CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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Interplay between Mesenchymal Stem Cells and Lymphocytes: Implications for Immunotherapy and Tissue Regeneration

ABSTRACT

In addition to their potential for replacing damaged and diseased tissues by differentiating into tissue-specific cells, mesenchymal stem cells (MSCs) have been found to interact closely with immune cells, such as lymphocytes. In this review, we will discuss current research regarding the immunomodulatory properties of MSCs and the effects of lymphocytes on MSCs. We will suggest how these findings could be translated to potential clinical treatment. MSCs can regulate immune response by inducing activated T-cell apoptosis through the FAS ligand (FASL)/FAS-mediated death pathway *via* cell-cell contact, leading to up-regulation of regulatory T-cells (Tregs), which ultimately results in immune tolerance. Conversely, lymphocytes can impair survival and osteogenic differentiation of implanted MSCs by secreting the pro-inflammatory cytokines IFN-γ and TNF-α and/or through the FASL/FAS-mediated death pathway, thereby negatively affecting MSC-mediated tissue regeneration. One novel strategy to improve MSC-based tissue engineering involves the reduction of IFN-γ and TNF-α concentration by systemic infusion of Tregs or local application of aspirin. Further understanding of the mechanisms underlying the interplay between lymphocytes and MSCs may be helpful in the development of promising approaches to improve cell-based regenerative medicine and immune therapies.

KEY WORDS: regulatory T-Lymphocytes, immunomodulation, cell therapy, regenerative medicine, interferon-gamma, tumor necrosis factor-alpha.

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INTRODUCTION

Mesenchymal stem cells (MSCs) are a population of plastic-adherent stromal cells with self-renewal and multipotent differentiation capabilities (Friedenstein *et al*., 1970; Caplan, 1991; Shi and Gronthos, 2003). MSCs reside in a wide spectrum of post-natal tissue types (da Silva Meirelles *et al*., 2006; Bi *et al*., 2007), and they have been successfully isolated from several orofacial tissues (Gronthos *et al*., 2000; Miura *et al*., 2003; Seo *et al*., 2004; Morsczeck *et al*., 2005; Sonoyama *et al*., 2006; Zhang *et al*., 2009; Yamaza *et al*., 2011). In addition to their potential for replacing damaged and diseased tissue by differentiating into tissue-specific cells, MSCs have been shown to interact with hematopoietic stem cells (HSCs) by controlling or directly providing a stem cell niche for HSCs (Sacchetti *et al*., 2007; Mendez-Ferrer *et al*., 2010). MSC ablation has been proven to disrupt hematopoiesis (Raaijmakers *et al*., 2010). Lymphocytes, originating from HSCs, are a type of white blood cell in the vertebrate immune system. It has recently been shown that MSCs are capable of interacting with lymphocytes. In this review, we discuss current studies on the immunomodulatory properties of MSCs and the effects of lymphocytes on MSCs.

MSCs TARGET LYMPHOCYTES

Lymphocytes constitute a vital part of the immune system and can be divided into large and small lymphocytes. Large lymphocytes are mainly natural killer cells (NK cells), which are important innate immune cells in the defense against viruses and tumors by cytolysis and secretion of cytokines. Small lymphocytes consist of T-cells and B-cells, which are capable of generating specific immune responses to pathogens, constituting major components of the adaptive immune system. T-cells include $CD8^+$ cytotoxic T-lymphocytes (CTLs) that induce death of target cells or $CD4^+$ helper T-cells (Ths) that regulate other immune cells (Uccelli *et al*., 2008). Both autologous and allogenic bone marrow MSCs have been found to suppress T-cell proliferation by secreting mediators, including transforming growth factor β1 (TGFβ1) and hepatocyte growth factor (HGF) (Di Nicola *et al*., 2002). Since then, the immunomodulatory properties of MSCs have attracted extensive attention. It

