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Mesenchymal Stem Cells: Mechanisms of Immunomodulation and Homing

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Abstract

Mesenchymal stem cell (MSC) transplantation has been explored as a new clinical approach to repair injured tissue. A growing corpus of studies have highlighted two important aspects of MSC therapy: (1) MSCs can modulate T-cell mediated immunological responses, and (2) systemically administered MSCs home to sites of ischemia or injury. In this review, we describe the known mechanisms of immunomodulation and homing of MSCs. First, we examine the low immunogenicity of MSCs and their antigen presentation capabilities. Next, we discuss the paracrine interactions between MSCs and innate (dendritic cells (DC)) and adaptive immune cells (T lymphocytes) with a focus on prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO) and toll-like receptor (TLR) signaling pathways. We transition to outline the steps of activation, rolling/adhesion, and transmigration of MSCs into target tissues during inflammatory or ischemic conditions. These aspects of MSC grafts - immunomodulation and homing - are contextualized to understand a reported side-effect of MSC therapy, cancer development.

Keywords

Immunosuppression; T-cell proliferation; Stem cell migration; IFN-γ; NFκB

INTRODUCTION

Within the bone marrow space multipotent stromal cells, also referred to as mesenchymal stem cells (MSCs), are known to be the precursor cells for stromal tissues that support hematopoiesis (15). MSCs are anchorage-dependent cells, as opposed to other cells from bone marrow aspirates, thereby making their isolation fairly straightforward. More importantly, MSCs can expand rapidly in vitro while maintaining their multipotency (9). Many studies have demonstrated their therapeutic potential as multipotent cells (ability to differentiate into a limited number of cell types). Traditionally, MSCs can differentiate to mesenchymal lineages

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such as osteoblasts, adipocytes, chondrocytes and potentially other skeletal tissue cells by culturing MSCs in defined mechanochemical conditions (72). MSCs are characterized for the expression of surface markers such as CD73, CD90 and CD105, and the absence of expression of hematopoietic lineage markers (47). It is theoreized that MSCs may reside in other locations other than the bone marrow, such as adipose tissue and surrounding vasculature structures, with the touted notion that they may be present in all adult tissues (13).

Although no specific surface marker or gene product to date distinguishes MSCs from other mesenchymal cells, the functional properties of MSCs make them unique and therapeutically relevant. MSCs have been shown to modulate immunological responses via T-cell suppression (1,4,19,44,59,98). As such, they have been investigated as a new therapeutic strategy for T cell-mediated diseases such as graft-versus-host disease (GVHD) (49,51), Crohn's disease (29), and the prevention of organ transplantation rejection (10). Moreover, the therapeutic benefit of MSC transplantation has been observed in acute tissue injuries of the lung (68,76), heart (30,67,107), kidney (45), and liver (33,46,100). In these disease contexts, MSCs have been observed to migrate to injured sites after systemic administration. Tissue-specific engraftment is referred to as homing (2,108), and this aspect of MSC therapy in disease may be essential for their medicinal effects.

Herein, we present evidence that mechanistically elaborates these two important components of MSC therapy - immunomodulation and homing. We discuss how the natural functions of MSCs, such as antigen presentation and cytokine secretion, may impact immune cells during disease with a focus on several key molecular mediators and cellular targets of MSC therapy. We transition then to understand the events associated with MSC trafficking and engraftment to injured tissues. Finally, we leverage this understanding of MSCs to interpret a potential side-effect of this cell therapy, namely cancer development.

MESENCHYMAL STEM CELLS AND ANTIGEN PRESENTATION

The physical location, or niche, of a stem cell provides invaluable information of their role and interactions within the tissue. MSCs are reportedly located on the abluminal surface of the main sinusoidal blood vessels in the adult bone marrow thus, forming an interface between the periphery and marrow cavity (5). Because of their location, cells entering or exiting the marrow may require engagement with MSCs. The "gatekeeping" aspect of the MSC niche, along with the known immune properties of MSCs, suggest that they are actively involved in homeostasis of bone marrow (74) as the first line of immunological defense. Since it would be desirable to rapidly clear insults to the bone marrow by infectious agents without overt inflammation, it should be expected that MSCs may transition from immunostimulatory to immunosuppressive depending on the circumstance. Indeed, there is evidence to support the duality in MSC immune status. MSCs have been reported to suppress immune rejection in different species (4,18). However, tolerance of MSCs across the allogeneic barrier might not be absolute since studies by another group report on experimental evidence that questions the status of immune privilege (22).

