Reviews

Crosstalk Between Gingival Mesenchymal Stem Cells and the Inflammatory Microenvironment

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Gingival mesenchymal stem cells (GMSCs) hold similar biological features to other MSCs, but also have some advantages that include being easily accessible with relatively few technical and ethical constraints, stronger proliferative capacity, and more stable morphological characteristics. A close bidirectional interaction exists between the biological functions of GMSCs and their inflammatory microenvironment: inflammatory factors can regulate the immunomodulatory and tissue repair capabilities of GMSCs, while GMSCs, in turn, can reshape the local microenvironment, suppressing excessive inflammation and promoting tissue regeneration. Herein, we discuss the biological properties and functional alterations of GMSCs under various pathophysiological conditions, aiming to provide new insights into the immunoregulatory mechanisms of GMSCs in tissue regeneration and therapeutic processes.

Introduction

Mesenchymal stem cells (MSCs) are a heterogeneous population of stem cells capable of self-renewal and multi-lineage differentiation, which engage in extensive interactions with immune cells[1]. Beyond their role in hematopoiesis by participating in immune cell generation, these cells also engage in complex crosstalk with immune cells during physiological processes such as tissue regeneration. Numerous *in vitro* and *in vivo* studies have documented that MSCs not only contribute to regenerative processes but also potently modulate various innate and adaptive immune functions. Human gingival tissue-derived mesenchymal stem cells (GMSCs), as a unique class of MSCs, are not only easily accessible but also demonstrate remarkable immunomodulatory properties and a favorable safety profile[2,3]. Consequently, they are considered a highly promising stem cell source for clinical applications in regenerative medicine. Notably, the therapeutic efficacy of GMSCs is not achieved in an isolation model, but rather through a dynamic and bidirectional interaction with their microenvironment, particularly in inflammatory conditions. In this review, we analyze this complex bidirectional regulatory network between GMSCs and the inflammatory microenvironment, with a focused emphasis on its underlying molecular mechanisms, aiming to inform clinical decision-making.

Biological Characteristics of GMSCs

GMSCs were first isolated and characterized in 2009. These cells possess the capacity to differentiate into multiple lineages and express a specific panel of MSC-associated surface markers, including CD73, CD90, CD105, SSEA-4, and STRO-1, while failing to express hematopoietic markers such as CD34 and CD45[4-7].Research has established that three key transcription factors, like OCT4, NANOG, and SOX2, are central to maintaining the self-renewal and pluripotency of embryonic stem cells[8]. These factors are also expressed in GMSCs and may influence their pluripotency[9]. Similar to bone marrow-derived MSCs and adipose-derived MSCs (BMSCs and ADSCs), GMSCs can be differentiated into osteoblasts, adipocytes, chondrocytes, and some neuro-like cells under specific *in vitro* induction protocols[6,7,10]. Despite these similar characteristics, GMSCs also have some unique features, especially relatively high proliferative capacity[11,12]. Compared to BMSCs, GMSCs show superior proliferative potential and stronger immunomodulatory capabilities[4]. Furthermore, GMSCs maintain a stable phenotype and do not lose their MSC proper- ties after long-term culture[12]. In addition to their lineage differentiation potential, our laboratory was the first to report the therapeutic utility of GMSCs in autoimmune arthritis[13]. Since then, GMSCs have gradually gained attention in the treatment of autoimmune and inflammatory diseases[14-28].

Interaction Mechanisms of GMSCs in Inflammatory Environments

Migration Ability and Functional Adaptability of GMSCs

In vitro expanded gingival mesenchymal stem cells showed stronger migratory capacity than other types of MSCs, such as dental pulp mesenchymal stem cells (PDSCs)[29] and skin-derived mesenchymal stem cells[30]. Some studies have shown that GMSCs can cross blood vessels and specifically implant into target tissues through factors like chemokines, recombinant human epidermal growth factor (rhEGF), and cytokines[30-33]. These factors are crucial for the migration and homing of mesenchymal stem cells. This chemotactic migration process involves the cascade activation of multiple signaling pathways and relies on the precise regulation between cell surface receptors (e.g., CXCR4, CCR2) and microenvironmental factors[34,35]. Among these factors, stromal cell-derived factor-1 (SDF-1), also known as CXCL12, plays an important role in mediating the directional migration and tissue homing of mesenchymal stem cells. It can activate the CXCR4, a kind of G-protein-coupled specific receptor, to regulate cell differe-

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ntiation, proliferation, migration, and morphology[35-38].