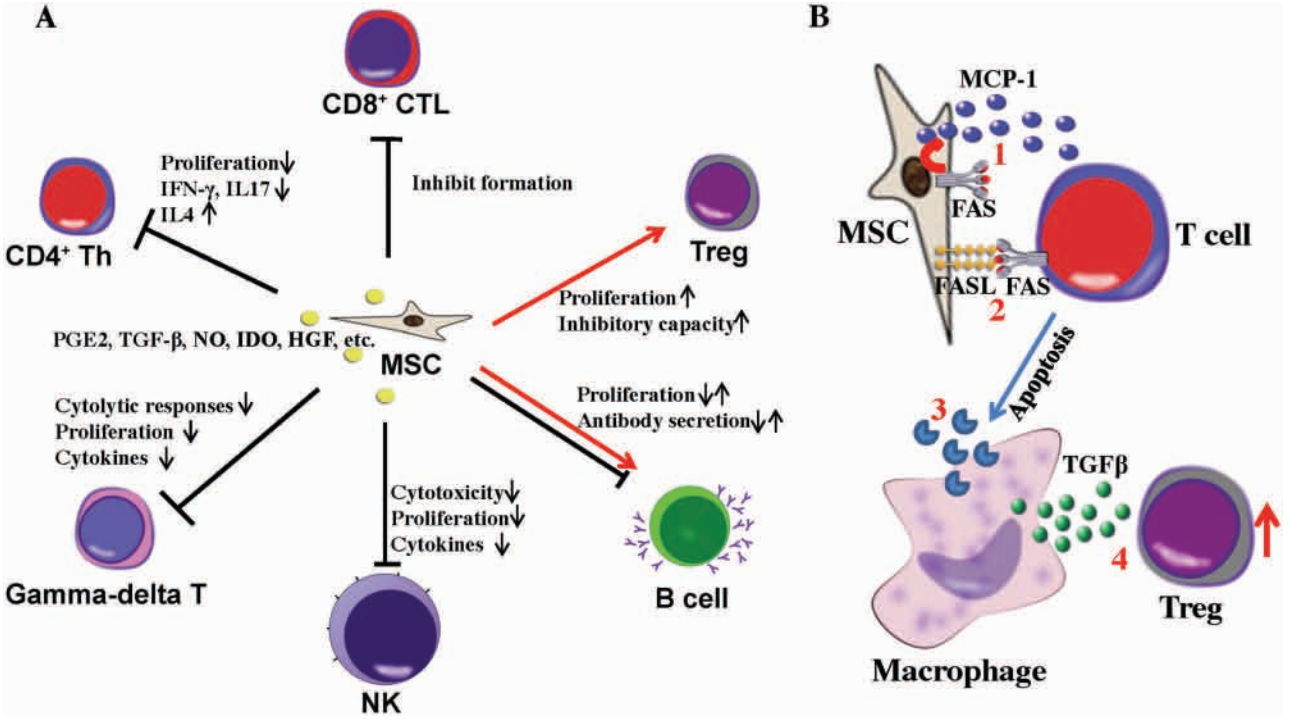

Figure 1. Immunomodulatory properties of mesenchymal stem cells (MSCs). **(A)** MSCs can target several subsets of lymphocytes, including $CD4^+$ helper T-lymphocytes (Ths), $CD8^+$ cytotoxic T-lymphocytes (CTLs), gammadelta T-cells, natural killer (NK) cells, B-lymphocytes, and regulatory T-lymphocytes (Tregs). These effects may be mediated by several soluble factors secreted by MSCs, including, for example, prostaglandin E_2 (PGE_2), transforming growth factor-β1 (TGF β1), nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), or hepatocyte growth factor (HGF). **(B)** Infused MSCs can induce T-cell apoptosis through FAS/FASL-mediated multiple paracrine interactions and cell-cell contacts, as well as promoting the generation of Tregs, which ultimately leads to immune tolerance. This process consists of the following stages: (1) MSCs use FAS to control monocyte chemotactic protein 1 (MCP-1) secretion, and MCP-1 recruits activated T-cells; (2) MSCs use FASL to induce activated T-cell apoptosis; (3) apoptotic T-cells subsequently trigger macrophages to produce high levels of TGFβ; and (4) the high level of TGFβ up-regulates Tregs to induce immune tolerance.

appears that MSCs derived from bone marrow, the orofacial region, and other areas of the body are able to target all subsets of lymphocytes (Fig. 1**)** (Ren *et al*., 2008; Zhao *et al*., 2010).

