

Mesenchymal stem cells: Emerging mechanisms of immunomodulation and therapy

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Abstract

Mesenchymal stem cells (MSCs) are a pleiotropic population of cells that are self-renewing and capable of differentiating into canonical cells of the mesenchyme, including adipocytes, chondrocytes, and osteocytes. They employ multi-faceted approaches to maintain bone marrow niche homeostasis and promote wound healing during injury. Biomedical research has long sought to exploit their pleiotropic properties as a basis for cell therapy for a variety of diseases and to facilitate hematopoietic stem cell establishment and stromal reconstruction in bone marrow transplantation. Early results demonstrated their usage as safe, and there was little host response to these cells. The discovery of their immunosuppressive functions ushered in a new interest in MSCs as a promising therapeutic tool to suppress inflammation and down-regulate pathogenic immune responses in graft-versus-host and autoimmune diseases such as multiple sclerosis, autoimmune diabetes, and rheumatoid arthritis. MSCs produce a large number of soluble and membrane-bound factors, some of which inhibit immune responses. However, the full range of MSC-mediated immune-modulation remains incompletely understood, as emerging reports also reveal that MSCs can adopt an immunogenic phenotype, stimulate immune cells, and yield seemingly contradictory

results in experimental animal models of inflammatory disease. The present review describes the large body of literature that has been accumulated on the fascinating biology of MSCs and their complex effects on immune responses.

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Key words: Mesenchymal stem cell; Immunosuppression; Immunogenic; Autoimmunity; Cell-based therapy

Core tip: Mesenchymal stem cells (MSCs) comprise a mixture of different stromal cell types that display remarkable pleiotropic properties, including those of anti-apoptosis, angiogenesis, growth factor production, anti-fibrosis, and chemo-attraction. It is because of these diverse biological properties that these cells have been intensively studied in the hopes of their utilization as a platform of cellular therapy in disease settings. Early experimental and preclinical studies focused on their stem cell renewal, differentiation, and regenerative properties for potential use in degenerative diseases of mesenchymal origin. Afterwards, MSCs were found to increase the success of bone marrow transplantation, reduce rejection of engrafted tissues, and display remarkable anti-inflammatory properties. Currently, much work centers on the immune-modulatory facets of MSCs, especially in reducing inflammation and suppressing immune cell function in preclinical injury and autoimmune disease settings. However, emerging reports suggest a multifunctional quality to MSC immune-modulation. This review dissects MSC manipulation of immune responses, which result in either immunosuppression or immuno-stimulation.

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INTRODUCTION

MSCs were originally discovered in the 1950s as the longest surviving cells of human and mouse bone marrow monolayer cell cultures^[1,2]. Friedenstein *et al.*^[3] later noted that these fibroblastic cells were very rare in the bone marrow^[3]. Over time in culture, these sparse colony-forming units divided prolifically and gave rise to expanded populations of fibroblastic clones. These spindle-shaped, fibroblastic cells were plastic adherent and were named MSCs as they could be induced *in vitro* and *in vivo* to differentiate into adipocytes, chondrocytes, connective stromal cells, and osteocytes-cells which all comprise the mesenchyme (Figure 1). MSC differentiation into parenchymal cells of the mesenchyme has become one of the principal criteria of establishing their identity. Additional, though controversial, reports indicate that MSCs may also be induced to transdifferentiate into cells of the endoderm (lung cells, muscle cells, and gut epithelial cells) and the ectoderm (epithelia and neurons)^[4,5].

The pleiotropic nature of MSCs has presented a challenge in their identification. Their functional characteristics of self-renewal and ability to differentiate along with some widely accepted markers together form a profile to help identify them. There is consensus that MSCs, though heterogeneous, share some common features: they are uniformly negative for the expression of key hematopoietic cell markers, including CD34, CD45, CD11b, CD11c, CD14, CD19, CD79 α , CD86, and MHC class II molecules. They express CD90, CD105, CD44, CD73, CD9, and very low levels of CD80. The International Society for Cellular Therapy has designated this expression pattern as the minimal criteria for human MSC discretion, but marker expression panels for MSCs continue to be updated over time^[6,7].

Though MSCs were first isolated from the bone marrow, they have since been harvested from the stroma of multiple organs and tissues, including adipose, tonsils, umbilical cord, skin, and dental pulp^[8-13]. MSCs derived from the marrow continue to be the most frequently studied. The cellular and tissue origins of MSCs have been elusive, but in one landmark study, Crisan and colleagues suggested a pericytic origin for MSCs. Pericytes are perivascular cells that inhabit multiple organ systems^[14]. This group identified pericytes on the basis of CD146, NG2, and PDGF-R β expression from human skeletal muscle, pancreas, adipose tissue, and placenta. They found that these cells expressed markers typical of MSCs and could be differentiated in culture to become myocytes, osteocytes, chondrocytes, and adipocytes. Though the study did not directly track the possible *in vivo* transition of pericytes to MSCs, they identified pericytes as potential progenitor cells to non-bone marrow-derived MSCs.

THE PHYSIOLOGY OF MSCS

MSCs strategically form niches in perivascular spaces in

almost every region of the body. It is thought that such localization allows them to detect local and distant tissue damage, as in wound infliction, and respond by migration to these sites and promoting tissue repair and healing (Figure 2)^[15]. While myriad studies show that exogenously administered MSCs migrate to healthy organs or to injured sites for inflammation suppression and wound healing, there has been sparse data to actually demonstrate *in vivo* mobilization of endogenous MSCs to sites of injury or participation in the wound healing process^[15,16], due in part to lack of unique markers expressed by MSCs.

One of the most insightful reports to address this issue utilizes a natural transplantation model of fetomaternal microchimerism, in which chimeric MSCs take up residence in maternal bone marrow in every pregnancy^[17,18]. Importantly, this study reported that collagen-I-promoter-driven, GFP⁺ MSCs derived from transgenic fetuses homed to wounds inflicted on mothers in as early as 24 h post-infliction^[18]. These cells were still detected 7 d post-infliction, exhibited a fibroblastic appearance, and were marked by vimentin expression, which is indicative of extracellular matrix synthesis and tissue repair. These data implicate endogenous MSCs as capable of travel from the bone marrow to wound sites for healing purposes.