In addition, GMSCs have significant functional adaptability. Studies have identified that GMSCs can be induced to differentiate into a pro-fibrotic phenotype in an inflammatory microenvironment[39]. Using ApoE−/− periodontitis mice, it was observed that transplanted GMSCs can actively migrate to periodontitis and alveolar bone loss sites, and differentiate into periodontal tissue cells. Meanwhile, the serum levels of pro-inflammatory cytokines (TNF-α and IL-6) decreased, while the level of anti-inflammatory cytokine (IL-10) increased[32]. In a rat model of sciatic nerve crush injury, GMSCs transplanted into the injury site could differentiate into neuronal cells. Interestingly, the transplantation of GMSCs significantly reduced the injury-induced increase in c-Jun expression and increased the expression of Krox-20/EGR2[40].

Direct Regulation of Adaptive Immune Responses

Early studies also have shown that GMSCs can effectively inhibit the proliferation and activation of human peripheral blood mononuclear cells (PBMCs) stimulated by phytohemagglutinin(PHA)[4] or allogeneic lymphocytes in mixed lymphocyte reactions(MLRs)[2,3]. This finding provides direct evidence that GMSCs possess immunomodulatory functions. GMSCs can express a variety of key molecules, including indoleamine 2,3-dioxygenase (IDO)[25], CD39/CD73[13,25,28], Fas ligand(FasL)[41], programmed death ligand 1 (B7-H1/PD-L1) [24,42], cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)[42], and prostaglandin E_2 (PGE_2)[43]. Many studies have figured out that these molecules play a vital role in regulating the activation, proliferation, and survival of T cells and B cells. These factors have also been confirmed to reduce the proportions of Th1 and Th17 cells as well as T follicular helper (Tfh) cells, and promote the differentiation of $Foxp3^+$ regulatory T (Treg) cells. Indeed, regulatory T cells are an important subset of immunosuppressive cells[44-47].

Since the function of Fas/FasL depends on direct cell-cell contact, the activation of its pathway requires the support of chemokines (e.g., monocyte chemoattractant protein 1, MCP-1). Hydrogen sulfide (H_2S) can promote the secretion of MCP-1 by stabilizing the expression of Fas in GMSCs, and MCP-1 then binds to CCR2 on the surface of T cells[48]. This process can recruit T cells to the vicinity of GMSCs and promote T cell apoptosis through the Fas/FasL pathway. In addition, GMSCs can also restore the proportions of Th1 and Th17 cells and increase the level of Treg cells through the Fas/FasL pathway[49]. In fact, the immune tolerance induced by GMSCs may also be related to the phagocytosis of apoptotic T cells by macrophages. After phagocytosis, macrophages release high levels of TGF-β to regulate Tregs[50]. Our laboratory was the first to report that TGF-β is a key cytokine with a unique role in inducing the differentiation of regulatory T cells[51-53], while IL-2 also plays a significant role[54,55]. In addition, the strong chemotactic effect on T cells may also enhance the function of immunosuppressive molecules bound to the membrane surface of GMSCs.

Interestingly, GMSCs from different sources seem to have differences in their pro-apoptotic ability. For example, GMSCs derived from the neural crest have significantly higher FasL expression and a stronger ability to induce apoptosis of activated T cells than those derived from the mesoderm[56]. The CD39 and CD73 molecules are involved in adenosine production and play an important role in coordinating the immunoregulation of various immune cells, especially Treg cells. In a mouse model of collagen-induced arthritis (CIA), inhibitors of CD39 or CD73 could eliminate the increase in FoxP3+ Treg cell frequency and the protective effect mediated by GMSCs[13]. Another study exploring the effect of GMSCs on mice with acute graft-*versus*-host disease (GVHD) further highlighted the key role of the CD39 pathway in the regulation of Treg production and immunosuppressive function by GMSCs[57].