$CD4^+$ T-helper cells (Ths) play an important role in the adaptive immune system by activating and directing other immune cells through cytokines or a combination of cell/cell interactions (*e.g.*, CD40 and CD40L). It has been shown that MSCs efficiently suppress proliferation of $CD4^+$ Ths by arresting T-cells in the G0/G1 phase (Di Nicola *et al*., 2002; Glennie *et al*., 2005; Krampera *et al*., 2006). Moreover, MSCs are able to reduce Th1-cell-produced interferon γ (IFN-γ) and Th17-cell-produced interleukin-17 (IL17), whereas they enhance Th2 cells to secrete IL-4 (Aggarwal and Pittenger, 2005; Sun *et al*., 2009). $CD8^+$ CTLs mediate major histocompatibility complex (MHC)-restricted killing of allogenic or virus-infected cells, and they are vital for the graft-*vs*.-leukemia effect. MSCs have been demonstrated to inhibit CTL formation, thereby down-regulating CTL-mediated cytotoxicity (Rasmusson *et al*., 2003).

Regulatory T-cells (Tregs) are a functionally distinct $CD4^+$ T-cell population in the peripheral blood. They express the transcription factor forkhead box P3 (FOXP3) to regulate their own development and function to actively suppress autoimmune response (Fontenot *et al*., 2003). MSCs have been reported to directly or indirectly promote the proliferation of Tregs and enhance their regulatory capacity (Aggarwal and Pittenger, 2005; Maccario *et al*., 2005; Di Ianni *et al*., 2008; Selmani *et al*., 2008). Gammadelta T-cells play an important role in the immunosurveillance of cancer and have been shown to be implicated in acute graft-*vs*.-host disease (GVHD). MSCs effectively suppress *in vitro* expansion of gammadelta T-cells without affecting their cytotoxicity (Petrini *et al*., 2009). MSCs are also potent suppressors of TCRVgamma9Vdelta2(+) gammadelta lymphocyte proliferation, cytokine production, and cytolytic responses *in vitro*, as mediated by the cyclooxygenase-2 (COX-2)-dependent production of prostaglandin E_2 (PGE_2) (Martinet *et al*., 2009). Natural killer (NK) cells are important effector cells of innate immunity and play a key role in antitumor and antiviral effects by their cytotoxic potential and secretion of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and IFN-γ. However, they also contribute to several pathophysiological autoimmune conditions by their cytotoxic activity (Malhotra and Shanker, 2011). MSCs can inhibit the proliferation, cytokine production, and cytotoxic activity of both resting and pre-activated NK cells (Sotiropoulou *et al*., 2006; Spaggiari *et al*., 2006).

B-lymphocytes produce antibodies and closely interact with T-cells, thereby contributing to several autoimmune diseases, such as multiple sclerosis. The effects of MSCs on B-cells remain controversial. Most studies have demonstrated that MSCs inhibit B-cell proliferation, differentiation, and antibody

Table. Systemic Infusion of Mesenchymal stem cells (MSCs) for Clinical and Pre-clinical Therapies