Beyond their role in tissue repair and wound healing, MSCs of the perivascular niche in the bone marrow construct and maintain the hematopoietic stem cell (HSC) microenvironment (Figure 2). MSCs have been demonstrated to migrate and situate in the bone marrow compartment in NOD-SCID mice and differentiate into pericytes, myofibroblasts, endothelia, stromal cells, osteocytes, and osteoblasts^[19]. In bone marrow sinusoids, CD146⁺ MSCs are thought to create the structural framework of the hematopoietic microenvironment, as they are capable of generating this environment at heterotopic sites, along with the establishment of subendothelial cells, upon transfer to miniature bone organs^[20]. These subendothelial cells are important producers of angiopoietin-1, which is known to contribute to HSC sustenance. MSCs in the vicinity that express Nestin are spatially associated with HSCs and may be the primary cells controlling their homeostasis^[21]. Nestin⁺ MSCs produce high levels of HSC-maintenance factors, including CXCL-12, c-kit ligand, angiopoietin-1, IL-7, vascular cell adhesion molecule-1 (VCAM-1), and osteopontin. When HSC mobilization out of marrow is required, these MSCs down-regulate HSC maintenance genes. In response to parathyroid hormone treatment, which promotes osteoblast differentiation and HSC expansion, Nestin⁺ MSCs proliferate and become primed towards osteoblastogenesis. When purified HSCs are transferred to lethally irradiated mice, they only efficiently home to bone marrow that is populated with Nestin⁺ MSCs. In addition, osteoblasts derived from Nestin⁺ MSCs form the endosteal niche that lines the surface of the trabecular bone^[20,22]. This niche, in concert with that formed by perivascular MSCs, regulates HSC survival, proliferation, and quiescent maintenance in

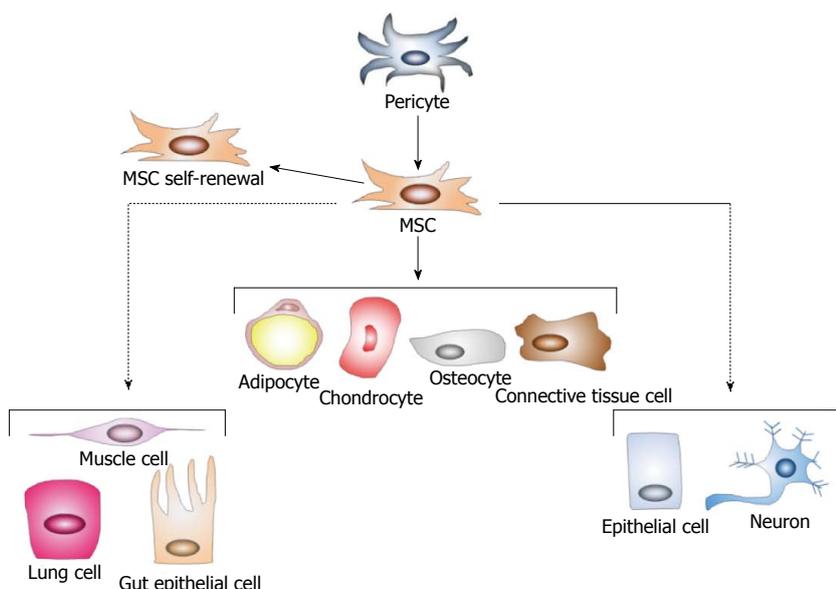


Figure 1 Basic properties of mesenchymal stem cells. Mesenchymal stem cells (MSCs) are a heterogeneous population of stromal cells thought to be derived from pericytes. These cells are defined by self-renewal and the ability to differentiate into the mesodermal cells (solid lines): adipocytes, chondrocytes, osteocytes, and connective tissue cells. Though controversial (dotted lines), they may also transdifferentiate into cells of the endoderm (lung, muscle, and gut epithelial cells) and of the ectoderm (neurons and epithelial cells). Adapted from ref [22].

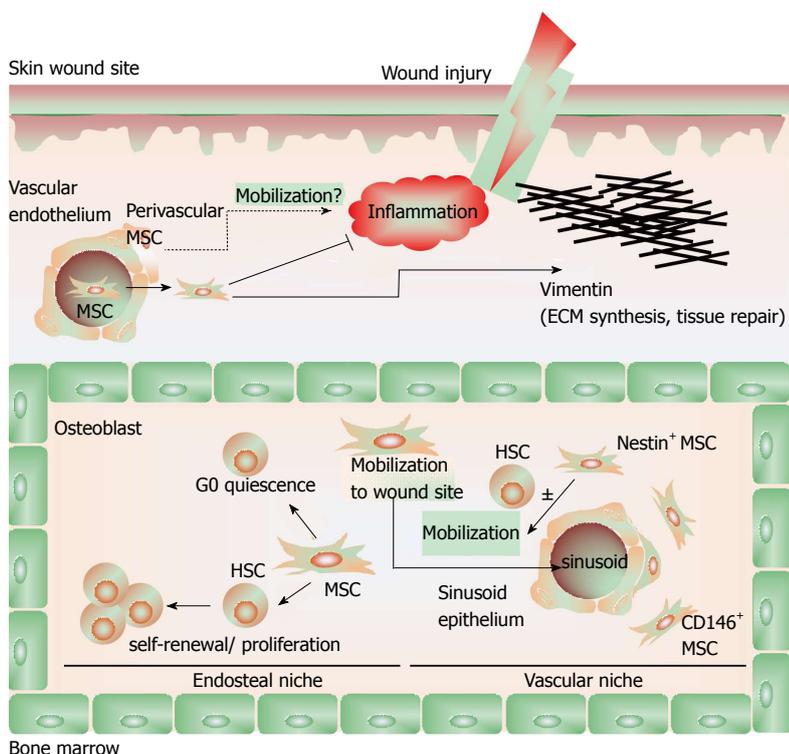


Figure 2 The biology of mesenchymal stem cells. In the bone marrow, mesenchymal stem cells (MSCs) aid in constructing the endosteal niche and regulate the homeostasis of HSCs. MSCs maintain HSCs in a state of quiescence defined by self-renewal and proliferation without differentiation. CD146⁺ MSCs in the vascular niche also maintain HSC homeostasis and, along with Nestin⁺ MSCs, regulate the mobilization of HSC into the vascular system. In response to inflammatory cues and chemokine gradients, MSCs mobilize out of the bone marrow and to peripheral sites of injury, where they suppress inflammation to facilitate wound healing. MSCs contribute to tissue reconstruction with the production and deposition of vimentin. It is incompletely understood whether perivascular MSCs may also migrate to sites of injury to contribute to wound healing. Adapted from ref [22].

the G₀ state^[22].

MSCS AND IMMUNOSUPPRESSION

Interest in Immuno-modulatory properties of MSCs

A key method by which MSCs and their stromal derivatives guard the HSC microenvironment is by protecting the niche from inflammatory insults, which could cause inadvertent HSC differentiation and reserve depletion. MSC-derived fibroblasts, which also populate the HSC niche, may exert an anti-inflammatory effect by eliminating survival factors for immune cells, such as T cells, and re-calibrating chemokine gradients, as has been studied

in the context of fibroblast dysfunction in the chronic autoimmune disease rheumatoid arthritis^[23]. This could promote T cell apoptosis and re-direction out of the initial site of inflammation to allow for tissue repair^[23,24]. In addition, MSCs and their derivatives from multiple normal sites within the body, including chondrocytes and fibroblasts from synovial joints, lungs, and skin, suppressed activated T cell proliferation and their cytokine production^[22,25]. MSCs may even influence T cell proliferation indirectly, as splenic stromal cells can induce nitric oxide (NO)-producing dendritic cell (DC) generation in a fibronectin-dependent fashion; these immune-regulatory DCs suppress T cell proliferation^[24,26]. Moreover, it is

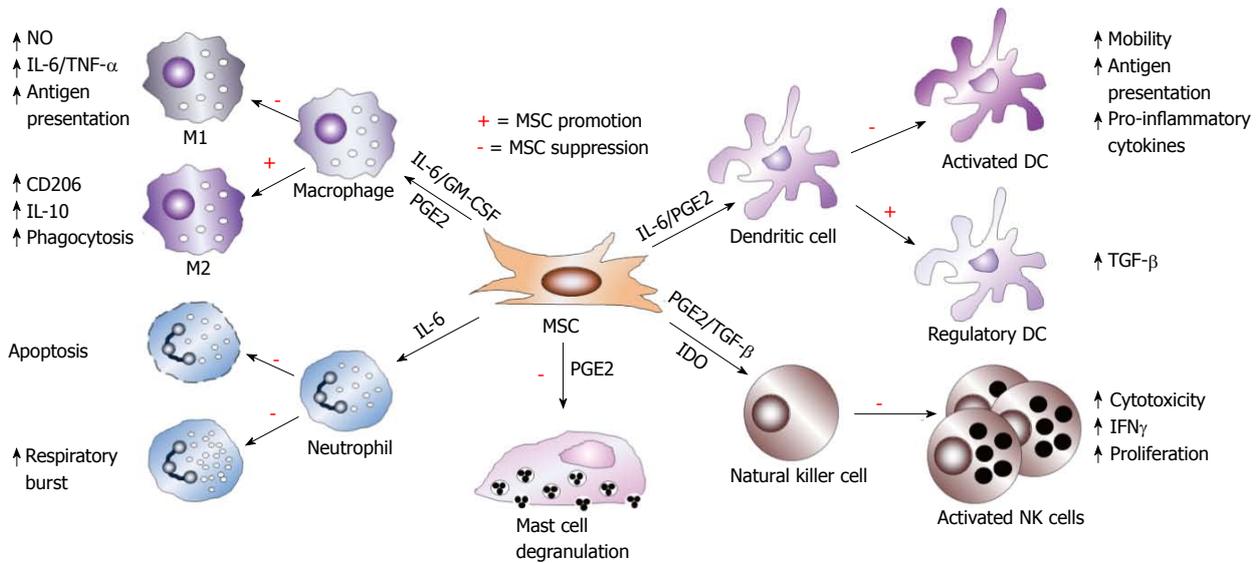


Figure 3 Mesenchymal stem cell immunosuppression of innate immune cells. Mesenchymal stem cells (MSCs) utilize diverse molecular mechanisms to suppress innate immune cells. MSCs suppress macrophage polarization to M1, though favors M2 polarization. MSCs inhibit mast cell degranulation of histamine-containing granules and inhibit NK cell and DC activation, differentiation, and effector functions. MSC-derived PGE2 contributes to all of these effects. MSC-produced IL-6 suppresses neutrophil apoptosis and respiratory burst and also contributes to inhibition of DC function. In the presence of IL-6 and GM-CSF, MSCs also affect macrophage function, while TGF- β and IDO suppress NK cell function. In addition, MSCs also favor the generation of regulatory DCs.

well-established that wound inflictions trigger MSC migration and suppression of inflammation to permit the proliferation of tissue-resident stromal cells, production of reconstructive molecules of the ECM, and wound healing^[15,16].

Mechanisms of MSC suppression of innate immune cells

The discovery of anti-inflammatory properties of MSCs led to investigation of their use as immunosuppressive agents. Innate immune cells have important roles in tissue homeostasis and are the first line of defense against invading pathogens such as viruses and bacteria. Cells of this system respond to pathogens rapidly and do so in a relatively non-specific manner, generally responding to pathogens as a class as opposed to pathogen subtypes and strains. These cells express a multitude of pattern recognition receptors to which they can detect pathogen-associated molecular patterns and respond accordingly (Figure 3).

Macrophages, specifically of the M1 subset, are specialized phagocytes that engulf and digest dead cells and invading microbes such as bacteria. M1 macrophages produce pro-inflammatory cytokines and the anti-microbial molecule nitric oxide (NO), in response to interferon alone or in combination with detection of microbial stimuli such as lipopolysaccharide^[27,28]. However, in the presence of interleukin-4 (IL-4) and IL-13, macrophages differentiate into an alternative, immunosuppressive M2 subset, which is characterized by IL-10 production and decreased expression of IL-12 and tumor necrosis factor- α (TNF- α)^[27,28]. Early work demonstrated that human MSCs antagonize the M1 phenotype and promote M2 polarization, as characterized by increased CD206

expression, increased IL-10 production and phagocytosis, and decreased pro-inflammatory cytokine and NO production^[29]. In transwell cultures, MSCs have also been shown to skew macrophages towards the M2 lineage, which indicates the involvement of soluble, MSC-derived factors that contribute to the polarization^[27]. In addition, MSCs reduce the expression of CD86 and MHCII on macrophages, thus diminishing their stimulatory potency^[30]. In an excisional wound repair model in mice, human gingiva-derived MSCs were shown to migrate to the wound site and polarize M2 for wound repair^[31]. One proposed mechanism is that multiple soluble factors are produced for MSCs to elicit M2 polarization. Prostaglandin E2 (PGE2) was found to be constitutively produced by human MSCs at levels able to suppress IL-6 and TNF- α expression in activated macrophages^[30]. In addition, neutralizing antibodies to IL-6 and granulocyte macrophage-colony stimulating factor (GM-CSF) showed that these cytokines synergistically promote human gingiva-derived MSC-mediated promotion of the M2 phenotype in macrophages^[31].

In addition to macrophages, neutrophils are important phagocytes of the innate immune system. In response to detection of microbial molecules, neutrophils produce a large quantity of microbicidal oxidative products in the so-called oxidative respiratory burst^[32]. Respiratory bursts are also closely associated with neutrophil apoptosis^[33]. MSCs inhibit neutrophil apoptosis, even under IL-8-mediated activation conditions, *via* MSC-derived IL-6^[34,35]. It is thought that MSCs may enact this effect to preserve the non-dividing neutrophil pool found in bone marrow sinusoids. MSCs also prevent respiratory bursts from neutrophils, an effect which aligns with MSC immunosuppression, but had no effect on neutrophil phagocytosis.

sis, matrix adhesion, or chemotaxis^[34].

Mast cells contribute heavily to allergic responses, especially through the release of pro-inflammatory cytokines and histamine-containing granules. Co-culture studies revealed that MSCs suppressed the ability of mast cells to degranulate and produce TNF- α ^[36]. In a passive cutaneous anaphylaxis *in vivo* model, MSCs also reduced inflammation promoted by mast cells. In these experiments, MSC-mediated immunosuppression was dependent on up-regulation of cyclo-oxygenase-2 in MSCs and their production of PGE2, which suppressed mast cells *via* EP4 receptor ligation^[36].

Natural killer cells (NKs) are innate immune cells that, in addition to producing pro-inflammatory cytokines, are cytotoxic toward intracellular pathogen-infected and cancer cells. NK cytotoxicity is regulated by both inhibitory and activating receptors, in addition to target cell MHC expression levels and antibody-dependent cell cytotoxicity. Studies showed that MSCs inhibited NK proliferation activation^[37,38] and reduced the expression of NK activating receptors, including 2B4 and NKG2D^[37]. MSCs also reduced pro-inflammatory cytokine production by NKs. Furthermore, freshly isolated NKs were not cytotoxic towards MSCs, but acquired cytotoxicity after 4 d cultures with IL-15. Neutralization of PGE2 and transforming growth factor- β (TGF- β), both thought to contribute to MSC immunosuppression, overrode MSC-mediated suppression of NK proliferation. Indoleamine-2,3-dioxygenase expression by MSCs has also been found to inhibit NK^[38]. Taken together, these studies indicate that the inhibitory effects of MSCs on NKs may depend on NK culture duration, NK activation state, and time after which MSCs are added to NK cultures.