Recent studies have confirmed that GMSCs can also partially inhibit B cell proliferation and the secretion of IgG and IgM in a mouse model of lupus nephritis through the CD39/CD73/adenosine signaling pathway[58]. Moreover, in the process of interfering with the progression of chronic graft-*versus*-host disease (cGVHD) in mice, GMSCs not only effectively inhibit the differentiation of B cells into plasma cells but also induce their differentiation into regulatory B (Breg) cells. Breg cells are a subset of B cells that regulate B cell effects and inhibit T cell activation through IL-10 and TGF-β[59]. Whether GMSCs can inhibit B cells and promote the production and function of Breg cells under different pathological conditions requires further research.

Existing studies have revealed part of the role of GMSCs in B-cell immunosuppression, but compared with T cells, reports on the regulation of B cells by GMSCs are still relatively scarce. Our laboratory recently found that GMSCs can also inhibit the formation of neutrophil extracellular traps (NETs) and inflammation[60], suggesting that GMSCs may have a broad range of immunoregulatory effects. Clarifying these regulatory mechanisms may provide ideas for designing application protocols to use GMSCs in intervening in various inflammatory diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Indirect Regulation of Adaptive Immune Responses

Mesenchymal stem cells (MSCs) interact with monocytes, macrophages, and dendritic cells (DCs) in various microenvironments, indirectly modulating T cell activation and proliferation. Among these, DCs serve as the most effective antigen-presenting cells (APCs), capable not only of antigen uptake, processing, and presentation but also of expressing costimulatory molecules. These highly specialized cells are indispensable for initiating robust adaptive immune responses[61]. By downregulating antigen-presentation-related genes (e.g., *Irf8*) or suppressing DC maturation and activation, GMSCs inhibit excessive T cell responses while increasing Treg cell populations[26,62]. Notably, GMSC-mediated immunosuppres- sion of DCs is primarily driven by prostaglandin E2 (PGE2), distinct from IL-10, TGF- β 1, or IDO[63]. This contrasts with the mechanism where regulatory T cells modulate DCs[64,65]. Indomethacin, a cyclooxygenase inhibitor, significantly reversed GMSC-induced DC functional impairment in both *ivo* and *in vitro* settings, whereas IL-10/TGF- β 1 neutralizing antibodies and IDO inhibitors did not alter this effect—aligning with prior evidence that BMSC-derived IDO is critical for DC immuno- regulation[66]. Plasmacytoid DCs (pDCs), a specialized innate immune subset, secrete IFN-I and IL-12 to support T cell function and induce Treg cells via IDO[67,68]. In experimental autoimmune uveitis (EAU), GMSCs restored aberrant pDC proportions[62]. Additionally, GMSCs upregulated CD73 in

pDCs — a key immunosuppressive enzyme generating adenosine[69]. These findings underscore the multifaceted pathways through which GMSCs regulate adaptive immunity, elucidating their mechanisms to advance clinical applications in inflammatory diseases.