Species	Disease	Major Organs Affected	Immunological Mechanisms	References
Human	Graft *vs.* host disease (GVHD)	Gut and liver	Inhibition of donor T-cell reactivity to the normal tissues of the recipient	Le Blanc *et al.*, 2004; Prasad *et al.*, 2011
Human and mouse	Systemic lupus erythematosus (SLE)	Bone and kidney	Osteoblastic niche reconstruction; inhibition of Th17 and promotion of Tregs	Sun *et al.*, 2009; Yamaza *et al.*, 2010
Human and mouse	Systemic sclerosis (SS)	Skin	Induction of T-cell apoptosis and up-regulation of Tregs through coupling of FAS/ FAS ligand (FASL)	Akiyama *et al.*, 2012
Human	Crohn's disease	Bowels and gastrointestinal tract	Mucosal T-cell apoptosis in the bowels and gastrointestinal tract	Ciccocioppo *et al.*, 2011; Mannon, 2011
Human and mouse	Chronic obstructive pulmonary disease (COPD), acute lung injury, lung fibrosis	Lung	Inhibition of pro-inflammatory cytokine production	Ortiz *et al.*, 2007; Matthay *et al.*, 2010; Pollack, 2012
Human, rat, and mouse	Diabetes	Pancreas and renal glomeruli	Alteration of T-cell cytokine pattern and preservation of Tregs; inhibition of macrophage infiltration	Lee *et al.*, 2006; Boumaza *et al.*, 2009; Mabed and Shahin, 2012
Human, swine, and mouse	Myocardial infarction	Heart	IL-10-mediated switch from infiltration of pro-inflammatory to anti-inflammatory macrophages; SDF-1/CXCR4-induced engraftment	Freyman *et al.*, 2006; Hare *et al.*, 2009; Dayan *et al.*, 2011; Dong *et al.*, 2012
Monkey	Graft rejection	Skin	Inhibition of T-cells	Bartholomew *et al.*, 2002
Rat	Acute renal failure	Kidney	Inhibition of pro-inflammatory cytokine production	Togel *et al.*, 2005
Mouse	Colitis	Colon and small intestine	Induction of T-cell apoptosis and up-regulation of Tregs through coupling of FAS/ FASL, or secretion of immunosuppressive factors	Zhang *et al.*, 2009; Akiyama *et al.*, 2012
Mouse	Encephalomyelitis (EAE) model of multiple sclerosis	Nerve system	Inhibition of myelin-specific T-cells	Zappia *et al.*, 2005
Mouse	Rheumatoid arthritis	Joint	Inhibition of pro-inflammatory cytokine-producing T-cells and induction of Tregs	Augello *et al.*, 2007
Mouse	Acute pancreatitis	Pancreas	Reducing infiltration of $CD3^+$ T-cells and up-regulation of Tregs	Jung *et al.*, 2011

secretion in *in vitro* co-culture assays and *in vivo* multiple sclerosis models (Augello *et al*., 2005; Corcione *et al*., 2006; Gerdoni *et al*., 2007; Asari *et al*., 2009). However, other *in vitro* studies showed that MSCs support B-cell proliferation and stimulate antibody secretion in B-cells (Rasmusson *et al*., 2007; Traggiai *et al*., 2008). It is possible that MSC-mediated regulation of B-cells may depend on the developmental stage of B-cells and the local microenvironment.

The immunoregulatory properties of MSCs provide a foundation for the clinical use of MSCs to treat a variety of immune diseases (Table). Since Bartholomew *et al*. first demonstrated that systemic infusion of allogenic MSCs can prolong skin-graft survival in monkeys by inhibiting T-cells *in vivo* (Bartholomew *et al*., 2002), MSC-based immunotherapy has shown successful outcomes in several pre-clinical disease models, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and systemic sclerosis (SS). In terms of using the systemic infusion of MSCs for patient treatment, Le Blanc *et al*. first reported that allogenic MSC infusion may provide appropriate therapy for a severe treatment-resistant acute GVHD patient (Le Blanc *et al*., 2004). Our group and collaborators demonstrated that allogenic MSCs can effectively ameliorate disease activity, improve serologic markers, and reverse renal dysfunction in patients with SLE, through up-regulating Tregs and down-regulating Th17 cells, leading to an immune tolerance (Sun *et al*., 2009). However, another group showed that autologous MSC infusion failed to ameliorate disease activity in SLE patients (Carrion *et al*.,

2010). These discrepant results may be attributed, at least in part, to the impairment of bone marrow MSCs as observed in SLE patients and SLE-like MRL/*lpr* mice (Sun *et al*., 2009). Therefore, it is critical to use healthy MSCs for cell-based immune therapies. MSCs have also shown efficacy and safety in several clinical trials for myocardial infarction, acute lung injury, chronic obstructive pulmonary disease (COPD), diabetes, and Crohn's disease, a painful inflammatory disease in the bowels and gastrointestinal tract (Boumaza *et al*., 2009; Hare *et al*., 2009; Ciccocioppo *et al*., 2011; Matthay *et al*., 2010; Mannon, 2011; Mabed and Shahin, 2012). Recently, Osiris Therapeutics, Inc. (Columbia, MD, USA) has received market authorization in Canada to market the first undifferentiated stem cell product, Prochymal®, an intravenously administered formulation of MSCs derived from human bone marrow of healthy adults, for the management of acute GVHD in children who are unresponsive to steroids (Prasad *et al*., 2011; Pollack, 2012). The emergence of such MSC products provides a promising opportunity for the management of autoimmune diseases by taking advantage of the immunomodulatory properties of MSCs.