One potential route by which MSCs can naturally switch immune states is based on the way they process antigens and express costimulatory molecules at the immunological synapse. Furthermore, many studies have begun to elucidate what factors govern the immune state of MSCs and have revealed important roles for chemical cues, particularly interferon (IFN)-γ, in defining MSC phenotype. MSCs have been reported to express major histocompatibility complex (MHC) molecules, including MHC class II (MHC-II), and the levels of MHC are altered by proinflammatory cytokines (4). Previous studies have shown that low levels of IFN-γ cause MSCs to express MHC-II as antigen presenting cells (APCs) and high levels of IFN-γ mediate decreased expression of MHC-II (11). Sheng *et al.* (86) describe a role for the IFN-

γdependent-expression of a negative costimulatory molecule, B7-H1 (PD-L1), by MSCs. This study showed upregulation of PD-L1 by T cell-mediated production of IFN-γ and the relevance of PD-L1 to the suppressive properties of MSCs. Taken together, a feedback loop may exist that alters MHC-II and PD-L1 expression by IFN-γ levels and ultimately coordinates the rise and fall of an immune response. Hypothetically, when MSCs are exposed to an insult, such as a bacterial infection, MHC-II molecules facilitate the presentation of bacterial antigens, which leads to the activation of T-cells. The latter cells produce IFN-γ. At high levels, IFN-γ mediates decreased expression of MHC-II to switch off antigen presentation and concomitantly with upregulate B7-H1, which inhibits activated T-cells (Figure 1). The roles of MSCs as both APCs and as immune suppressor cells can be explained as a function of IFN-γ levels and this balance between the immune stimulatory and inhibitory properties should be considered for future clinical applications using MSCs.

EVIDENCE THAT MSCs ARE IMMUNOMODULATORY

The ability of MSCs to modulate the immune system was first recognized after it was observed that they could evade immunosurveillance after cell transplantation (52). Now, this ability of MSCs to alter an immune response has been exploited for therapeutic purposes as by ongoing clinical trials of MSCs for the treatment of steroid-refractory graft-versus-host disease (GVHD) (49).

MSCs can suppress several T-lymphocyte activities both in vitro and in vivo (1,4,19,44,59, 98). Naive and memory cells are subjected to MSC-mediated suppression and the MSC inhibitory effect does not require the presence of APCs and is not mediated through CD4+/ CD25+ regulatory T cells (44). Though, the mechanisms by which these cells exert their immunosuppressive function are still unclear, it is likely that mechanisms involving both cell-to-cell contact and soluble factors are involved in supporting T-cell inhibition in antigen-specific and non-specific manners (1,44,59,98).

There are a number of cellular targets of MSC therapy that span both the innate and adaptive arms of the immune system. MSCs altered the cytokine secretion profile of dendritic cells (DCs), naive and effector T cells (T helper 1 [TH1] and TH2), and natural killer (NK) cells to induce a more anti-inflammatory or tolerant phenotype. Specifically, MSCs caused: (1) mature DCs type 1 (DC1) to decrease tumor necrosis factor-a (TNF-α) secretion and mature DC2 to increase interleukin-10 (IL-10) secretion; (2) TH1 cells to decrease IFN-γ and caused TH2 cells to increase secretion of IL-4; (3) an increase in the proportion of regulatory T suppressor cells; and (4) decreased secretion of IFN-γ from NK cells (1).