The Function of Exosomes or Extracellular Vesicles

However, a critical challenge in mesenchymal stem cell (MSC) therapy is their limited survival within the recipient's body, with typically less than 1% of administered MSCs successfully reaching and engrafting at the target disease site[70,71]. Despite this, therapeutic effects are still evident, which is primarily attributed to their paracrine activity and the subsequent apoptosis of the MSCs. This paracrine signaling is partially mediated through extracellular vesicles or exosomes[27,72,73]. These nano-sized vesicles encapsulate a molecular cargo from their parent cells — including miRNA, mRNA, and proteins — and thus inherit a subset of their functional capabilities[74-76]. Extracellular vesicles (GMSC-EVs) or exosomes (GMSC-Exo) derived from gingiva-derived MSCs (GMSCs) that have been pre-conditioned with inflammatory factors have demonstrated efficacy in promoting anti-inflammation[77,78], bone regeneration[79], neuroprotection[22], angiogenesis[80], tissue regeneration, and wound healing[81-83], underscoring their broad biological activity and therapeutic potential. They exert regulatory control over multiple immune cell populations. For instance, upon uptake by macrophages, GMSC-Exo can drive their polarization toward an M2 phenotype by either activating the CD73/adenosine pathway or inhibiting the HIF-1α signaling cascade [79,84]. In a manner analogous to macrophages, GMSC-Exo can also prevent excessive activation of microglia and reduce apoptosis in retinal ganglion cells (RGCs) by delivering miR-21a-5p to inhibit the downstream target gene PDCD4 in a mouse model of retinal ischemia-reperfusion injury (IRI)[22]. Regarding T cell modulation, GMSC-EVs can restore the Treg/Th17 immune balance by delivering miRNA-148a to regulate the IKKB/NF-κB signaling pathway[27]. Furthermore, in mouse models of rheumatoid arthritis (RA), GMSC-Exo have shown an even greater capacity to rebalance T cell subsets than their parent GMSCs[77]. Thus, the combined therapeutic and regulatory efficacy of GMSC-derived exosomes and extracellular vesicles, coupled with their advantageous properties such as a long circulation half-life, low immunogenicity, high tissue penetration, and excellent biocompatibility, positions them as a highly promising cell-free therapeutic strategy.

The Plasticity of GMSCs in the Inflammatory Microenvironment

A bidirectional regulatory relationship exists between gingival mesenchymal stem cells (GMSCs) and the inflammatory microenvironment. Under pathological conditions, the dynamic changes within this microenvironment can influence the immunomodulatory function of GMSCs, causing them to exhibit dual effects, such as either immunosuppression or immunopromotion[85,86]. The stimulatory role of inflammatory molecules was first observed in experiments where IFN-γ activated the immunosuppressive capabilities of GMSCs. Only after being treated with IFN-γ do GMSCs significantly suppress the proliferation of peripheral blood mononuclear cells (PBMCs) and reduce IFN-γ secretion levels. The dose- dependent upregulation of IL-10 and IDO, rather than iNOS or COX2, is critical to the immunomodulatory characteristics of GMSCs. Likewise, IFN-γ, which is produced by immune cells like activated T cells, serves a regulatory function in the feedback loop between T cells and GMSCs[4]. Moreover, IFN-γ can enhance the ability of GMSCs to suppress the aberrant activation and cytokine secretion of plasmacytoid dendritic cells (pDCs) by promoting the co-expression of CD39/CD73 and subsequent adenosine generation[69]. Beyond IFN-γ, several other cytokines in the inflammatory microenvironment can also modulate GMSC-mediated immunoregulation[86]. For instance, *in vitro* experiments have demonstrated that under inflammatory conditions, the expression of IL-1α, IL-6, Collagen type I (Col-1), and TNF-α in GMSCs increases in a time-dependent manner, and these cytokines can promote systemic inflammation[39]. Following pre-stimulation with IL-1β, GMSCs also exhibit elevated secretion of the immunosuppressive factor TGF-β, which in turn promotes wound healing[21]. IL-1β treatment has also been shown to significantly enhance the capacity of GMSCs to inhibit neutrophil apoptosis[87]. Low concentrations of TNF-α induce the production of COX-2 and PGE_2 in GMSCs in a dose-dependent manner, thereby inhibiting mast cell (MC) activation[63]. Another study demonstrated that low concentrations of TNF-α significantly increase the release of the immunosuppressive factor TGF-β; conversely, excessively high concentrations of inflammatory cytokines can impair GMSC health and their immunosuppressive function by promoting GMSC apoptosis, increasing levels of pro-inflammatory factors IL-6 and COX-2, and reducing TGF-β release. Notably, the presence of blackcurrant bud extract (RBE) alongside high concentrations of TNF-α can partially restore suppressed TGF-β secretion, helping to mitigate the detrimental effects of inflammatory cytokines on MSCs and their immunosuppressive function[88]. Most recently, a study on salicylic acid (ASA) rescuing the impaired immunomodulatory function of inflammatory gingiva-derived mesenchymal stem cells (iGMSCs) has further underscored the potential of pharmaceuticals in optimizing GMSC-based therapies[41]. ASA salvaged the T cell apoptosis mediated by iGMSCs and the therapeutic efficacy against murine colitis by upregulating FasL[41].