The promising results of treating immune-related diseases by MSC infusion have led to exploration of the underlying mechanisms. It has been shown that MSCs target lymphocytes through several soluble factors, such as PGE_2, TGF-β, nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), HGF, and human leukocyte antigen G (HLA-G) (Meisel *et al*., 2004; Sotiropoulou *et al*., 2006; Sato *et al*., 2007; Ren *et al*., 2008, 2009; Selmani *et al*., 2008; English *et al*., 2009). Although these studies provided fundamental knowledge for MSC-based immunoregulation, the diverse and conflicting results indicate that the immunomodulatory effects of MSCs are, most likely, a dynamic process, which may be involved in multiple factors. Very recently, our group revealed a new signaling cascade that may contribute to understanding the interplay between infused MSCs and recipient immune cells in MSC-mediated immune therapies. We found that MSCs produce FAS ligand (FASL) to induce activated T-cell apoptosis *via* cell-cell contact. Additionally, MSCs use FAS, a death receptor known as tumor necrosis factor receptor superfamily member 6, to control secretion of monocyte chemotactic protein 1 (MCP-1), which attracts T-cell migration to ensure cell-cell contact between MSCs and activated T-cells (Akiyama *et al*., 2012). In a diseased mouse model, including systemic sclerosis (SS) and dextran-sulfate-sodium-induced experimental colitis, apoptotic T-cells, caused by systemic MSC infusion, triggered macrophages to produce high levels of TGFβ, leading to an up-regulation of $CD4^+CD25^+Foxp3^+$ Tregs. Eventually, up-regulation of Tregs results in an immune tolerance and ameliorates disease phenotype in the animal models (Akiyama *et al*., 2012). The systemically infused MSCs may also lead to their lodging in the ischemic brain or myocardium, and stromal-cell-derived factor-1 (SDF-1) may play an important role in guiding MSCs to the sites of injury (Li *et al*., 2005; Dong *et al*., 2012). Moreover, bone marrow MSCs express C-X-C chemokine receptor type 4 (CXCR-4), the specific receptor of SDF-1, suggesting that the interaction of SDF-1 with CXCR4 may mediate the trafficking of these stem cells to the impaired site (Kortesidis *et al*., 2005).

The large study-to-study variations in the effects and underlying mechanisms of MSC-lymphocyte interaction may be attributed to the following: (1) variations in MSC properties and status which are due to batch-to-batch variations in MSCs, culture conditions, and human MSC cell division number, etc. (Song *et al*., 2008; Lee *et al*., 2012); and (2) variations in *in vivo* environments derived from different individuals and immune-related diseases (Ren *et al*., 2008). Rather than only through a single molecule, it is most likely that MSCs exert immunoregulatory effects through a multi-staged biological process involving the use of receptor FAS to control MCP-1 secretion for recruiting activated T-cells and ligand FASL to induce T-cell apoptosis (Akiyama *et al*., 2012). A full understanding of the mechanisms is the key to solving this problem, and may allow for the use of non-cell-based therapies that replicate the key factors secreted by MSCs.

Importantly, orofacial tissue-derived MSCs have also been demonstrated to have immunoregulatory properties. MSCs from human exfoliated deciduous teeth (SHED) can inhibit secretion of IL-17 *in vitro*, and they are capable of effectively reversing SLE-associated disorders in MRL/*lpr* mice by elevating the ratio of Tregs to Th17 cells (Yamaza *et al*., 2010). Swine MSCs from apical papilla (SCAP) can suppress T-cell proliferation *in vitro* through an apoptosis-independent mechanism (Ding *et al*., 2010a). Human MSCs from periodontal ligament (PDLSCs) also possess immunosuppressive properties when co-cultured with activated peripheral blood mononuclear cells (PBMNCs) (Wada *et al*., 2009). Accumulated evidence shows that gingiva-derived MSCs are a unique and promising cell source for immune therapies (Zhang *et al*., 2009).

LYMPHOCYTES AFFECT MSC SURVIVAL AND DIFFERENTIATION

Apart from the promising applications in immune therapies, exogenously added MSCs have long been thought capable of generating new bone and associated tissues to replace damaged tissues. The use of culture-expanded MSCs in conjunction with scaffolds has been widely reported for tissue engineering in preclinical models and clinical trials. Seed cells, bio-scaffold, and growth factors have long been considered as key factors for tissue engineering, and the majority of studies in this field focus on the development of better bio-scaffolds, especially biocompatible nanomaterials, as well as improvement in the tissue-specific differentiation capabilities of seed cells by exogenous application of growth factors. Despite the marked progress in MSC-based tissue engineering, the main challenge remains the formation of large quantities of high-quality tissue or even complex organs that meet the functional requirements. Recently, it was reported that cells from the recipient microenvironment may participate in cell-based tissue regeneration. Although MSCs are generally considered to be less immunogenic because they constitutively express low levels of MHC class I and are negative for MHC class II (Le Blanc *et al*., 2003), the survival of implanted MSCs may be affected by the recipient immune system. It has been proved that cytokine-activated NK cells can efficiently lyse both autologous and allogenic MSCs *in vitro*

(Spaggiari *et al*., 2006; Sotiropoulou *et al*., 2006). Moreover, T-cells activated by CD3 and CD28 T-cells can induce bone marrow MSC apoptosis through the FAS/FASL pathway (Yamaza *et al*., 2008). Similarly, activated T-lymphocytes impair orofacial bone/bone-marrow-derived MSCs (OMSCs), suggesting that OMSCs are capable of interacting with systemic immunity (Yamaza *et al*., 2011). In addition, T-cells induce bone marrow MSC and osteoblast apoptosis through the CD40/CD40L pathway, as observed in some bone-disease-related animal models, such as osteoporosis (Li *et al*., 2011). Conversely, immune components have been proven to regulate the differentiation of MSCs. For example, it has been shown that pro-inflammatory cytokine TNF-α inhibits MSC adipogenesis and osteoblastogenesis (Suzawa *et al*., 2003; Lu *et al*., 2011). These studies suggested that the crosstalk between implanted MSCs and recipient immune cells may play a key role in determining the success of MSC-based tissue regeneration.

Most recently, our group found that host lymphocytes secrete IFN-γ and TNF-α to block MSC-based bone regeneration (Liu *et al*., 2011). When treating bone marrow MSCs with IFN-γ alone or a combination of IFN-γ and TNF-α *in vitro*, we found that IFN-γ alone blocks osteogenic differentiation by inducing up-regulation of SMAD family member 6 (SMAD6), thereby inhibiting Runt-related transcription factor 2 (RUNX2), a key transcription factor associated with osteoblast differentiation. In contrast, TNF-α induces MSC apoptosis in a dose-dependent manner. More interestingly, the combination of IFN-γ and TNF-α can accelerate MSC apoptosis through internalization of FAS, with reduction of the anti-apoptotic factors nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), X-linked inhibitor of apoptosis protein (XIAP), and FLICE-like inhibitory protein (FLIP). By grafting bone marrow MSCs subcutaneously in a mouse model, using hydroxyapatite tricalcium phosphate (HA-TCP) particles as a carrier, we confirmed that recipient T-cells inhibit MSC-based bone regeneration using the same mechanism observed *in vitro*. Based on this finding, we further applied systemic infusion of Tregs, or local administration of aspirin, to reduce IFN-γ and TNF-α concentration, and found that both methods can markedly alleviate IFN-γ/TNF-α-induced MSC apoptosis, thereby improving MSC-mediated subcutaneous bone formation (Liu *et al*., 2011). Furthermore, we showed that local aspirin treatment and systemic Treg infusion are able to significantly improve MSC-mediated calvarial bone repair *via* inhibition of IFN-γ and TNF-α levels (Liu *et al*., 2011). Therefore, treatment with aspirin or Tregs may provide promising approaches for improving MSC-based tissue engineering (Fig. 2).

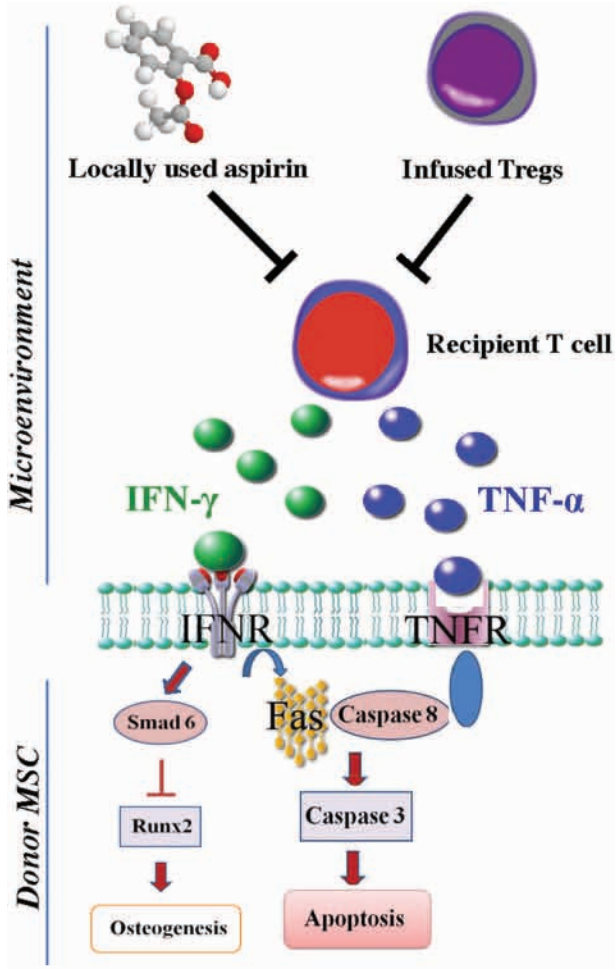

Figure 2. Recipient T-lymphocytes govern Mesenchymal stem cell (MSC)-based bone regeneration *via* IFN-γ and TNF-α. Recipient T-cells secrete IFN-γ to inhibit osteogenic differentiation of implanted MSCs by inducing Smad6/Runx2 signaling and TNF-α to trigger apoptotic pathway *via* activation of caspase 8 and caspase 3. However, a combination of IFN-γ and TNF-α treatment initiates FAS internalization and accelerates caspase 8/3 apoptotic process. As a novel strategy to improve MSC-mediated bone regeneration, local administration of aspirin or systemic infusion of Tregs can reduce the levels of IFN-γ and TNF-α, thereby protecting implanted MSCs from recipient T-cell attack.

MSC IMMUNOMODULATORY PROPERTIES CONTRIBUTE TO ORAL DISEASE THERAPY AND REGENERATIVE DENTISTRY

Immunomodulatory properties of MSCs may play an important role in treating immune-related oral diseases. Among the many immune-related diseases in the orofacial region, bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a critical side-effect of bisphosphonate therapy for metastatic cancer or osteoporosis patients, especially in those who undergo high-dose bisphosphonate and immunosuppressant drug administration. To date, appropriate therapy has not yet been established for the treatment of BRONJ, largely due to a lack of understanding of its patho-physiological mechanisms. We have developed a mouse model of BRONJ-like disease by the administration of zoledronate and dexamethasone, an immunosuppressant drug, and found that such BRONJ-like disease in mice is caused by suppression of Tregs and activation of Th17 cells (Kikuiri *et al*., 2010). Interestingly, systemic infusion of MSCs is able to prevent and cure BRONJ-like disease, possibly *via* induction of peripheral tolerance, shown as an inhibition of Th17 cells and elevation of Tregs, thereby supporting the rationale for the use of MSCs as an immunomodulatory approach for BRONJ treatment (Kikuiri *et al*., 2010). Additionally, local transplantation of

bone marrow MSCs with platelet-rich plasma was reported to alleviate BRONJ lesion of a patient undergoing alendronate and pamidronate treatment for osteoporosis, with a complete healing observed in a 30-month follow-up (Cella *et al*., 2011).

The crosstalk between the locally implanted MSCs and recipient cells also presents implications for cell-based regenerative dentistry, which has attracted extensive attention in the past decade. In a swine model of periodontal defects, autologous and allogenic PDLSC-mediated treatment has been demonstrated to result in a regeneration of PDL and recovery of alveolar bone height (Liu *et al*., 2008; Ding *et al*., 2010b). Furthermore, SHED have been proved to engraft and regenerate bone to repair critical-size craniofacial bone defects generated in mouse and swine models (Seo *et al*., 2008; Zheng *et al*., 2009). In terms of tooth regeneration, it has been demonstrated that a combination of SCAP and PDLSCs is able to generate a bio-root with periodontal ligament tissues in a swine model (Sonoyama *et al*., 2006). Because of their capability of forming dentin-pulp-like complexes, DPSCs, SHED, and SCAP have also been demonstrated to lead to dentin/pulp tissue regeneration (Gronthos *et al*., 2000; Huang *et al*., 2008). However, the oral cavity is a challenging environment with active immune responses, which potentially affects periodontal, jaw bone, and tooth regeneration. For example, a wide spectrum of micro-organisms is colonized in periodontal regions, and produces a variety of factors that elicit a host response of inflammatory cell recruitment with secretion of pro-inflammatory mediators (Thomas and Puleo, 2011). Such active immune responses may, in turn, hamper the performance of MSC-based tissue engineering in repairing periodontitis-induced alveolar bone defects. Therefore, it is critical to seek anti-inflammatory treatments, for example, by using aspirin or Tregs, to provide promising approaches for improving MSC-based regeneration in orofacial regions.

Emerging evidence shows that dental MSCs are preferable for regenerative dentistry and treating immune-related oral diseases because of the following: (1) Compared with MSCs derived from bone marrow or other sources, dental MSCs present easier accessibility with minimal trauma. Notably, SHED are the first MSCs derived from human exfoliated tissue, a very accessible tissue resource (Miura *et al*., 2003). (2) Dental MSCs, including SHED, SCAP, PDLSCs and jaw bone MSCs, show a strong immunomodulatory capacity, possibly because of the high frequency of exposure to the inflammatory environment in the oral cavity (Wada *et al*., 2009; Ding *et al*., 2010a; Yamaza *et al*., 2010, 2011). (3) Because of their neural crest origins, dental MSCs show robust multi-potential differentiation capabilities, benefiting the regeneration of orofacial tissues in orofacial context (Chung *et al*., 2009; Yamaza *et al*., 2011). (4) Dental MSCs usually present high proliferation rates to provide sufficient numbers of cells for therapy (Gronthos *et al*., 2000; Miura *et al*., 2003).

CONCLUSIONS AND OUTLOOK

Understanding the role of MSCs and their therapeutic potential has led to great strides over the past decade. MSCs were initially considered as having the potential to differentiate into only tissue-specific cells for regenerative medicine; however, they are now appreciated as an essential cell type that possesses important immunomodulatory properties capable of treating a variety of immune-related diseases. MSCs can regulate the intensity of immune response by inducing T-cell apoptosis through the FAS/FASL-pathway, along with multiple paracrine interactions and cell-cell contacts, as well as promote the generation of Tregs, resulting in immune tolerance. Conversely, lymphocytes can inhibit MSC survival and differentiation by secreting the pro-inflammatory cytokines IFN-γ and TNF-α and/or through cell-cell-contact-induced MSC apoptosis, thereby negatively affecting MSC-based tissue regeneration. In light of such an in-depth understanding of the interplay between lymphocytes and MSCs, novel strategies to improve MSC-based tissue engineering have been proposed to reduce IFN-γ and TNF-α levels by local aspirin treatment or the systemic infusion of Tregs.

Given the complexity of immune profiles in different individuals and various immune-related diseases, the final outcome of the interplay between lymphocytes and MSCs is very likely to be significantly influenced by the *in vivo* microenvironments. Therefore, it is important to further characterize differences in the immunomodulatory performances of infused MSCs in individuals with different diseases. Conversely, it will be necessary to further understand how the host lymphocytes affect MSCs in various scenarios, such as during tissue injury and immune diseases. Moreover, it will be interesting to clarify whether the locally implanted MSCs can contribute to both tissue repair and immunomodulatory response, thereby preventing potential autoimmune reactions by the host immune system at the site of injury. Through better understanding of the mechanisms underlying the interplay between lymphocytes and MSCs under different physiological and pathological conditions, we will be able to develop promising strategies to improve regenerative medicine and the treatment of immune-mediated diseases.

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