA (kOA).[109]

High Lipid Microenvironment and MSCs Fate

Abnormal lipid levels in vivo interfere with MSCs function, affect MSCs homing, and inhibit tissue regeneration.[110] Multispectral differentiation capacity of MSCs is key to their use as clinical regenerative therapy for kOA. Studies have shown an inverse correlation between adipogenesis and osteogenesis in MSCs. The presence of fat may increase adipocyte proliferation, differentiation, and fat accumulation while inhibiting osteoblast differentiation and bone formation.[111] The lipid-lowering agent lovastatin inhibits adipogenesis and stimulates osteogenic differentiation by inhibiting peroxisome proliferator-activated receptor γ2 (PPARγ2) and increasing Runx2 expression in BMSCs.[112]

Although lipid accumulation affects multiple functions of stem cells, exosomes secreted by MSCs also play a role in inhibiting lipid accumulation. HucMSCs attenuate injury associated with lipid deposition, collagen deposition, or inflammation in vivo and in vitro.[113] HucMSCs-derived exosomes ameliorate inflammation, abnormal lipid accumulation, and mitochondrial oxidative stress in non-alcoholic steatohepatitis (NASH) mice.[114] Notably, MSCs survival, proliferation, and terminal differentiation are associated with ROS regulation, and ROS affects MSCs adipogenesis or osteogenic differentiation by modulating the MSCs differentiation signaling cascade response.[115] Obesity is an important cause of the formation of a high glucose and high lipid microenvironment, and the accumulation of excess lipids in diabetic bone tissue causes changes in the bone marrow microenvironment, which reprograms bone metabolism.[116] Moreover, intermittent hypoxia is an independent risk factor for metabolic dysfunction-associated fatty liver disease (MAFLD).

Conclusion and Discussion

This paper reviews five kinds of articular cavity microenvironments that affect the fate of MSCs. MSCs play a therapeutic role in damaged articular cartilage, including ameliorate inflammation, chondrogenic differentiation, proliferation, migration and tissue repair. As shown in Table 1, the microenvironment of the articular cavity largely determines the fate of MSCs. A healthy articular cavity microenvironment can regulate the proliferation and differentiation of MSCs, enabling MSCs to function normally in immunomodulation and tissue repair. In a diseased articular cavity microenvironment, the function of MSCs is compromised and instead aggravates the process of OA.[117]

In fact, the articular cavity microenvironments are crosstalk with each other, and the mechanism of determining the fate of MSCs by the microenvironment is very complex, which is need more research to change the articular cavity microenvironment to make it more suitable for the survival of MSCs. For the time being, organoids may be useful in helping to study the effects of the microenvironment on MSCs. Organoids are self-assembled 3D structures in vitro, mainly generated from primitive tissues or MSCs, that can be used to mimic the complex microenvironments corresponding to organs.[118] The articular cavity microenvironments of different OA patients vary to a large extent, and the development of 3D organoids can help personalize treatment for different patients and achieve precision medicine.[118] As a clinical disease, OA's joint microenvironment is far more complex than we imagined. According to individual differences in patients' microenvironment, treatment methods also need to be personalized. By detecting the joint fluid of OA patients and analyzing what kind of microenvironment the joint cavity is in, it is helpful to realize the symptomatic treatment of OA for different joint cavity microenvironments in the future.

Table 1 Fate of MSCs in Different Microenvironments

Microenvironment types	Effects	Mechanisms	References
Inflammatory microenvironment	chondrogenesis↓, anti-inflammatory↑, immunomodulatory↑, homing↑	DAMPs	[15,45,52]
Senescence microenvironment	inflammatory↑, immunoregulatory↓, proliferation ↓, differentiation↓	SASP	[70,71]
Hypoxic microenvironment	chondrogenesis↑, migration↑, tissue repair↑, apoptosis↓, adhesion↓, mobility↓, senescence↑	HIFs	[85,86,88–91]
High glucose microenvironment	regeneration↓, repair↓, anti-inflammatory↓, apoptosis↑, differentiation↓	ACEs	[98–100]
High lipid microenvironment	homing↓, tissue regeneration↓	Lipid accumulation	[110]

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.

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Disclosure

The authors declare that they have no competing interests in this work.

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