The plasticity of the immunomodulatory function of GMSCs is also affected by Toll-like receptors (TLRs). A prior study revealed that under inflammatory conditions, GMSCs upregulate the expression of TLRs 1, 2, 4, 5, 7, and 10 while downregulating TLR6 expression. Significantly, after 24 hours of stimulation with Poly (I: C), GMSCs demonstrated bidirectional inflammatory regulation: they increased anti-inflammatory cytokine IDO and downregulated IL-12 expression, while simultaneously elevating TNF-α levels. In contrast, other TLR agonists conferred pro-inflammatory properties upon GMSCs[89]. Another study indicated that the pro-inflammatory transition induced by Pg-LPS stimulation is mediated by the NF-κB pathway, not the Wnt/β-catenin pathway[90].

Extracellular vehicles (EVs) or exosomes derived from gingival mesenchymal stem cells (GMSCs) are also affected by inflammatory cytokines. For instance, TNF-α and IFN-α can stimulate GMSCs to release EVs that modulate macrophage differentiation[91], while TNF-α has been shown to enhance the neuroprotective and anti-inflammatory properties of GMSC-derived exosomes in the context of retinal ischemia-reperfusion injury[22]. However, while *in vitro* experiments control single variables to provide simplified models for mechanistic analysis, the inflammatory microenvironment in physiological or

pathological states is far from being influenced by a single factor. Instead, it constitutes a dynamic and interconnected web composed of various cytokines, chemokines, and stromal components. Thus, understanding the inflammatory microenvironmental context under various conditions is essential for optimizing the immunomodulatory potential of GMSCs and for advancing their clinical applications.

Regulation of Macrophages and Neutrophils to Restore Immune Homeostasis

Macrophages are generally divided into pro-inflammatory M1 and anti-inflammatory M2 phenotypes[92]. In tissue injury and pathological conditions, local infiltration by neutrophils and macrophages is a common phenomenon. After an injury, monocytes from the circulatory system migrate specifically to the affected area, where they differentiate into macrophages under the influence of the local microenvironment[93]. In response to inflammatory cytokines, macrophages can polarize towards a pro-inflammatory state, a process that may contribute to the development of autoimmune diseases, metabolic syndrome, atherosclerosis, fibrosis, impaired tissue repair, and organ failure[92,93]. To counteract excessive inflammation and restore tissue homeostasis, macrophages can adopt an anti-inflammatory phenotype that promotes tissue repair[94,95]. Consequently, understanding the mechanisms for regulating macrophages to re-establish immune homeostasis is crucial. Research has demonstrated that in animal models of atherosclerosis, full-thickness skin excision, hyperlipidemia-related periodontitis, and sciatic nerve injury in rats, the administration of GMSCs results in significant macrophage modulation and the restoration of immune homeostasis within the microenvironment[23,96-98]. GMSCs achieved this by reducing the recruitment of inflammatory monocytes, inhibiting the formation of pro-inflammatory macrophages, facilitating the transition of pro-inflammatory cells to anti-inflammatory cells, and reprogramming cells to possess anti-inflammatory characteristics. Investigations revealed that the regulation of macrophages involves in mechanisms operating on multiple levels. For example, GMSCs secrete IDO, which suppresses pro-inflammatory macrophage activation, and produce CD73, which promotes anti-inflammatory macrophage activation. This multifaceted regulation of macrophage phenotypic shifts ultimately restores immune homeostasis and ameliorates chronic inflammatory conditions like atherosclerosis[23]. Moreover, GMSCs can polarize macrophages to the M2 phenotype by enhancing the secretion of IL-6 and GM-CSF[100].