The Contribution of MSC Soluble Factors and Cell-Cell Interaction

Several studies have shown that MSCs actively inhibit the function of several immune cells through secreted cytokines, growth factors and enzymatic action. For instance, the immunosuppressive function of lung resident-MSCs was noted in the absence of direct cell contact (38). Collectively, secreted molecules from MSCs delivered by bolus injection of concentrated conditioned medium or by MSC extracorporeal bioreactor treatment can reverse a rat model of multiorgan dysfunction syndrome (100). In contrast to those studies that support a central role for MSC soluble factors others suggested that cell-cell contact is more important (39,89). Tse *et al*. (98) demonstrated that close proximity to MSCs was important in suppressing T cell responsiveness and suggested that direct contact between lymphocytes and MSCs was more important than soluble mediators in the immunosuppressive function of MSCs. Krampera *et al.* stated that inhibition requires the presence of MSCs in culture and MSC-T-cell contact (44). Recently, several reports stated the importance of combined soluble factors and cell-cell contact in MSC-mediated immunosuppression (25,108). In order for MSCs to provide a pleiotropic immunomodulatory effect that is responsive to different stimulants

such as cytokines and chemokines and targets different effector cells such as T-cells, NK-cell and DCs, it seems reasonable for MSCs to employ both by direct and soluble mediators that coordinate for a multi-pronged approach to therapy.

Immunomodulation by Soluble Factors

1. MSC-derived lipid intermediates suppresses T-cell proliferation—Prostaglandin E2 (PGE2) is a lipid intermediate that has been implicated as one of the potential candidates responsible for T cell inhibition by MSCs (1,25,38). Like all prostanoids, PGE2 is synthesized from arachidonic acid via the actions of either the constitutive cyclooxygenase-1 (COX-1) or the inducible COX-2 enzyme (26). Murine and human MSC constitutively express COX-2. PGE-2 production is upregulated after co-culture of human MSC with peripheral blood mononuclear cells (PBMCs) (98), suggesting communication between MSC and lymphocytes that leads to the increased production of immunosuppressive factors such as PGE-2 (23,25). Both COX-2 and PGE-2 expression by MSC were upregulated by IFN-γ and TNFα, suggesting a level of control based on the inflammatory microenvironment. Aggarwal *et al.* (1) demonstrated that the human MSCs produced elevated PGE2 in coculture with T cells, and inhibitors of PGE2 production mitigated MSC-mediated immunomodulation in vitro. Also, Jarvinen *et al.* (38) showed PGE2 synthetic capacity of lung allograft-derived MSCs isolated from bronchioalveolar lavage samples from lung transplant recipients. Lung resident (LR)-MSCs significantly inhibited proliferation of third party, HLA-mismatched T cells, which was abrogated by using COX inhibitors. These findings suggest that PGE2 is one of the key molecules involved in the immunomodulatory effect of MSCs.

2. MSC Metabolism of Tryptophan suppresses T-cell proliferation—Recent data has shown a role for indoleamine 2,3 deoxygenase (IDO) in human MSC mediated immune suppression (59). IDO is the rate-limiting enzyme involved in the catabolism of the essential amino acid tryptophan into its breakdown product kynurenine (95). IDO is involved in the inhibition of T cell proliferation by dendritic cells (34). MSC do not constitutively express IDO, however when stimulated with IFNγ, but not TNFα, MSCs can be induced to express IDO and previous reports suggested a role for this enzyme in human MSC suppression (23, 44,59). Ryan *et al.* (80) demonstrated the contribution of IDO to IFN-γ induced immunomodulation by MSC using of an antagonist of IDO, 1-methyl-L-tryptophan. Moreover, the tryptophan catabolite kynurenine had been examined in mixed lymphocyte reactions (MLR), and was found to block alloproliferation. These findings support a model where IDO exerts its effect through the local accumulation of tryptophan metabolites rather than through tryptophan depletion. However, Tse *et al.* (98) did not find a significant restoration of proliferation by IDO. This finding indicates that, IDO is not an exclusive mechanism for MSC immunomodulation in basal states, but it is essential for MSC suppression in the presence of IFN-γ.