Dendritic cells (DCs) bridge the innate and adaptive immune systems as they function both as cytokine producers and potent antigen-presenting cells. DCs take up antigen and during maturation and activation up-regulate MHCs, increase the expression of co-stimulatory molecules (*i.e.*, CD40, CD80, CD83 and CD86), and migrate to secondary lymphoid organs and present antigen to T cells for the generation of a primary adaptive immune response. During T cell-priming, DCs also produce a medley of cytokines that affect downstream T cell effector function. MSCs have been shown to affect most of these processes: MSCs inhibit DC endocytosis, up-regulation of MHC, CD40, CD80, CD83, and CD86 during differentiation and prevent further increase of CD40, CD83, and CD86 expression during maturation^[39,40]. They also interfered with DC capacity to produce IL-12 and activate allogeneic T cells^[39,40]. Furthermore, MSCs block the generation of dermal DCs from CD34-derived CD14⁺CD1a⁻ precursors and those derived from immature monocytes^[40]. Monocytes cultured under DC-differentiating conditions in the presence of MSCs fail to proliferate and remain at the G₀ state^[41]. MSC treatment inhibited *in vivo* DC maturation, cytokine secretion, and migration to lymph nodes^[42], which results in insufficient T-cell priming in the lymph nodes. As in previous cellular

contexts, diverse molecular contributions are thought to mediate MSC-modulation of DCs. For example, IL-6 has been shown to at least partially contribute to MSC-mediated inhibition of DC differentiation from bone marrow progenitors^[43], and PGE2 from MSCs has been shown to convert mature CD11c⁺B220⁻DCs into a regulatory subset^[44].

Mechanisms of MSC suppression of adaptive immune cells

Cells of the adaptive immune system, particularly B and T lymphocytes, are composed of billions of unique clones that, as opposed to innate immune cells, recognize highly specific molecules (usually peptides). Each clone expands upon antigen recognition and reaches an effector state in order to eliminate the pathogen present (Figure 4).

B cells are specialized in producing antibodies, which play multiple roles in directly neutralizing pathogens, promoting opsonization for neutralization and phagocytic intake, and activation of other immune cells. Naïve B cells are activated by B-cell receptor (BCR) ligation, CD40/CD40L binding, and Toll-like receptor (TLR) binding of microbial products^[45]. In response to activation, B cells proliferate and differentiate into plasma cells, which produce antibodies. Studies have reported that MSCs inhibit B cell proliferation by arrest at the G₀/G₁ check point, without induction of apoptosis^[45-47]. In addition, MSCs reduced production of IgG, IgM, and IgA during *in vitro* co-culture of B cells^[46]. MSCs also suppressed chemokine receptor expression on B cells^[46]. *In vivo*, MSCs have also been shown to suppress B cell function. In an MRL/Lpr model of systemic lupus erythematosus^[48], a single MSC injection along with cyclophosphamide reduced dsDNA auto-antibodies^[49]. In the context of transplantation, MSC injections led to a reduction of allo-specific antibodies and promoted long-term graft acceptance^[50,51]. In a proteolipid protein (PLP)-mediated form of experimental autoimmune encephalomyelitis (EAE), a murine form of multiple sclerosis^[52], mice given MSCs exhibited an inhibition of PLP-specific antibodies^[53]. Cell-cell contact and soluble factors synthesized by MSCs are thought to suppress B cell function. Programmed death-1 (PD-1)/PD ligand-1 (PD-L1) ligation have been shown to enact B cell suppression by MSCs, with soluble factors largely remaining unidentified^[45,54].

T cells of adaptive immune systems are divided into CD4⁺ and CD8⁺ lineages, both of which can be sub-grouped into different effector subsets. Upon activation through unique T-cell receptors (TCRs) and co-stimulation by APCs such as DCs, T cells rapidly proliferate and differentiate into effector cells. Effector CD4⁺ T cells develop as IFN γ -producing T_H1 cells, IL-4- and IL-13-producing T_H2 cells, IL-10-producing Treg, and IL-17-producing T_H17. CD8⁺ T cells are mainly considered as cytotoxic T lymphocytes (CTLs) and produce cytotoxic granules that kill infected and cancerous cells; however, they can differentiate into many of the same effector

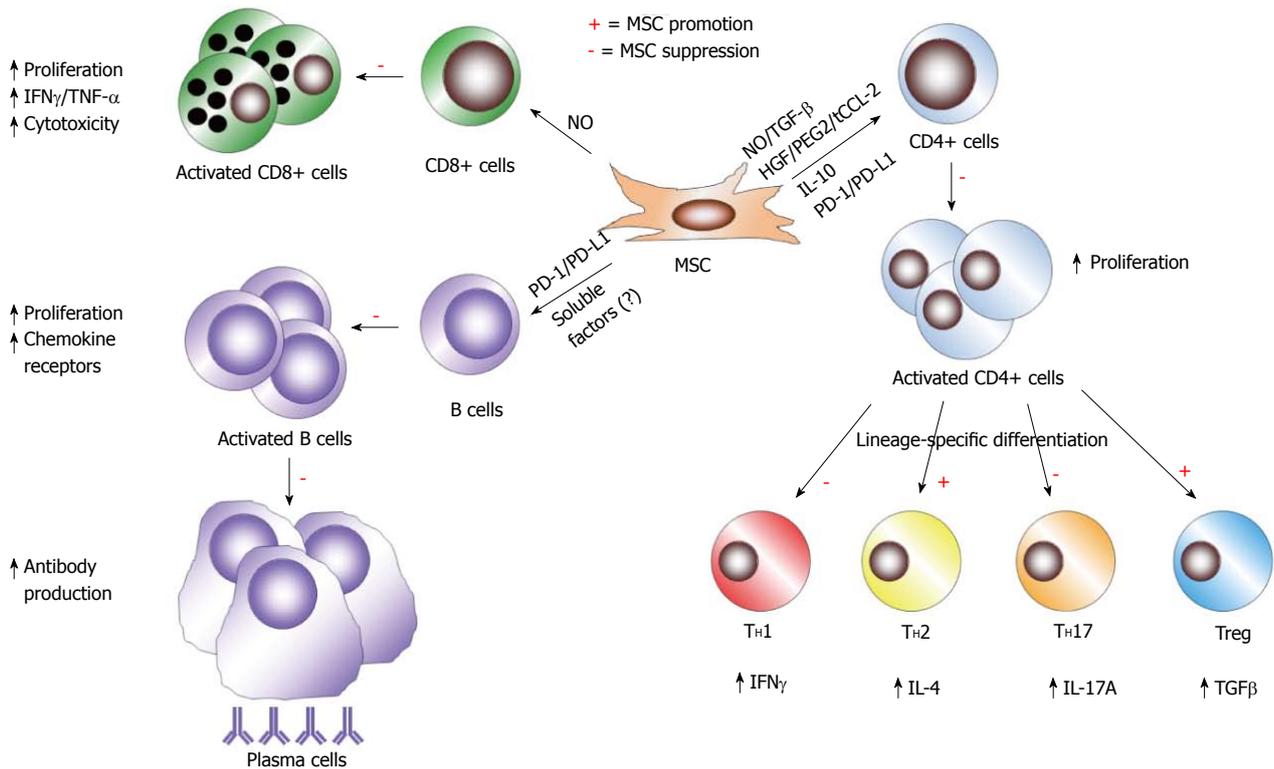


Figure 4 Mesenchymal stem cell immunosuppression of adaptive immune cells. In the context of B cells, mesenchymal stem cells (MSCs) inhibit various facets of B cells activity, including activation, proliferation, chemokine receptor expression, and differentiation to becoming antibody-secreting plasma cells. Unknown soluble factors and PD-1/PD-L1 ligation mediate these effects of MSCs on B cells. MSC have been shown to induce NO in response to inflammatory cytokine detection to suppress CD8+ T cell proliferation, cytokine production, and cytotoxicity. In response to activation in specific cytokine milieu, CD4+ T cells can differentiate into numerous effector populations. MSCs produce soluble factors (NO, TGF-B, HGF, PGE2, truncated CCL-2, and IL-10) and membrane-bound molecules (PD-1 ligation) to achieve suppression of CD4+ T cell proliferation and the polarization of CD4+ T cells towards TH1 and TH17 cells. MSCs favor the development of TH2 and anti-inflammatory Treg populations.

subtypes as their CD4+ T cell counterparts.

MSCs inhibit T cell proliferation, regardless of stimulus type, by arrest at the G₀/G₁ cell cycle phase^[55-57]. This inhibition is also MHC-independent, as both autologous and allogeneic MSCs exert this same anti-proliferative effect. T cells inhibited by MSCs also exhibit increased survival and less apoptosis, but this state can be partially reverted *via* IL-2^[55]. One study showed that MSCs repressed T cell proliferation *via* up-regulation of inducible nitric oxide synthase (iNOS), which produces the NO which produces such effect^[58]. MSCs also modulated cytokine production of T cells. It was reported that these cells suppressed IFN γ production from TH1, promoted IL-4 secretion from TH2, and increased the proportion of Treg present in culture^[59]. MSCs produce immunomodulatory molecules such as hepatocyte growth factor (HGF), TGF-B, and PGE2, which may enact these cellular effects^[55]. MSCs have also been reported to inhibit TH17 development through various means, including inhibition with the effector molecules PGE2, a truncated peptide of C-C chemokine ligand-2 (CCL-2), IL-10, and PD-1/PD-L1 ligation^[52,60-63]. Importantly, MSCs must be pre-exposed to a combination of effector cytokines, including IFN γ and TNF α or IL-1 β , in order to efficiently suppress T cell function^[58]. Moreover, MSCs have been

shown to suppress the cytotoxicity of CTLs, presumably by a soluble factor^[64]. When administered viral peptides and tumor antigens, the cells suppress CTL killing and were not recognized as targets of infection or foreign cells, despite enhanced MHC-I expression post-IFN γ treatment^[22,65,66].

In vivo, MSCs have been extensively used in pre-clinical experimental disease settings involving pathogenic T cells. Some of the earliest reports show MSC-mediated amelioration of EAE induced by the peptide, myelin oligodendrocyte glycoprotein (MOG) 35-55, which preferentially induces a neuro-inflammatory disease mediated by TH1 and TH17 cells^[52,57]. In this setting, the polarization of these cells was inhibited *in vivo*, and MSC-derived HGF alone suppressed EAE while also promoting a beneficial neurotropic effect^[52,57,67]. MSCs suppressed skin-graft rejection in monkeys, which was associated with T cell suppression of proliferation^[68]. In a model of streptozotocin-induced autoimmune diabetes, MSCs inhibited T-cell mediated destruction of insulin-secreting β -cells in the pancreas^[69]. MSCs also suppressed proliferation of auto-reactive T cells in collagen-induced arthritis, in addition to decreasing TNF- α production and supporting the generation of Treg cells^[70]. These studies demonstrate immense potential for the use of MSCs in modulating

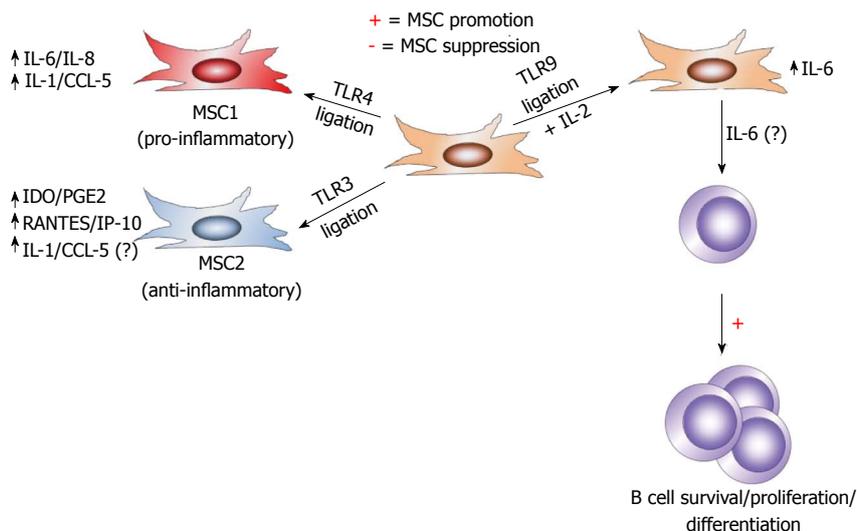


Figure 5 Differential toll-like receptor stimulation affects mesenchymal stem cell immunomodulation. Mesenchymal stem cells (MSCs) are situated throughout the body as sentinels in virtually all organs and the perivascular space and are equipped with pattern-recognition receptors, including Toll-like receptors (TLRS), to detect DAMPs from dying cells and PAMPs from pathogens. In response to TLR3 signaling, MSCs maintain an anti-inflammatory MSC2 phenotype, marked by induction of IDO, PGE2, RANTES, and IP-10 (in addition to IL-1 and CCL-5). However, in response to signaling through TLR3, MSCs adopt the pro-inflammatory MSC1 phenotype and up-regulate IL-6 and IL-8, in addition to IL-1 and CCL-5. In the presence of IL-2 in combination with TLR9 signaling, MSCs have been shown to also produce IL-6, which promotes B cell survival, proliferation, and differentiation, though MSC-derived IL-6 has not been demonstrated to directly exert these effects on B cells.

the immune response in inflammatory settings for therapeutic benefit, especially of autoimmune diseases.

MSCS AND IMMUNOGENICITY

Although the majority of investigations of MSC effects on immune cell function and pre-clinical immunogenic and inflammatory conditions have indicated immunosuppression, other studies have shown immunostimulatory properties, which are discussed next.

Microbial molecule detection

In vivo, MSCs are present in virtually all tissues of the body and express multiple receptor types that permit detection of changes in tissue homeostasis. Differential TLR stimulation of MSCs has been shown to influence the downstream effect of MSCs on immune responses (Figure 5)^[71]. Stimulation of TLR3 with poly (I:C), which mimics viral double-stranded RNA detection, in MSCs causes them to polarize towards an anti-inflammatory phenotype (MSC2 phenotype) characterized by increased production of the immune-regulatory factors IDO and PGE2 and of RANTES and IP-10. However, when MSCs are stimulated with LPS, a TLR4 agonist, they develop a pro-inflammatory MSC1 phenotype in which they up-regulate the pro-inflammatory cytokines IL-6 and IL-8. MSC1, but not un-primed or MSC2, support PBMC activation and proliferation. In opposition to the previous findings, Romieu-Mourez *et al*^[72] found that stimulation of either TLR3 or TLR4 lead to the production of the pro-inflammatory cytokines IL-6, IL-8, IL-1, and the chemokine CCL-5; however, such differences may be due to differences in stimulation protocols, especially for MSC exposure time differences to TLR agonists^[72]. When MSCs are co-cultured with naïve and transitional B cells in the presence of IL-2 and the TLR9 agonist CpG 2006 (viral/bacterial PAMP mimic), B cell survival, differentiation, and antibody production are enhanced^[73]. Though the effect was cell-contact dependent, the MSCs produced increased IL-6 in co-culture, which is

known to increase B cell proliferation. *In vivo*, MSCs are also postulated to not only support the viability of naïve, but also more differentiated, B cell subsets in the bone marrow^[73].

The rationale for the different MSC polarization types in response to different microbial stimuli detection remains unknown. MSCs are thought to exhibit a homeostatic default immunosuppressive phenotype for the purposes of inhibiting inappropriate HSC differentiation and potential depletion of HSC reserves in the bone marrow. However, outside of the bone marrow, they may adopt the pro-inflammatory MSC1 phenotype to aid in the formation of an immune response in tissues during early tissue damage and/or pathogen invasion. It is interesting to note that tissue necrosis and damage leads to the release of intracellular danger-associated molecular patterns (DAMPs) such as heat shock proteins, high mobility group proteins, and degraded ECM molecules, which trigger stimulation of innate immune cells through TLR4 and TLR2 ligation for resolution of tissue damage^[74]. It is possible that TLR4 stimulation of MSCs, whether derived from PAMP or DAMP, could still lead to the same pro-inflammatory outcome due to the apparent necessity of generating an inflammatory environment for the recruitment and activation of immune cells to respond to either tissue damage and/or pathogen invasion. In contrast, the MSC2 phenotype could be adopted for the down-regulation of immune responses to limit inflammatory damage to tissues and permit ECM reconstruction and healing.

Cytokine milieu

MSCs are pleiotropic cells that are highly sensitive to different microenvironments, especially those containing cytokines. Importantly, cytokines exert immune-suppressive or immunogenic effects on cells and tissues dependent on multiple variables, including cytokine identities, combinations, and concentrations (Figure 6).

In continuation of the differential TLR stimulation on MSC polarization, the downstream effects of TLR

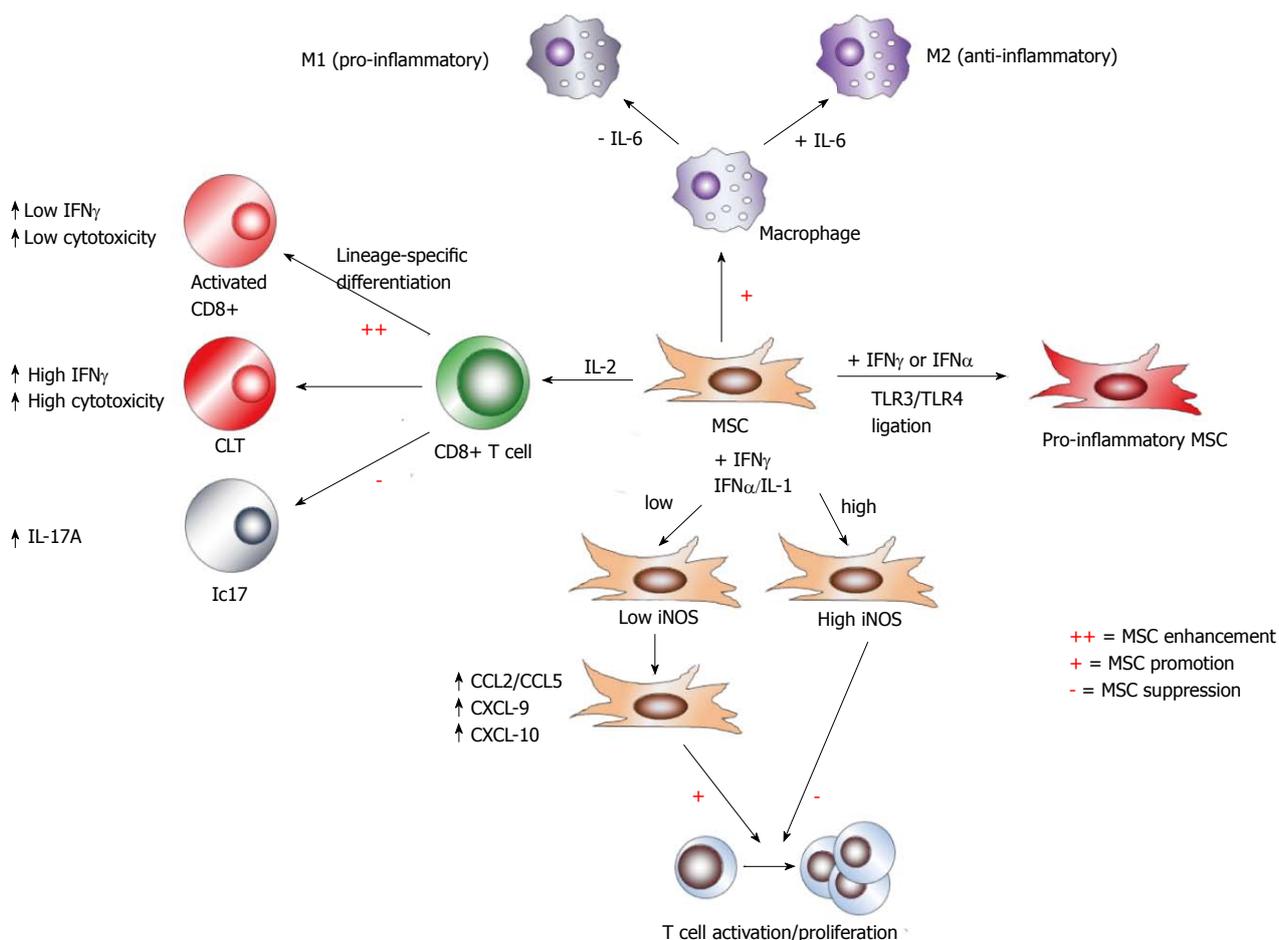


Figure 6 Effects of cytokine milieu on mesenchymal stem cell immune-modulation. Mesenchymal stem cell (MSC) modulation of immune responses is strongly affected by the makeup of cytokine milieus. Toll-like receptor (TLR) ligation in conjunction with interferon signaling drives MSCs down a pro-inflammatory route. While high concentrations of the pro-inflammatory cytokines IFN γ and either tumor necrosis factor- α (TNF- α) or IL-1 have been shown to induce iNOS and NO in MSCs to mediate suppression of T cell proliferation, low concentrations of these factors fail to fully induce iNOS, and instead enhance T cell proliferation, presumably via cytokine-induced chemokines. Furthermore, MSCs differentially affect the polarization of effector CD8+ T cell subsets: through enhanced early IL-2 expression induced by MSCs, activated CD8+ T cells exhibit increased IFN γ expression and cytotoxicity, while fully differentiated cytotoxic T lymphocytes (CTLs) are largely unaffected by MSC action. In contrast, MSCs potently suppress Tc17 development. Moreover, IL-6 signaling acts as a switch for MSC immune-modulation of macrophages. In the presence of IL-6, MSCs retain promotion of M2, but favor M1 polarization in the absence of this cytokine.

stimulation in MSCs can be affected by prior cytokine priming. Initial priming of human MSCs with either IFN- α or IFN- γ synergizes with downstream TLR3 or TLR4 stimulation to enhance the production of pro-inflammatory cytokines by MSCs^[72]. The concentration of inflammatory cytokines has also been postulated to regulate MSC polarization. IFN- γ and IL-1 or TNF- α induction of iNOS and NO production have been demonstrated as an effector mechanism MSCs used for inhibition of T cell proliferation. However, under closer scrutiny, it was discovered that their concentrations must be relatively high, for low/insufficient levels of these cytokines failed to up-regulate iNOS to adequate levels for T cell functional suppression, and led to an induction of T cell responses^[73]. In this scenario, MSCs still retained upregulation of the T-cell activity enhancing chemokines such as CCL2, CCL5, CXCL9, and CXCL10. When iNOS-/-MSCs were injected into normal C57BL/6 mice and challenged with a suboptimal dose of OVA for induction of a delayed type hypersensitivity (DTH) re-

sponse, swelling occurred in injected footpads of mice^[75]. However, when these mutant MSCs were injected into CCR5 -/-CXCR3-/- mice, they could not promote the DTH response, highlighting the importance of chemokine ligation on T cells as an immune-enhancing effect of MSCs in the absence of iNOS induction. Thus high pro-inflammatory cytokine concentrations are thought to promote an MSC2 phenotype while an MSC1 phenotype may result from low level of such cytokines^[76].

As a testament to the importance of the cytokine milieu on influencing MSC function, we recently showed that MSCs differentially affected the generation of different effector CD8+ T cell subsets^[77]. In this study, we found that MSCs had little effect on the functions of IL-2 and IL-12-generated CTLs, increased cytokine production and cytotoxicity of non-polarized, activated CD8+ T cells, and potently suppressed IL-17A-producing, Tc17 development. IFN γ -producing CD8+ T cells were also cytotoxic towards MSCs, which was associated with heavily increased MHC-I expression on MSCs. These effects

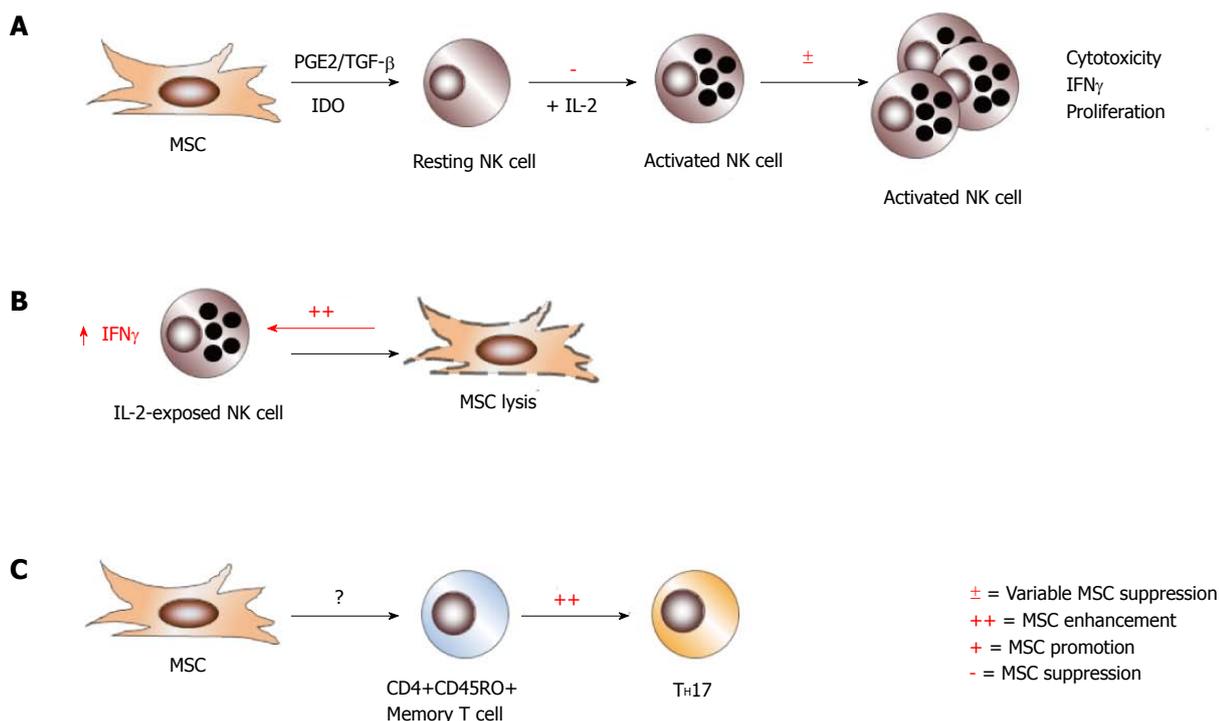


Figure 7 Effects of immune cell activation state on mesenchymal stem cell immune-modulation. The differentiation state of immune cells can render them susceptible or refractory to mesenchymal stem cell (MSC) action. Though MSCs efficiently inhibit the activation and downstream cytotoxicity of resting NK cells, they exert variable suppression on IL-2-activated NK cells, which is partially ratio dependent (A). MSCs themselves may become targets of activated NK cells for lysis, and enhance NK cell production of IFN γ in the process (B). Interestingly, MSCs promote TH17 differentiation from CD4+CD45RO+ memory T cells, but no other CD4+ or CD8+ T cell population (C).

were associated with the early enhancement of IL-2 production, which is known to promote CTLs but antagonize the IL-17-producing program. In a the MOG₃₇₋₅₀ model of EAE, which is mediated by pathogenic CD8+ T cells, MSCs exacerbated the disease and increased the CD8+ T cell presence in the brains of diseased mice. Here, the MSCs appeared to alter the activation program of the developing T cells, but the precise mechanisms of MSC-induced IL-2 production and downstream effector function remain undefined.

In another report of MSC modulation of neuro-inflammatory autoimmune disease, MSCs were found to ameliorate mild MOG-induced EAE, but worsen the severe form, with intracerebroventricular (ICT) injection into mice^[78]. In almost two-thirds of severe-EAE animals, these MSCs migrated into the parenchyma and formed masses characterized by focal inflammation, demyelination, axon loss, and collagen and fibronectin deposits. Importantly, these MSCs do encounter an inflammatory environment when injected ICT, and may undergo a polarization similar to the aforementioned MSC1 type, which could be dependent on the cytokine and molecular milieu.

In addition to the pro-inflammatory cytokines mentioned above, production and detection of IL-6 also acts as a switch for MSCs during immune responses^[76]. This molecule, which is constitutively produced by MSCs, polarized macrophages towards the M2 type upon cell-cell contact^[79]. This polarization was also dependent upon MSC production of IDO and PGE2. However, in the

absence of IL-6, MSCs induced polarization of macrophages towards the M1 phenotype, which is characterized by IFN γ , TNF- α , and CD40L expression^[76]. In contrast, a positive correlation with IL-6 *in vivo* production and MSC administration in mice exhibiting collagen-induced arthritis was reported to worsen this disease^[80]. The molecular milieu that governs the production of IL-6 from MSCs in the context of macrophage polarization has not been determined, but may involve pre-exposure to certain cytokine combinations that influence MSCs in a concentration-dependent manner, as in the case of iNOS. The *in vivo* milieu must also be taken into account, for increased IL-6 production could theoretically enhance inflammation by promoting effector immune cell differentiation, as in the case of IL-17A-producing T cells.

Immune cell differentiation state

Upon activation through cell-specific receptor signaling, immune cells undergo successive stages of differentiation towards a terminal phenotype characterized by optimal effector function, usually before subsequent apoptosis or transition into memory status. The specific stage of an immune cell's differentiation may render it susceptible or refractory to any MSC action (Figure 7).

NK cells are generally in a resting state, but upon IL-2 activation, proliferate and differentiate into activated cytolytic and cytokine-producing cells capable of efficient lysis of target cells. MSCs robustly prevented resting NK cell activation and proliferation, but were only partially

Table 1 Effects of mesenchymal stem cells on preclinical disease models

Disease	Species	Route of administration	Effect	MSC mechanism of action	Ref.
Skin-graft rejection	Monkey	Systemic	Prolonged skin graft survival	Inhibition of T cell proliferation	[68]
Skin-graft rejection	Mouse	Systemic	Increased rejection	Induction of memory T cell response	[85]
Skin-graft rejection	Mouse	Systemic	Increased rejection	Potential increased T cell alloreactivity	[48]
Graft-v-Host disease	Mouse	Systemic	Disease prevention	Cytokine-induced iNOS to inhibit T cell proliferation	[58]
Graft-v-Host disease	Mouse	Systemic	No clinical benefit	Lack of suppression of donor T cell proliferation	[86]
Skin wound	Mouse	Systemic	Wound healing	M2 polarization, decreased inflammation, increased IL-10	[31]
Acute lung injury	Mouse	Systemic	Protected lungs from injury	Blockade of TNF α and IL-1 production	[87]
Acute lung injury	Mouse	Local	Decreased severity	Down-regulation of inflammation, increased IL-10	[88]
Melanoma	Mouse	Local	Increased tumor growth	Inhibition of tumor-specific T cell response	[89]
MOG ₃₅₋₅₅ EAE	Mouse	Systemic	Disease amelioration	Inhibition of CD4+ T cell proliferation	[57]
MOG ₃₅₋₅₅ EAE (severe)	Mouse	Local	Disease worsening	Focal cell mass formation and increased inflammation	[78]
MOG ₃₇₋₅₀ EAE	Mouse	Systemic	Disease worsening	Increased pro-inflammatory CD8+ T cell frequency in CNS	[77]
Experimental autoimmune neuritis	Mouse	Systemic	No clinical benefit	Unknown	[90]
Rheumatoid arthritis	Mouse	Systemic	Prevention	Reduced T cell proliferation, decreased inflammation, Treg induction	[70]
Rheumatoid arthritis	Mouse	Systemic	No clinical benefit	Accentuation of TH1 response	[91]
Systemic lupus erythematosus	Mouse	Systemic	Multi-organ dysfunction reversal	Suppression of TH17 and induction of Treg	[92]
Type-I-diabetes	Mouse	Systemic	Delayed onset	Promotion of TH2 response	[93]
Inflammatory bowel disease	Mouse	Systemic	Prevention	Decreased neutrophil infiltration	[94]

MSC: Mesenchymal stem cell; MOG: Myelin oligodendrocyte glycoprotein; EAE: Experimental autoimmune encephalomyelitis; TNF- α : Tumor necrosis factor- α .

capable of suppressing this process on NK cells that have been pre-exposed to IL-2^[38]. Moreover, the extent of MSC suppression of NK cell proliferation in the latter case was ratio dependent, with decreasing suppression with increasing NK:MSC ratio. IL-2-pre-exposed, but not resting, NK cells also efficiently lysed autologous and allogeneic MSCs, and exhibited increased IFN γ production with MSC co-culture. Interestingly, IFN γ -pre-exposed MSCs had a better capacity of inhibiting pre-activated NK cell activity, presumably due to increased MHC-I expression on MSCs in response to inflammatory cytokine signaling, which negatively affects NK cell function.

Under the arm of adaptive immunity, MSCs have been extensively shown to suppress TH17 and Tc17 development, but less work has addressed MSC effects on memory T cells. Hsu and colleagues showed that MSCs specifically enhanced IL-17 expression in CD4+CD45RO+ memory T cells, but not in any other populations of CD4+ or CD8+ T cells^[81]. These TH17 subsequently enhanced neutrophil function. It is thought that, since these memory T cells rapidly react to a pathogen challenge *in vivo*, they could interact with MSCs at peripheral sites to enhance their function and increase the T cell response for efficient pathogen elimination. Thus immune cell activation state is an important factor in influencing outcome with MSC interactions.

THERAPEUTIC CONSIDERATIONS AND CONCLUSION

Initial pre-clinical animal models of inflammatory con-

ditions suggested that MSCs exerted a beneficial effect for a range of diseases and ushered in their potential use in controlling human diseases, especially autoimmune disease (Table 1). However, additional studies also indicate an exacerbation of disease symptoms, thus raising points to consider regarding the safe use of these cells in humans^[82,83]. Importantly, MSCs represent a highly heterogeneous and pleiotropic population of stem cells. The intrinsic variability in the cellular make-up may influence multiple properties of how MSCs affect immune cell function and disease. Therefore, an intensified focus on further characterizing the subtypes of MSCs is desperately needed. The heterogeneity in the isolation, culturing, and expansion of MSC populations are known to affect the phenotype of MSCs^[84]. For potential clinical use, a more thorough standardization for isolating and culturing these cells is needed along with the ability to project the specific immune-modulatory effects of a given MSC population depending on its subtype make-up.

When injected systemically, MSCs accumulate in the lungs and capillary beds of other tissues, which could decrease the number of MSCs migrating to target areas for treatment. Several lines of genetic and chemical engineering research are already working to improve cell delivery^[82]. There still remains a dearth of information on the long-term engraftment of MSCs in target organs, which is important in light of their initial lung entrapment. Importantly, more research is necessary for a better understanding of the fate of injected MSCs, to determine whether they maintain their primary phenotype or differ-

entiate, depending on the molecular milieu and microenvironment encountered.

The use of MSCs for immune-modulation represents an exciting new step in cellular therapy. However, a number of considerations and further characterizations of the precise nature of these cells will improve their future use in a number of different settings. The conditions of culture can greatly impact the phenotypes of the cells, which is a consideration of *in vitro* culture of cells for therapy. As the MSCs respond to their environments, a more difficult variable to control will be the *in vivo* setting in which they are introduced; cells introduced into an inflammatory environment may respond differently from those introduced into a suppressive environment, for example.

Thus, future studies that further address these questions and are geared toward a more precise characterization of MSC populations and how they respond to these different pathological settings may help promote safe and effective clinical utility of these cells.

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