Neutrophils usually accumulate at sites of injury or infection. Activated by inflammatory cytokines, they persistently infiltrate these sites and release reactive oxygen species (ROS), proteases (such as elastase), and neutrophil extracellular traps (NETs). These molecules directly damage cells and act as autoantigens, thereby intensifying the inflammatory response[99,100]. For instance, in Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA), preventing neutrophils from entering tissues can inhibit NETs production, slow bone erosion, and reduce joint swelling, highlighting the pathological role of neutrophil recruitment in inflammatory arthritis[101-103]. Therefore, neutrophils are pivotal for sustaining and amplifying inflammation and for initiating autoimmune responses, positioning them as a potential therapeutic target for immune-mediated diseases. GMSCs reduce neutrophil infiltration and the release of pro-inflammatory factors and NETs via the PGE2-PKA-ERK signaling pathway. This intervention disrupts the "neutrophil-inflammation" vicious cycle, alleviates arthritis symptoms, and suppresses immune dysregulation and tissue damage[60]. In a mouse model of pulmonary fibrosis, GMSC treatment diminished neutrophil infiltration in the lung, liver, and kidney and reduced apoptosis of healthy cells in the lung tissue[106]. However, it must be noted that neutrophils constitute the body's primary defense against infection, and their complete inhibition could elevate infection risk. Recent studies have confirmed that GMSCs can inhibit neutrophil apoptosis, an effect that is more significant when the GMSCs are pre-treated with IL-1 β [87]. Compared to chemical agents or drugs, such as DNase-1 (a NETs-degrading enzyme), which may also increase infection risk, the systemic regulatory capabilities and established clinical safety profile of GMSCs in preclinical models present a more advantageous therapeutic approach[105,106].

Applications of the Immunomodulatory Functions of Gingival Mesenchymal Stromal Cells

Successful cases of treatment using gingival mesenchymal stromal cells (GMSCs) have already been documented. For instance, in the treatment of plaque psoriasis, a 19-year-old male patient who was unresponsive to multiple local and systemic therapies achieved complete remission following five infusions of allogeneic human GMSCs. This remission was sustained without recurrence or adverse effects over a three-year follow-up period[109]. Numerous preclinical studies have demonstrated that systemic infusion of GMSCs ameliorates several inflammatory conditions in animal models, including colitis[4], collagen-induced arthritis (CIA)[13], graft-versus-host disease (GvHD)[57], and type 1 diabetes (T1DM)[28]. This substantiates the broad-spectrum immunomodulatory and tissue repair potential of GMSCs in autoimmune and inflammation-related diseases, where they exert therapeutic effects by modulating aberrant immune responses and mitigating inflammatory injury.

Crucially, despite their high proliferative capacity, GMSCs do not undergo malignant transformation into tumor cells. For example, three weeks post-infusion, no tumors were detected in the skin of mice receiving GMSCs, whereas control groups with HeLa cells exhibited clear tumor formation[12]. Although the long-term outcomes of these cell transplantations are still under investigation, this data suggests that GMSCs may be a safer therapeutic option compared to other mesenchymal stem cells. Moreover, research indicates that GMSCs maintain satisfactory stem-like characteristics and differentiation potential in both hyperplastic and inflammatory gingival tissues[3], implying that they can be sourced extensively as seed cells for therapy. Additionally, GMSCs derived from patients with rheumatoid arthritis show no functional disparity with GMSCs from healthy individuals after certain patient-derived MSCs have lost efficacy[110]. This finding suggests the potential utility of autologous GMSCs for treating diseases.

Conclusion

Validation of gingival mesenchymal stem cells (GMSCs) and

subsequent research have established them as a promising and ideal source for mesenchymal stem cells (MSCs), owing to distinct advantages including ease of acquisition, rapid proliferation, and cellular stability. Current studies indicate a reciprocal regulatory relationship between gingival stem cells and the inflammatory microenvironment. This bidirectional interaction not only profoundly influences the cells' proliferation, migration, and homing capacities, multi-lineage differentiation potential, and inflammatory responses but also modulates the severity of the local inflammatory milieu. However, the precise molecular mechanisms governing this interaction remain to be fully elucidated. The existing theoretical frameworks are incomplete and lack substantiation from clinical trials. Consequently, further investigation into the mutual regulatory mechanisms of GMSCs and the inflammatory microenvironment is essential to establish a robust theoretical basis for their future application in clinical treatments.

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