3. The role of TGFβ, HGF and other soluble factors in MSC immunotherapy—Previous studies demonstrated that exposure to IFN-γ did not ablate MSC inhibition of T cell proliferation, but induced expression of hepatocyte growth factor (HGF) and transforming growth factor (TGF)-β1 at concentrations that suppressed alloresponsiveness (79). Another report demonstrated that quantitative real time PCR confirmed significant HGF mRNA upregulated by IFNγ and TNFα (23). Di Nicola *et al.* (19) suggested that HGF worked in synergy with TGF-β1 to resist T cell recognition by simultaneous neutralization of HGF and TGF-β1 in the latter study restoring T cell proliferation. In addition, there are several reports suggesting that other soluble factors such as nitric oxide (83) can regulate immunosuppressive effect of MSC.

Inhibition of NK-cell Proliferation and DC Maturation by Soluble Factors and Cell-Cell Interaction

1. NK-cell proliferation and NK-cell mediated cytotoxicity—In effect, MSC modulate different aspects of the rejection process, including the inhibition of DC differentiation (24), skewing of CD4+ T helper population phenotypes, and modulation of CD8+ cytotoxic T lymphocyte and NK cell functions (80). NK cells are major effector cells of the innate immunity and are generally thought to play a fundamental role in antiviral responses (7). MSCs and NK cells have been shown to interact in vitro (44,89,91). The outcome of this interaction may depend on the state of NK-cell activation and/or the cytokines present in the milieu. Previous studies have described that cytokine-induced proliferation of NK cells was highly susceptible to MSC-mediated inhibition (91). In addition, the levels of surface expression of activating NK receptors were positively correlated with NK-cell function (62,87). There is growing evidence that IDO, PGE2, and TGF-β1 may represent relevant mediators of MSC-mediated inhibition of NK-cell function (1,19,59). Spaggiari *et al.* (91) demonstrated a strong inhibition of NK-cell proliferation when NK cells were cultured in the presence of MSCs. Remarkably, the simultaneous blocking of IDO and PGE2 could almost completely restore NK-cell proliferation. They also showed the ability of NK-cells in killing target cells was markedly reduced when cultured with MSCs (90). These data further confirm that IDO and PGE2 may exert a synergistic effect in the immunosuppressive activity mediated by MSCs.

2. DC maturation—DCs play a key role in the initiation of primary immune responses and in tolerance, depending on the activation and maturation stage of DCs (3). Immature DCs behave as sentinels in peripheral tissues, with highly efficient antigen uptake and processing, and low ability to stimulate T cells. Locally produced inflammatory cytokines or microbial components promote the maturation of DCs from a processing to a presenting stage, characterized by up-regulation of MHC class II and costimulatory molecules (CD80 and CD86), production of IL-12, and migration to lymphoid tissue (60). DC maturation is a prerequisite to induce immunogenic T cell responses, whereas tolerance is observed when antigens are presented by immature or semimature DCs (23). Therefore, DC maturation plays a key role in initiating T cell responses (55). Recent evidence demonstrates that MSC disrupt the three major functions that characterize the transition of DC from immature to mature stages, namely the upregulation of antigen presentation/costimulatory molecule expression, the ability to present defined antigens, and the capacity to migrate to CCL19 (24). Furthermore, reduction of IL-12 secretion was also observed after MSC coculture (39).

MSCs produce several cytokines, including interleukin (IL)-6, and monocyte-colony stimulating factor (M-CSF), which have been shown to have an important role in DC differentiation (65). It is now clear that modulation of DC maturation by MSC requires IL-6 and a contact-dependent signal (20,24). Djouad *et al.* observed that MSC secrete higher levels of IL-6 which was involved in the reversion of the maturation of DC to a less mature phenotype and in the partial inhibition of bone marrow progenitors to DC (20). PGE2 has also been observed to contribute to the modulation of DC maturation (12,20). Chen *et al.* (12) demonstrated that blockade of PGE2 synthesis in MSCs could revert most of the inhibitory effects on DCs differentiation and function. Taken together, these findings suggest that PGE2 and IL-6 can mediate DC maturation by MSCs and that leads to T-cell suppression in trans.

MSCs Induce T-Cell Suppression through NFκB Pathway

Toll-like receptors (TLRs) are conserved family receptors that recognize pathogen-associated molecular patterns and promote the activation of immune cells (104). It is recognized that TLRs mediate stress responses of bone marrow-derived progenitor cells (64). A recent study described the importance of TLRs in migration and immune regulation of MSCs (71,97). The common signaling feature among all TLRs is the activation of the transcription factor nuclear

factor kB (NFkB), which has been implicated in controlling the expression of inflammatory cytokines and cell maturation molecules (53). Pevsner-Fischer *et al*. (71) demonstrated that cultured MSCs express TLR molecules 1 to 8. Activation of MSCs by TLR ligands induced IL-6 secretion and NFkB nuclear translocation. Liotta *et al.* (53) demonstrated that LPS was able to induce NFkB activation in MSCs, as well as cytokine and chemokine production such as IL-6, IL-8, and CXCL10. However, the addition in culture of LPS could significantly reduce the suppressive activity of MSCs on T-cell proliferation. They showed that ligation of TLR3 or TLR4 on MSCs inhibited their suppressive effect on T-cell proliferation by hampering Jagged-1 expression, which impaired signaling to its cognate Notch receptor expressed on T cells. TLRs were critical players in the immunoregulation observed in vivo when MSCs were transplanted in vivo (41,97). The intersection of pathways triggered by IFNγ was observed in the immunomodulatory effect of MSCs by the activation of NFkB through the upregulation of COX-2 and PGE-2 (23,66). In addition, TNF-α has been shown to be a critical modulator of NFkB, and there is evidence that MSCs can express TNF receptor (TNFR) (14). Recently, Nemeth *et al.* reported that MSCs, when activated by LPS or TNF-α, could reprogram macrophages by releasing PGE2 that acts on the macrophages through EP2 and EP4 receptors, for the treatment of sepsis (66,71). These findings suggest that NFkB activation via both TLR and TNFR expressing on MSCs can suppress T-cell proliferation and DC maturation (Figure 1).

HOMING OF EXOGENOUS MSCs

Homing is the process by which cells migrate to, and engraft in, the tissue in which they can exert local, functional effects. While the homing of leukocytes to sites of inflammation is well studied (35,54), the mechanisms of progenitor cell homing to sites of ischemia or injury are poorly understood. Yet, we will describe the lessons learned from leukocyte homing to provide insight into MSC transplantation (Figure 2).

Homing involves a cascade of events initiated by shear resistant adhesive interactions between flowing cells and the vascular endothelium at the target tissue (Step 1). This process is mediated by ‘homing receptors’ expressed on circulating cells that engage relevant endothelial co-receptors, resulting in cell-tethering and rolling contacts on the endothelial surface. This is typically followed by chemokine triggered activation of integrin adhesiveness (Step 2), firm adhesion (Step 3) and extravasation (Step 4) (81). The cellular expression of adhesion molecules is critically important for cell-based therapy to mediate adhesion of the implanted cells to the extracellular matrix of targeted tissue in host animals (37). The homing of MSC after systemic or local infusion has been studied in animal models in a variety of experimental settings. A growing number of studies of various pathologic conditions have demonstrated that MSC selectively home to sites of injury, irrespective of the tissue (68,76). The homing ability of MSC has been demonstrated in the settings of wound healing, and tissue regeneration (58). Since most of the studies have been investigated by systemic infusion of MSCs for clinical application, the understanding of homing mechanisms might be crucial for enhancing MSC engraftment particularly when cells are infused via the vascular route.

Integrins and MSC Homing

Integrins have been known to play a key role in cell adhesion, migration, and chemotaxis (35,75,102). Among the family of integrins, integrin α4/β1 is a cell surface heterodimer, which mediates cell-cell and cell-extracellular matrix interactions through adhesion to the vascular cell adhesion molecule (VCAM)-1 and to the V-region of fibronectin (31). This integrin α4/β1 -VCAM interaction has been studied to regulate T cell and natural killer cell trafficking (103).

The expression of integrins has been known to contribute to the process of neutrophil locomotion including members of integrin β1 and β2 (35,102). Integrin β1 also involves cell-to-cell adhesion (102), which may be important for the anchorage of the engrafted cells. The process of the integrin expression is enhanced upon leukocyte activation by chemokines leading to integrin-mediated firm adhesion on endothelial cell monolayers, diapedesis through the endothelial cell wall and finally the migration/invasion into the extracellular matrix using integrin-dependent processes and matrix degrading proteases (35). Stimulated by a chemotactic gradient, leukocytes traverse the extracellular matrix by way of transient interactions between integrin receptors and components of the extracellular matrix that serve as adhesive ligands (48,69). As expected, blockade of integrin b1 diminishes neutrophil migration to the lung during inflammation (75).

VCAM-1 has been shown to promote the adhesion of endothelium, lymphocytes, monocytes and DCs (92,96). Primarily, VCAM-1 is an endothelial ligand for integrinsα4β1, β1, and α4β7. Upregulation of VCAM-1 by endothelial cells due to cytokines occurs as a result of increased gene transcription in response to TNF-α and IL-1β (105). Stimulation of leukocyte adhesion to the endothelium is one of many TNF–α activities and is coordinated with the upregulation of adhesion molecules on the endothelial cell surface (57). A recent study demonstrated that anti-VCAM-1 antibodies reduce the adhesion of rat MSCs to microvascular endothelial cells (85).

It has been demonstrated that bone marrow derived MSCs expressed many integrins on their surface (17), including high levels of integrin β1 and α4, and their binding partners were up-regulated in the ischemic myocardium (36). Ip et al. (36) demonstrated that a significant reduction in the total number of MSC in the infarcted myocardium was observed after integrin β1 blockade. Also some studies revealed that the integrin α4/β1 is one of the integrins that can mediate initial capture, rolling, and firm attachment of MSCs to the bone marrow (37). Ruster *et al.* (78) showed that MSCs interact in a coordinated fashion with endothelial cells, not only by integrin α4/β1-VCAM-1 interaction or integrin β1, but also by the endothelial phenotype, P-selectin, MMP-2 secretion, and cytokines. The requirement of integrin α4 for bone marrow engraftment of stem cells has been substantiated in other studies where murine or sheep bone marrow was incubated with anti-integrin α4 antibody and the repopulating stem cells failed to engraft in bone (108). The expression of several adhesion molecules modulate the homing of MSCs to endothelial cells as demonstrated by coculture experiments (94), a flow chamber model (78), and an intra-arterial injection (85) (Figure 2A).

MSC Interactions with Extracellular Matrix Components

Fibronectin binds extracellular matrix components such as collagen, fibrin and heparan sulfate proteoglycans (77). It plays a major role in cell adhesion, growth, migration and differentiation, and it is important for wound healing processes (99). Along with fibrin, plasma fibronectin is deposited at the site of injury to form a blood clot that stops bleeding and protects the underlying tissue. As repair of the injured tissue continues, fibroblasts and macrophages begin to remodel the area, degrading the proteins that form the provisional blood clot matrix and replacing it with a matrix that more resembles the normal, surrounding tissue (93). Fragmenting fibronectin further exposes its V-region, which contains the site for integrin α4β1 binding which is expressed on MSCs. These fragments of fibronectin are believed to enhance integrin α4β1 expressing cell binding allowing them to adhere to and forcefully contract the surrounding matrix (99). These reports support a notion that integrin α4/β1-fibronectin interaction plays a major role in transmigration of MSCs into extracellular matrix (Figure 2C).

CXCR4 Expression on MSC and Interaction with SDF-1

Stromal cell-derived factors 1 (SDF-1) which is officially designated Chemokine (C-X-C motif) ligand 12 (CXCL12) is a small chemotactic cytokine that activates leukocytes and is often induced by proinflammatory stimuli such as TNF-α or IL-1 (27). The receptor for this chemokine is CXCR4 and the SDF-1-CXCR4 interaction is considered to be exclusive (56). However, Bleul *et al*. suggested that since SDF-1 is expressed constitutively in a broad range of tissues it may have a role in immune surveillance and in basal extravasation of lymphocytes and monocytes rather than solely in inflammation (8). This interaction between SDF-1 and its ligand CXCR4 plays an important role in homing as shown by studies on engraftment of hematopoietic stem/progenitor cells (70) and on colonization of bone and bone marrow by metastatic breast and prostate cancer cells (63). SDF-1, required for stem-cell homing to bone marrow, was upregulated immediately after myocardial infarction and downregulated within 7 days. Askari *et al.* (2) concluded by these findings that SDF-1 was sufficient to induce therapeutic stem-cell homing to injured myocardium and suggest a strategy for directed stem-cell engraftment into injured tissues.

Sordi *et al*. reported the chemotactic responsiveness of MSCs to chemokines. MSCs released chemokines and displayed a restricted response pattern to chemokines. MSCs migrated appreciably in response to SDF-1 and CX3CL, consistent with they're expression of chemokine receptors CXCR4 or CX3CR1, respectively. Based on these data, they stated that the SDF-1-CXCR4 axis is involved in MSC migration and this is conserved also in tissue MSCs (88). Also Wynn *et al.* (106) showed that CXCR4 is important for MSC migration to bone marrow. However, cell surface receptor levels of CXCR4 on MSC is low, with large amounts found intracellularly. Although, CXCR4 is present at the cell membrane of 3.9% of MSCs, high levels of receptor expression were found in 83% to 98% of cells intracellularly. This was in contrast to CD34+ cells, in which only 12.2% of the cells were positive as previously published (43). CXCR4 intracellular storage has been previously described in response to cytokines (101). In the study, the response of the CXCR4 receptor to SDF-1 was shown in dose-dependent manner. Thus, the CXCR4 receptor, which is present at low levels at the cell surface, is likely to be translocated to the surface upon chemokine stimulation and contributes to MSC migration (106) (Figure 2B).

However, there are several studies contradict these results. One report stated that MSCs lack many effectors of homing, especially E-selectin ligands and CXCR4 (82). Another study indicated that MSCs use integrin β1 but not CXCR4 for myocardial migration and engraftment (36). Taken together, the mechanism of MSC migration is still unclear and further investigation is required.

Other Factors Modulating MSC Migration

1. Basic Fibroblast Growth Factor (bFGF)—Large stores of bFGF are typically embedded in extracellular matrix molecules. bFGF was able to increase the migratory activity of MSCs by activation of the Akt (protein kinase B) pathway. Surprisingly, bFGF could have opposing effects on MSC migration depending on the concentration. Gradient experiments using bFGF showed that low concentrations of bFGF lead to an attraction of the cells, whereas higher concentrations resulted in repulsion. This ambivalent effect of bFGF provides the possibility of purposeful routing of MSCs (84).

2. Matrix Metalloproteinases (MMPs)—As evidenced by ELISA, MSCs secrete MMP-2 but not MMP-9. Recently, De Becker *et al*. demonstrated a functional involvement of MMP-2 expressed in MSC homing through bone marrow endothelium (16). Steingen *et al.* also showed that transendothelial migration of MSCs is at least partially regulated by MMP-2 (94).

3. TLR-Mediated Migration—We previously described TLR signaling in the context of MSC differentiation into immunosuppressive cells. TLR-mediated differentiation may also prime the cells to migrate. Using transwell migration assays, TLR ligation promoted human MSC migration and disruption of TLRs by neutralizing antibodies compromised MSC migration (97).

The Global Role of Inflammation and MSC Homing

It is likely that increased inflammatory chemokine concentration at the site of inflammation is a major factor causing MSCs to preferentially migrate to these sites. Chemokines are released after tissue damage and MSC express the receptors for several chemokines (28). The migration capacity of MSCs was found to be under the control of a large range of receptor tyrosine kinase growth factors such as platelet-derived growth factor (PDGF) or insulin-like growth factor 1 (IGF-1) and chemokines such as CCR2, CCR3, CCR4 or CCL5 as assessed by in vitro migration assays. In addition, most chemokines are more effective when stimulated by TNF-α or IL-1β. These findings suggested that the mobilization of MSCs and their subsequent homing to injured tissues might depend on the systemic and local inflammatory state (73).

Cancer and MSCs

Recently MSCs have been found to have a central role in the pathogenesis and progression of tumors. Because there is evidence that tumors can be considered sites of potential inflammatory cytokine and chemokine production, these properties may enable MSC to home to, and immunomodulate, the tumor environment (32). One of the distinct compartments generalized solid tumors is the stroma, which is the non-malignant supportive tissue that includes extracellular matrix, blood vessels, immune and inflammatory cells, and connective tissue (50). Stroma is placed between malignant cells and normal host tissues and is crucial for tumor growth. Recent evidence showed that MSCs actively migrate to, and proliferate in, tumors. MSCs were found to contribute to the tumor-associated stroma within sites of inflammation and were in close proximity with tumor cells as part of the remodeling process (42). Homing and migration of MSCs to tumors was found to be mediated by monocyte chemotactic protein-1 (MCP-1) secreted by primary breast cancers (21), or SDF-1 in response to prostate cancer, colorectal cancer and breast cancer cell lines (61). Malignant gliomas seem to recruit MSCs by secreting a large array of angiogenesis related cytokines including IL-8, TGFβ and VEGF (6). The incorporation of MSC into an otherwise non-malignant cell mass may lead to metastatic growth as observed in a breast tumor implants (42).

CONCLUSIONS AND FUTURE PERSPECTIVES

The objective of this review was to provide a clear and unified theory of MSC therapy from initial injection to therapeutic response. It is clear that MSCs have a capacity to home and integrate into damaged tissues and provide immunomodulatory effects by paracrine and/or cell-cell contact that is regulated by the inflammatory microenvironment. This approach is now being successfully used to cotransplant MSCs with other parenchymal cells, such as hepatocytes or islet cells, to enhance the engraftment and function of parenchymal cells in an immunoprotected fashion (40,46). These findings may extend future prospects of the clinical application of MSCs into broader applications. Furthermore, the opportunity exists to use genetic engineering of MSCs to express specific factors for homing and therapy (82). In summary, a rational understanding of MSCs mechanisms of action will allow for the translation of our basic knowledge of MSC biology into the design of new clinical therapies. Ongoing and future clinical trials with MSCs will provide a rich resource of bedside information that can be studied extensively in the laboratory to further advance this burgeoning field.

References

1. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105(4):1815–1822. [PubMed: 15494428]
2. Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ, Penn MS. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003;362(9385):697–703. [PubMed: 12957092]
3. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392(6673): 245–252. [PubMed: 9521319]
4. Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, Hardy W, Devine S, Ucker D, Deans R, Moseley A, Hoffman R. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002;30(1):42–48. [PubMed: 11823036]
5. Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. Stem Cells 2001;19(3):180–192. [PubMed: 11359943]
6. Birnbaum T, Roider J, Schankin CJ, Padovan CS, Schichor C, Goldbrunner R, Straube A. Malignant gliomas actively recruit bone marrow stromal cells by secreting angiogenic cytokines. J Neurooncol 2007;83(3):241–247. [PubMed: 17570034]
7. Biron CA. Activation and function of natural killer cell responses during viral infections. Curr Opin Immunol 1997;9(1):24–34. [PubMed: 9039782]
8. Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). J Exp Med 1996;184(3):1101–1109. [PubMed: 9064327]
9. Caplan AI. Mesenchymal stem cells. J Orthop Res 1991;9(5):641–650. [PubMed: 1870029]
10. Casiraghi F, Azzollini N, Cassis P, Imberti B, Morigi M, Cugini D, Cavinato RA, Todeschini M, Solini S, Sonzogni A, Perico N, Remuzzi G, Noris M. Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells. J Immunol 2008;181(6):3933–3946. [PubMed: 18768848]
11. Chan JL, Tang KC, Patel AP, Bonilla LM, Pierobon N, Ponzio NM, Rameshwar P. Antigen-presenting property of mesenchymal stem cells occurs during a narrow window at low levels of interferon-gamma. Blood 2006;107(12):4817–4824. [PubMed: 16493000]
12. Chen L, Zhang W, Yue H, