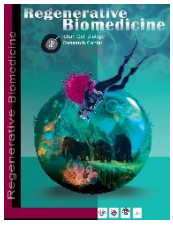

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Review Article

The Niche of the Mesenchymal Stem Cells Displays a Vital Determinant Role of Immunoregulatory Dynamics

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Abstract

Mesenchymal stem cells (MSCs) have emerged as pivotal players in immunomodulation, offering immense therapeutic potential for autoimmune diseases, tissue regeneration, and inflammatory disorders. Their dual capacity to exert pro-inflammatory or anti-inflammatory effects depends significantly on the microenvironment they inhabit. This review delves into the intricate interplay between MSCs and their microenvironment, emphasizing their plasticity and how it is influenced by cytokines, chemokines, and cellular components. Furthermore, it examines the mechanisms underlying MSC-mediated immunosuppression, including their role in regulating innate and adaptive immune responses. Special attention is given to the priming processes, such as exposure to inflammatory cytokines and pathogen-associated molecular patterns (PAMPs), that enhance their immunoregulatory properties. Emerging evidence from tumor microenvironment studies and preclinical research highlights the importance of understanding MSC plasticity to optimize their therapeutic application. This comprehensive analysis underscores the need for tailoring MSC-based therapies to specific microenvironmental contexts for improved efficacy and safety.

Keywords: Immunomodulation, Mesenchymal stem cells, Microenvironment Plasticity, Priming

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Introduction

Mesenchymal stem cells (MSCs) have garnered significant attention in the literature for their remarkable ability to modulate and suppress immune responses (1). This characteristic positions MSCs as promising candidates for clinical applications in inflammatory diseases and regenerative medicine. The efficacy of MSCs in immune modulation is largely determined by their interactions with immune cells (1). However, several studies have highlighted that MSCs can also enhance inflammatory processes, particularly within an inflamed in vivo microenvironment, which can compromise their immunoregulatory functions by altering cytokine expression profiles (2-4). Indeed, the surrounding microenvironment can polarize MSCs towards either a pro-inflammatory or anti-inflammatory phenotype.

Early research on the immunosuppressive functions of MSCs focused on their inherent ability to produce anti-inflammatory cytokines. However, recent studies, including in vitro investigations using mixed lymphocyte reactions (MLRs) and co-culture experiments with peripheral blood mononuclear cells (PBMCs) exhibiting different MHC haplotypes (5), as well as in vivo research on allograft and xenograft transplantation of human MSCs (hMSCs) in inflammatory disease models (6), have revealed additional mechanisms. These studies demonstrated that MSCs significantly inhibit T-cell activation and proliferation, which are crucial for immune responses.

Despite these findings, the inhibitory effects of MSCs on T-cells are not universally observed. Some studies suggest that these effects are contingent upon the presence of stimulatory signals (7). For example, in co-culture studies involving MSCs and T-cell hybridoma or blastoma—cell lines that lack the capacity to secrete pro-inflammatory cytokines but can proliferate without external stimulation—no immunosuppressive effects were detected (6). This suggests that the immunosuppressive properties of MSCs require induction by pro-inflammatory cytokines or other elements in the microenvironment (8). Interestingly, when exposed to MSCs along with a cocktail of pro-inflammatory cytokines, including IFN-γ, TNF-α, and IL-1α/β, the proliferation of T-cell hybridoma and blastoma was almost entirely inhibited (6). These findings underscore that the immunosuppressive capacity of MSCs is not intrinsic but is activated by pro-inflammatory signals within their microenvironment.

In conclusion, the ability of MSCs to modulate immune responses highlights their potential in clinical applications. However, their function is intricately tied to the microenvironment, which can polarize MSCs towards pro-inflammatory or anti-inflammatory phenotypes. Understanding the mechanisms and conditions that govern MSC plasticity and their immunoregulatory roles will be critical for optimizing their therapeutic applications in autoimmune diseases, inflammatory-related conditions, and tissue regeneration.

Plasticity of MSCs

The plasticity of MSCs is central to their immunoregulatory functions. These cells exhibit remarkable adaptability, capable of adopting pro-inflammatory or anti-

inflammatory roles in response to external stimuli (2). This duality enables MSCs to regulate tissue homeostasis and immune responses by acting as "sensors and switchers." Specifically, MSCs can amplify inflammatory responses in underactive immune systems while mitigating inflammation in overactive ones, thereby preventing autoimmune attacks and promoting balanced immune activity (9).

The microenvironment's type and strength of signals are decisive in polarizing MSCs toward pro-inflammatory (MSC1) or anti-inflammatory (MSC2) phenotypes. For example, pro-inflammatory stimuli like IFN-γ and TNF-α induce an MSC1 phenotype, enhancing their immunostimulatory properties, while anti-inflammatory cytokines such as TGF-β and PGE2 promote an MSC2 state that supports immunosuppression (10). This dynamic polarization is governed by a complex interplay of cytokines, chemokines, and cell-surface receptors, mediating the MSCs' roles during tissue repair and immune modulation (3).

Emerging studies emphasize that MSC plasticity is also influenced by toll-like receptor (TLR) activation. TLR4 engagement often shifts MSCs towards a pro-inflammatory phenotype, whereas TLR3 activation can favor immunosuppressive functions, highlighting the nuanced roles of these receptors in shaping MSC behavior (11). Additionally, MSCs demonstrate a capacity for re-polarization in response to changes in their microenvironment, underscoring their therapeutic potential in dynamically modulating immune responses during conditions like sepsis and autoimmune diseases (10).

These insights into the plasticity of MSCs further illustrate their potential in therapeutic applications, particularly in balancing immune responses during tissue regeneration and immune-mediated disorders.

Regulators of plasticity in the microenvironment

The interplay between MSCs and the microenvironment is a finely tuned process that dictates tissue regeneration, immune modulation, and homeostasis. The local microenvironment is a dynamic and complex niche that includes both cellular and non-cellular components. The cellular constituents consist of immune cells, pericytes, endothelial cells, tissue-resident fibroblasts, and MSCs. The non-cellular components comprise structural proteins, glycoproteins, and proteoglycans found in the extracellular matrix (ECM), as well as bioactive molecules such as cytokines, chemokines, growth factors, and angiogenic factors, collectively referred to as the secretome (12, 13). While the biophysical properties of the ECM are closely related to specific tissues, the biochemical signals that make up the secretome are primarily influenced by the recruitment of circulating MSCs and immune cells to damaged tissues, in addition to the contributions from tissue-resident MSCs (14). Together, these components create a complex milieu within the in vivo microenvironment that regulates tissue homeostasis, repair, and regeneration.

The ECM and hypoxia are crucial regulators of MSC functionality. Hypoxic conditions upregulate VEGF and angiogenic factors, enhancing tissue repair capabilities while

simultaneously maintaining low immunogenicity. The ECM provides structural support and modulates MSC behavior through integrin-mediated signaling, influencing migration and differentiation (15). Furthermore, recent studies highlight metabolic reprogramming as a key factor in MSC plasticity. MSCs adjust their metabolic pathways—shifting between glycolysis and oxidative phosphorylation—based on microenvironmental cues (16). Accordingly, glycolysis predominates under inflammatory conditions, supporting immunosuppressive functions, whereas oxidative metabolism facilitates tissue repair during resolution phases (17). Finally, genetic and pharmacological modifications of MSCs are being explored to enhance their immunomodulatory properties. Preconditioning MSCs with pro-inflammatory cytokines or hypoxic conditions has shown to amplify their therapeutic efficacy in clinical applications such as autoimmune diseases and graft-versus-host disease (15, 18).

Plasticity and orchestration of immune modulation

MSCs exhibit remarkable plasticity, enabling them to balance pro- and anti-inflammatory responses essential for preserving tissue integrity and immune homeostasis (19). MSCs exert their effects predominantly via paracrine signaling, through which they secrete a complex repertoire of bioactive molecules, including cytokines, chemokines, growth factors, and extracellular vesicles (EVs) (20). These secreted factors coordinate interactions with both innate and adaptive immune cells—such as T and B lymphocytes, macrophages, dendritic cells (DCs), and natural killer (NK) cells—to fine-tune immune responses, ultimately fostering tissue repair and regeneration (17, 18). In addition to their paracrine effects, MSCs contribute to the regeneration of the local microenvironment by releasing bioactive agents that influence the self-renewal and differentiation of neighboring tissue progenitors, further promoting the healing process (19). Notably, MSCs are also regulated by autocrine signaling mechanisms, enabling them to sustain core properties such as multipotency, survival, senescence, and the ability to home to inflamed tissues upon in vivo administration (21).

Their surrounding microenvironment profoundly influences the behavior of MSCs. Inflammatory signals such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) can polarize MSCs to secrete immunosuppressive mediators, including prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and transforming growth factor-beta (TGF-β). These factors facilitate the expansion of regulatory T cells (Tregs) and promote macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype (15). Conversely, MSCs may adopt a pro-inflammatory role in low-inflammatory contexts, amplifying immune responses by engaging with Th1 cells and other effector populations. This bidirectional plasticity underscores MSCs' ability to adaptively restore immune balance under diverse pathophysiological conditions (18).

At sites of inflammation, MSCs employ sophisticated mechanisms to modulate immune cascades. They suppress Th1 cell activity, induce Treg differentiation, and promote Th2 cell responses while facilitating

the M1-to-M2 macrophage transition. These effects are mediated through a network of signaling molecules and pathways that allow MSCs to dynamically recalibrate immune activity, preventing pathological inflammation or excessive immunosuppression (1, 17). Furthermore, MSC-derived EVs enable long-distance communication, influencing apoptosis, inflammation, and fibrosis in both immune and tissue cells (22, 23).

This intricate interplay between MSCs and their microenvironment highlights the crucial role of extrinsic and intrinsic regulatory factors in shaping their therapeutic potential. As versatile modulators of immune responses and tissue repair, MSCs stand as a cornerstone in regenerative medicine.

MSC licensing: an indispensable step in immunoregulation

Emerging evidence underscores the pivotal role of the inflammatory microenvironment in "licensing" or "priming" MSCs to optimize their immunomodulatory functions. Priming stimuli extend beyond pro-inflammatory cytokines, such as IFN-γ, TNF-α and IL-1α/β, to include growth factors, hypoxic conditions, and biochemical signals such as lipopolysaccharide (LPS), as well as biophysical factors like three-dimensional (3D) substrates (24). These stimuli influence MSCs' biological functions, including their capacity for proliferation, self-renewal, migration, differentiation, and resistance to senescence—core processes essential for effective tissue regeneration and repair (25, 26).

Priming MSCs with IFN-γ triggers early phosphorylation of signal transducers and activators of transcription (STAT1/STAT3) and inhibits mammalian target of rapamycin (mTOR) activity. This results in the upregulation of genes associated with immunoregulation and the downregulation of genes related to differentiation, proliferation, and stemness. In human MSCs, mTOR pathway inhibition further enhances their immunoregulatory potential (27). Single-cell analyses have revealed that IFN-γ/TNF-α-stimulated MSCs exhibit elevated expression of immunosuppressive factors, chemokines, cytokines, growth factors, and receptors compared to untreated MSCs (28).

Proteomic studies have identified significant alterations in protein expression in primed MSCs. For example, IFN-γ-primed human bone marrow MSCs (hBM-MSCs) demonstrate overexpression of immunomodulatory proteins such as IDO, PDL-1, ICAM-1, VCAM-1, and BST-2, alongside downregulation of proteins like ANTXR1, APCDD1L, NPR3, and FADS2 (29). Priming also increases the production of anti-inflammatory molecules, including PGE2, hepatocyte growth factor (HGF), TGF-β, and CCL2, as well as the expression of human leukocyte antigen (HLA) class I and II molecules and co-stimulatory molecules (30). Licensing MSCs through inflammatory cytokines unlocks their immunosuppressive potential while influencing their inherent properties. For example, while priming enhances the immunomodulatory potential of MSCs, it can also increase their immunogenicity. The upregulation of HLA class I and II molecules during priming makes MSCs more susceptible to recognition by host immune cells (31). This dual effect necessitates a careful balance to optimize the therapeutic efficacy of MSCs while

minimizing potential adverse immune reactions (32). Therefore, understanding the molecular mechanisms underlying these interactions is critical for advancing MSC-based therapies. Future research should focus on refining priming strategies to maximize therapeutic benefits while mitigating immunogenic risks, thereby enhancing the clinical utility of MSCs in regenerative medicine and immunotherapy.

Pro-inflammatory mediators significantly enhance MSC secretion of chemokines, iNOS, and IDO, which collectively suppress immune responses via the chemokine-iNOS/IDO axis. This pathway not only modulates immune cell recruitment and activity but also fine-tunes MSCs' ability to restore immune homeostasis (33).

Adaptive immunity regulators in microenvironment

MSCs express multiple immunosuppressive factors that affect their ability to suppress Th1 inflammatory responses, including iNOS, IDO, FasL, PD-L1, galectins, HO-1, and HLA-G5 (34). Studies have shown that these factors play a crucial role in MSC-mediated immunosuppressive effects on adaptive immune cells, particularly through the iNOS/IDO axis (34). This mainly relies on the production of chemokines by MSCs, including CXCL9, CXCL10, and CXCL11, which bind to CXCR3 expressed on T cells (35). Figure 1 depicts the chemokine-iNOS/IDO axis in MSC-mediated regulation of adaptive immunity and illustrates the dynamic interaction between these cells and the inflamed microenvironment.

Chemokine-iNOS/IDO axis and immunoregulation

The chemokine-iNOS/IDO axis is a critical mechanism through which MSCs regulate immune responses. MSCs secrete chemokines such as CXCL9, CXCL10, and CXCL11, which bind to CXCR3 receptors on T cells, modulating lymphocyte trafficking and immune activity (36). Depending on the inflammatory context, this axis can either amplify or suppress immune responses, with high levels of iNOS and IDO synergizing with these chemokines to attenuate excessive immune activation. Conversely, lower levels of these molecules may enhance T cell proliferation and function, highlighting the pivotal influence of microenvironmental conditions on MSC behavior (Ren et al., 2009; Wang et al., 2022).

Chemokines not only mediate immune modulation but also govern cell migration and positioning during inflammation, homeostasis, and tissue repair. Secreted as soluble mediators or bound to ECM components, chemokines establish spatial concentration gradients detected by receptors on target cells (37). For instance, pro-inflammatory stimulation of MSCs triggers the release of chemokines such as CCL5, CXCL9, CXCL10, and CXCL11. These chemokines bind to CXCR3 and CCR5 receptors on T cells, guiding their migration toward MSCs. In vitro time-lapse microscopy studies confirm that T cells surround MSCs following this chemokine-mediated recruitment (33). Functional studies employing chemical inhibitors or transgenic models further validate the essential role of CXCR3 and CCR5 pathways in MSC-mediated T cell suppression, with disruption of these pathways impairing MSC immunomodulatory efficacy (38).

The production of iNOS and IDO by licensed MSCs is indispensable for their immunosuppressive function. Knockout models have demonstrated that deletion or inhibition of these mediators diminishes MSCs' immunosuppressive activity and therapeutic efficacy, particularly in models of acute liver injury and fibrosis (39-44). Nitric oxide (NO), produced by iNOS, contributes to immune modulation by inducing T cell cycle arrest via the JAK-STAT signaling pathway and suppressing pro-inflammatory cytokine production in macrophages through modulation of MAPK and NF-κB signaling (45). Similarly, IDO reduces local tryptophan availability, creating an immunosuppressive environment that limits T cell proliferation and activity (46).

The combined action of high levels of iNOS/IDO and chemokines in MSCs can suppress chemokine-recruited lymphocytes. Conversely, insufficient iNOS/IDO levels, coupled with the presence of chemokines, can lead to lymphocyte accumulation and amplify the immune response (34). As anti-inflammatory factors apply their function locally within the microenvironment, the chemokine/receptor mechanisms are vital in recruiting the immune cells to the inflammatory microenvironment and exerting a suppressive effect on their activation, proliferation, and immune functions (32). While the inhibitory mechanisms on T cells are well-established, the precise method by which MSCs influence B cell proliferation and antibody production remain unknown (47, 48). Together, the chemokine-iNOS/IDO axis underscores the ability of MSCs to finely regulate immune cell recruitment, activation, and suppression in a manner tailored to the inflammatory milieu. These mechanisms form the basis for MSC-based therapies targeting immune dysregulation in diverse pathologies.

Inflammatory cytokines and immunoregulation

Inflammatory cytokines, particularly IFN-γ and TNF-α, play pivotal and dual roles in the regulatory framework of MSC-mediated immunomodulation. At elevated concentrations, these cytokines act as "licensing" agents, significantly enhancing MSC immunosuppressive capabilities. This effect is mediated through the upregulation of key mediators such as iNOS and IDO. Conversely, at lower cytokine levels, MSCs may shift to a stimulatory phenotype, enhancing T cell function and proliferation (Li et al., 2012; Wang et al., 2014). This bidirectional responsiveness underscores the complex, context-dependent nature of MSC activity, highlighting the importance of tailoring MSC-based therapies to the inflammatory state of the target tissue to optimize therapeutic outcomes (36).

The concentration-dependent effects of inflammatory cytokines are not limited to IFN-γ and TNF-α. Other cytokines, such as IL-17, TGF-β, and type I interferons, also influence MSC function and fate in the inflammatory microenvironment (49, 50). For instance, an IFN-γ-enriched milieu typically associated with damaged tissue induces the expression of IFN-stimulated genes, including chemokines and adhesion molecules, which facilitate immune cell recruitment and tissue repair. However, the effect of IFN-γ on tissue-resident MSCs during pathological conditions remains incompletely understood, particularly

regarding how this cytokine interacts with other components of the damaged microenvironment (32).

Recent research suggests that the inflammatory state of the damaged tissue critically determines the therapeutic efficacy of MSC-based interventions. High levels of pro-inflammatory cytokines during the early stages of inflammation may "prime" MSCs to exert their immunosuppressive effects effectively, thereby restoring tissue function and immune homeostasis. In contrast, “unmatched” inflammatory signals, such as insufficient levels of pro-inflammatory cytokines or the presence of immunosuppressive agents, can impair MSC function, leading to suboptimal immune regulation and failed tissue regeneration (34).

These findings suggest that the timing and context of MSC administration are critical for their success in clinical settings. Inflammatory cues must align with the MSCs' licensing requirements to optimize their therapeutic potential. Such insights emphasize the need for precision in designing MSC-based therapies, including preconditioning MSCs with appropriate cytokine environments or administering them at stages of inflammation where their activity aligns with the immune and tissue repair demands of the host (49, 50).

Innate immunity regulators in microenvironment PAMP/DAMP-PRR axis

Pathogen- or damage/danger-associated molecular patterns (PAMPs and DAMPs, respectively) are pivotal components of inflammatory microenvironments. These molecular patterns bind to pattern recognition receptors (PRRs) as part of the innate immune system, activating inflammatory signaling pathways during the early phase of inflammation (51). PAMPs are structurally conserved molecules commonly found on bacterial, viral, and fungal surfaces, while DAMPs are endogenous molecules originating from ECM components such as hyaluronan and heparan sulfate, or intracellular molecules like high mobility group box 1 (HMGB1) protein and ATP (52, 53).

Figure 1 depicts the PAMP/DAMP-PRR axis in MSCs, highlighting the dynamic interaction between these cells and the inflamed microenvironments. By detecting signals indicating molecular danger or the presence of pathogens, MSCs can adjust their responses to either stimulate or suppress innate immune activity. This ability makes them vital mediators of inflammation, infection control, and tissue repair (14).

DAMPs and PAMPs collectively act as danger signals critical not only for inflammatory responses but also for tissue repair. DAMPs, for instance, influence the immunomodulatory function of antigen-presenting cells (APCs) such as DCs and macrophages, altering their maturation, polarization, and antigen-processing abilities. Furthermore, DAMPs can modulate the activities of eosinophils, mast cells, and neutrophils, indicating their wide-reaching impact on immune responses (54).

PRRs are a cornerstone of the innate immune system, located in cellular compartments such as the plasma membrane, cytosol, endosome, and nucleus (55). These receptors, encompassing seven major subfamilies, respond to diverse PAMPs and DAMPs. PRRs expressed by immune cells and tissue-

resident MSCs initiate different polarizing responses in the microenvironment, steering either inflammation or tissue repair mechanisms (51). Among PRRs, Toll-like receptors (TLRs) are especially significant. TLR3 and TLR4, for instance, play vital roles in regulating MSC-mediated immunomodulation in response to stimuli (34). The plasticity of MSCs is influenced by the timing and intensity of TLR stimulation. For example, MSCs acquire immunosuppressive capabilities after brief exposure to the TLR3 agonist poly(I:C), while a short exposure to lipopolysaccharide (LPS) induces a pro-inflammatory phenotype (56). Prolonged LPS exposure (24-48 hours), however, shifts MSCs back to an immunosuppressive state (57).

HMGB1 is a well-known DAMP that influences the self-renewal and differentiation of MSCs and hematopoietic stem cells (HSCs) by interacting with PRRs in inflamed tissues and the bone marrow (BM) niche, respectively. HMGB1 also regulates genomic stability, promotes senescence, and modulates immunoregulatory pathways by interacting with immune mediators in inflammatory environments (53). Moreover, HMGB1 serves as a chemoattractant for MSCs, stimulating them to secrete pro-inflammatory cytokines. This activity involves the formation of a heterocomplex with CXCL12 (SDF-1), which binds to CXCR4 on leukocyte surfaces, enhancing leukocyte recruitment (58, 59). The IKKα/noncanonical NF-κB pathway is essential for sustained CXCL12 production, facilitating migration toward HMGB1. This highlights the role of the HMGB1-CXCL12 heterocomplex in promoting cell migration via the NF-κB pathway (53).

Therapeutic implications

Preconditioning processes such as TLR priming can significantly impact the outcome of MSC-based therapies (57, 60). TLR priming, particularly TLR3 and TLR4 activation, is a promising strategy to modify the immunomodulatory properties of MSCs. For example, TLR3- and TLR4-primed MSCs have shown enhanced abilities to polarize macrophages towards an anti-inflammatory M2 phenotype and reduce pro-inflammatory cytokine secretion in models of acute inflammation (11). This suggests a potential for TLR-primed MSCs or their EVs in mitigating inflammation-induced tissue damage, furthering their therapeutic applications in regenerative medicine, as well as inflammatory and degenerative diseases (61, 62). For instance, priming MSCs with TLR4 stimuli in a left ventricular dysfunction (LVD) model led to the acquisition of a pro-inflammatory phenotype, resulting in failed tissue repair (60). Understanding the inflammatory microenvironment under varying pathological conditions is thus essential for optimizing MSCs' immunomodulatory potential and clinical applications (34).

Preconditioning MSCs with inflammatory cytokines, such as IFN-γ, can enhance their immunosuppressive capabilities. This approach increases the secretion of factors like IDO, PGE2, and HGF while promoting the expression of adhesion molecules and anti-inflammatory cytokines. These changes help MSCs regulate the immune response more effectively, as observed in colitis and other inflammatory models (63, 64). Furthermore, the involvement of PAMPs and DAMPs in modulating the MSC microenvironment highlights their

therapeutic potential. Targeting these pathways with specific inhibitors or through controlled TLR activation can enhance MSC-mediated immunoregulation and tissue repair by reducing chronic inflammation while preserving regenerative capacities (54, 65).

Combining TLR-primed MSCs with pharmacological agents or cytokine therapies may synergistically improve outcomes in chronic inflammatory diseases (61). Additionally, MSC-derived EVs, which retain many of the beneficial immunomodulatory effects of MSCs, present a novel cell-free therapeutic strategy with reduced immunogenicity and logistical challenges (66, 67). Integrating these developments into your manuscript will enrich the discussion and provide a broader context for the potential clinical applications of MSCs in immune modulation and tissue repair. Let me know if you'd like me to draft specific text updates.

Metabolic adaptations in inflammatory microenvironment Glycolytic reprogramming and mitochondrial dysfunction

The inflammatory microenvironment is defined by acidic and oxidizing conditions that influence immune cell metabolism. Innate immune cells, such as macrophages, undergo a metabolic shift from oxidative phosphorylation (OXPHOS) to glycolysis in response to these conditions. This glycolytic reprogramming facilitates rapid ATP production and supports biosynthetic processes essential for pro-inflammatory responses (16, 68). Conversely, tissue repair and the resolution of inflammation require a neutral and reductive environment. In this phase, macrophages transition to an anti-inflammatory phenotype, relying on OXPHOS and fatty acid oxidation to promote healing and mitigate inflammation (69, 70).

Continuous infusion of LPS-contaminated polyethylene particles (cPE) serves as a model for investigating periprosthetic osteolysis and chronic inflammatory bone destruction. The persistent inflammatory responses triggered by implant-associated particulate debris foster a chronic inflammatory microenvironment. This environment recruits regulatory cells such as macrophages, lymphocytes, MSCs, and fibroblasts, exacerbating periprosthetic osteolysis (71). Studies have shown that cPE exposure disrupts mitochondrial metabolism in both macrophages and MSCs, impairing bioenergetic activity and diminishing immunoregulatory functions in the bone niche (72, 73). These findings align with the hypothesis that chronic inflammation impairs bone regeneration and immunoregulation by inducing glycolytic reprogramming and mitochondrial dysfunction in macrophages, neutrophils, and MSCs (16).

Recent research by Teissier et al. highlights the metabolic plasticity of immune and stromal cells in inflammatory conditions. Under the stress of cPE exposure, MSCs displayed a metabolic shift toward glycolysis, whereas macrophages demonstrated an adaptive response to restore mitochondrial function and OXPHOS. Intriguingly, coculturing MSCs with uncommitted macrophages (Mφ) resulted in their polarization into both pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. This dynamic interplay suggests a mechanism for metabolic reprogramming within the inflammatory microenvironment (72).

Regulation of metabolic adaptation

Hypoxia: a biochemical cue of inflammatory microenvironment

Hypoxia, a defining biochemical characteristic of in vivo microenvironments, e.g., BM niches and damaged/inflamed tissues, plays a pivotal role in regulating the functional plasticity of MSCs. Hypoxic conditions are frequently employed in vitro to prime MSCs and mimic their natural niches, enhancing their immunomodulatory capacities and therapeutic efficacy (74). This feature is also critical in immunological niches, where hypoxia significantly influences immune cell responses (75).

Hypoxia in MSC niches mitigates oxidative stress, cellular senescence, and DNA damage

Hypoxia in MSC niches mitigates oxidative stress, cellular senescence, and DNA damage

caused by high oxygen exposure, thereby enhancing proliferation, secretory activity, and regenerative potential (76-78). Hypoxia also induces the expression of hypoxia-inducible factor 1-alpha (HIF1α), a critical transcription factor that orchestrates metabolic adaptation to low oxygen. HIF1α upregulates genes such as pyruvate dehydrogenase kinase 1 (PDK1) and glucose transporter 1 (GLUT1), reduces mitochondrial respiration and minimizes reactive oxygen species (ROS) production, delaying senescence and telomere shortening (79).

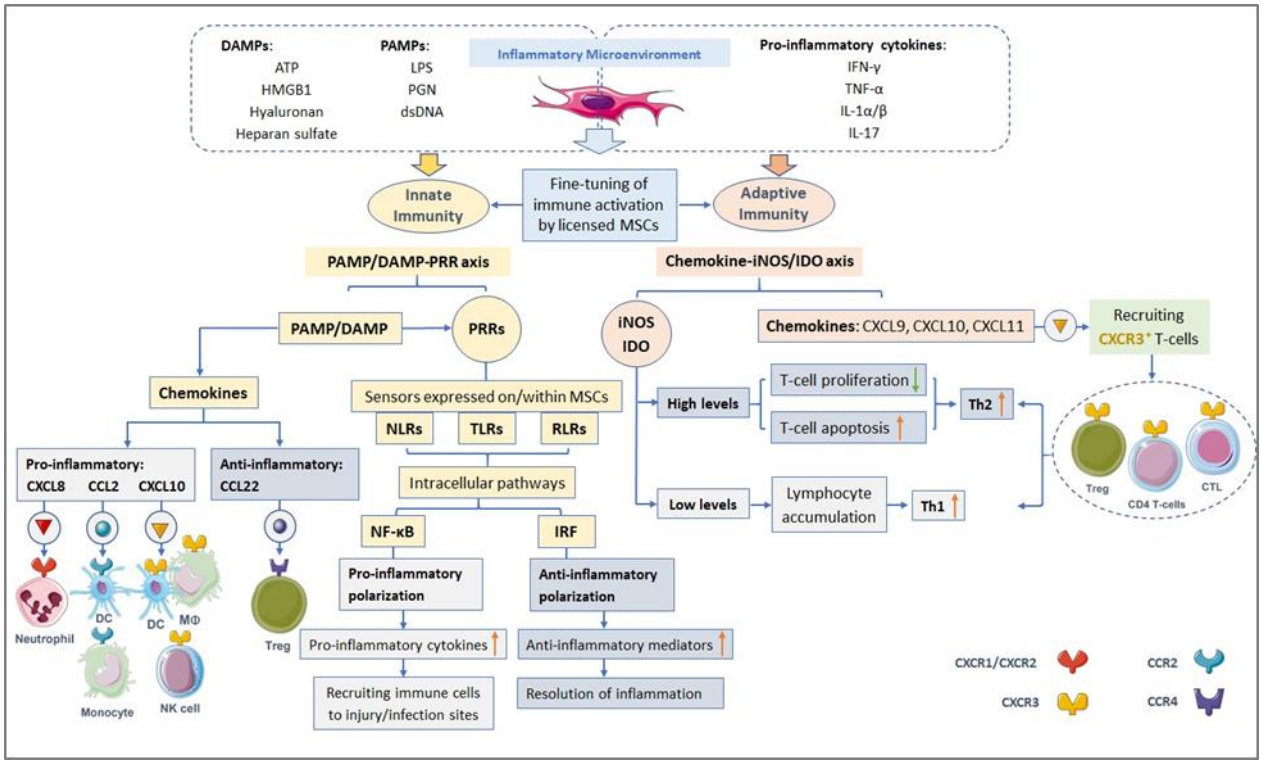

Figure 1. Key mechanisms of MSC-mediated immune regulation in adaptive and innate immunity within the microenvironment. **Abbreviations:** Pathogen-associated molecular patterns (PAMPs); Damage/danger-associated molecular patterns (DAMPs); Pattern recognition receptors (PRRs); Toll-like receptors (TLRs); NOD-like receptors (NLRs); RIG-I-like receptors (RLRs); Interferon regulatory factor (IRF) pathway; Nuclear factor-kappa B (NF-κB) pathway; Dendritic cell (DC); Macrophage (MΦ); Natural killer (NK) cell; regulatory T cell (Treg); High mobility group box 1 (HMGB1); Lipopolysaccharide (LPS); Proteoglycan (PGN); Double-strand DNA (dsDNA).

Hypoxic preconditioning (e.g., at 1% O_2) enhances MSC therapeutic efficacy, notably by enriching EVs and exosomes with regenerative microRNAs (74, 80, 81). For instance, hypoxia-induced miR-125b-5p packaging is upregulated in EVs released by MSCs that has been shown to improve wound healing in both in vitro and in vivo models (74). Moreover, hypoxia-primed MSCs exhibit robust paracrine effects that promote tissue repair. In a mouse hindlimb ischemia model, hypoxia-primed MSCs enhanced cell survival and stimulated myoblast differentiation through Wnt4 secretion (82).

HIF1α: a master regulator of metabolic shifts

HIF1α is the central mediator of cellular adaptation to hypoxia, regulating the shift from OXPHOS to glycolysis. This metabolic reprogramming is essential for rapid energy production and biosynthesis, particularly in inflammatory and regenerative processes. In immune cells such as macrophages, HIF1α promotes polarization toward the pro-inflammatory M1 phenotype, fueling inflammation (75). Conversely, in MSCs, HIF1α induces a glycolytic metabolic profile that enhances their secretion of anti-inflammatory cytokines, including interleukin-10 (IL-10). This mechanism promotes macrophage polarization toward the tissue-repairing M2 phenotype, highlighting HIF1α's dual roles in inflammation and tissue repair (54, 83).

Under hypoxic conditions, stabilization of HIF1α in MSCs enhances their viability and immunomodulatory properties. This involves increased glycolysis and reduced mitochondrial ROS production, enabling MSCs to persist in hostile environments (81). Hypoxia-primed MSCs exhibit enhanced secretion of paracrine factors such as vascular endothelial growth factor (VEGF) and HGF, critical for tissue repair and angiogenesis (84). Hypoxia also augments MSCs' capacity to suppress T-cell proliferation and modulate macrophage activity, key mechanisms underlying their therapeutic effects in inflammatory and regenerative contexts (85, 86). In addition, HIF1α stabilizes key signaling pathways that support MSC differentiation into osteogenic and chondrogenic lineages. For instance, hypoxia-induced expression of VEGF and GLUT1 facilitates ECM remodeling and cellular survival, particularly beneficial in ischemic or inflamed tissues (87, 88).

HIF1α's role as a master regulator of metabolic adaptation under hypoxic conditions underscores its significance in regenerative medicine. By harnessing its ability to reprogram MSC metabolism and enhance their immunomodulatory properties, researchers can further develop advanced therapeutic strategies. Understanding the molecular pathways governed by HIF1α will be pivotal in optimizing MSC-based interventions for inflammatory and ischemic conditions (85, 87).

Therapeutic implications

Leveraging metabolic shift regulators, particularly those targeting HIF1α, represents a promising avenue for enhancing MSC-based therapies in inflammatory microenvironments. Activation of HIF1α through hypoxia priming or pharmacological agents, such as prolyl hydroxylase inhibitors (PHIs), can simulate hypoxic conditions and

precondition MSCs for improved therapeutic efficacy. Preclinical studies have demonstrated that these strategies enhance MSC survival, engraftment, and paracrine signaling, contributing to successful outcomes in models of ischemia, chronic inflammation, and bone regeneration (89, 90).

Fine-tuning the activity of HIF1α offers a means to optimize the metabolic balance between glycolysis and OXPHOS in both MSCs and macrophages. This metabolic regulation can reduce oxidative stress and foster an anti-inflammatory environment conducive to tissue repair and regeneration (91). For example, MSCs preconditioned with hypoxia or HIF1α activators show improved immunomodulatory properties, such as increased secretion of anti-inflammatory cytokines and enhanced mitochondrial transfer to neighboring cells under stress, which supports tissue healing in conditions such as chronic wounds and inflammatory bone diseases (76, 91).

Additionally, targeting mitochondrial dysfunction and glycolytic shifts in inflammatory microenvironments has gained traction as a therapeutic strategy. Pharmacological agents that modulate mitochondrial dynamics, such as mitophagy enhancers or inhibitors of mitochondrial reactive oxygen species (mtROS), have shown potential to restore bioenergetic balance and enhance the reparative functions of MSCs and macrophages (16, 68). For instance, therapies that improve mitochondrial biogenesis in MSCs not only bolster their survival in oxidative environments but also enhance their osteogenic differentiation capacity, which is critical for effective bone regeneration (92).

Recent advancements also highlight the therapeutic implications of modulating glycolytic reprogramming. Small molecules, such as dichloroacetate (DCA) and 2-deoxyglucose (2-DG), can regulate glycolytic activity in MSCs, promoting metabolic adaptability in challenging inflammatory microenvironments (93). These agents may improve MSC-mediated immunoregulation by reducing pro-inflammatory cytokine release and enhancing anti-inflammatory signaling in macrophage-MSC interactions (94). Moreover, the interplay between MSCs and immune cells in the inflammatory niche offers opportunities for therapeutic interventions. Coculture approaches or engineered MSCs that release targeted metabolites or exosomes containing bioactive molecules could further enhance metabolic crosstalk and functional outcomes (95). For example, exosomes derived from hypoxia-primed MSCs have demonstrated superior anti-inflammatory and pro-regenerative effects compared to non-primed controls, indicating their potential as standalone or adjunct therapies in inflammatory diseases (96, 97).

These findings underscore the potential of metabolic shift regulators to enhance MSC-based therapies by improving cell function, survival, and reparative efficacy in hostile inflammatory environments. Continued research into combining metabolic preconditioning with pharmacological agents or advanced biomaterials could revolutionize therapeutic strategies for managing chronic inflammation and tissue regeneration.

Immunoregulatory dynamics of MSCs in physiologic/pathologic conditions

Physiologic conditions: Dual roles of MSCs in the healing process

MSCs demonstrate a dual role in the wound-healing process, functioning critically during both the inflammatory and resolution phases (98). In the acute inflammatory phase, MSCs promote inflammation by recruiting neutrophils and other immune cells through the secretion of interleukin-8 (IL-8) and migration inhibitory factor (MIF), which support debris clearance and antibacterial activity (99). Beyond these effects, MSCs contribute to angiogenesis by secreting VEGF and fibroblast growth factor (FGF), ensuring sufficient blood supply to the wound area (100). Additionally, their influence on mast cells and T-cells aids in regulating early immune responses, fostering a balanced inflammatory milieu crucial for effective wound repair (101).

In the resolution phase, MSCs shift their role to immunomodulation, critical for transitioning the inflammatory environment toward tissue regeneration. They recruit granulocytes through CCL2, CCL3, and CCL12 secretion and induce macrophage polarization toward the anti-inflammatory M2 phenotype by producing PGE2, IDO, and TNF-stimulated gene-6 (TSG6) (99, 102). These functions limit excessive inflammation while promoting tissue repair and remodeling. MSCs also influence Th1/Th17 balance, ensuring a reduction in pro-inflammatory cytokines and creating an environment conducive to healing (99). Their role in fibroblast recruitment and ECM remodeling further enhances tissue regeneration (23).

Recent studies highlight MSCs' paracrine signaling and immunomodulatory functions as critical for wound healing (103). For instance, MSC-derived exosomes containing bioactive molecules such as miRNAs have shown potential in optimizing healing outcomes (22, 23). Strategies combining MSCs with bioengineered scaffolds or preconditioning approaches aim to amplify their therapeutic effects by enhancing their survival, differentiation potential, and secretory profiles (101, 104).

These findings underline the need for further research into MSC-based therapies, particularly their integration with tissue engineering and the potential for cell-free exosome-based treatments, which hold promise for enhanced healing outcomes and reduced complications in chronic wounds or severe tissue damage (100, 101).

Pathologic conditions: Dual roles of MSCs in tumor microenvironment

Recent studies on the tumor microenvironment (TME) have highlighted the significant role of the microenvironment in influencing the plasticity of MSCs. Specifically, chronic inflammation in the TME can signal the MSCs to favor tumor progression. In addition to MSCs, there are other subsets of tumor-associated stromal cells (TASCs) such as tumor-associated fibroblasts (CAFs), tumor-associated adipocytes (CAAs), tumor endothelial cells (TECs), and pericytes (PCs) (105). These cells, along with immune cells recruited to the TME, can interact with each other and the microenvironment using cytokines and mediators. This interaction can have an impact on various aspects of tumor progression including invasion, metastasis, angiogenesis, drug resistance, and disease recurrence (106). As a prominent subset of stromal cells within the TME, MSCs serve

distinct functions during different phases of tumor growth. Investigations into exogenous MSCs have demonstrated a variety of outcomes in terms of cancer progression and the proliferation of tumor cells in vitro (107-109). While some cases indicate that MSCs can inhibit tumor growth, it has been observed that these cells are recruited to the tumor site during the advanced stages of tumor growth. At this point, the tumor cells and other cells in the TME "re-educate" the MSCs, causing them to acquire characteristics that promote tumorigenesis, development, and metastasis (105, 110). Therefore, cell therapy approaches require a comprehensive understanding of the behavior of MSCs in the local microenvironment of target tissues in patients (18). Increasing our understanding of the controlling mechanisms on the plasticity of MSCs can also aid in developing novel therapeutic methods (34).

Conclusion

The immunoregulatory dynamics of MSCs are intricately linked to their microenvironment, which determines their functional phenotype. MSCs maintain immune homeostasis and facilitate tissue repair by acting as pro-inflammatory and anti-inflammatory agents. However, their efficacy in therapeutic applications is contingent upon thoroughly understanding the factors influencing their behavior. Advancing our understanding of MSC plasticity and its regulation through cytokines and chemokines can inform the development of precision MSC-based therapies. Matching the inflammatory signals of damaged tissue with MSC activity holds promise for improving outcomes in inflammatory diseases and tissue regeneration. Additionally, insights into the behavior of MSCs in pathological environments, including the TME, can aid in designing safer and more effective therapeutic strategies. Future research should focus on elucidating the molecular mechanisms underlying MSC plasticity and developing strategies to harness their full potential in regenerative medicine and immunotherapy.

Conflict of interest

The authors have no conflict of interest to declare.

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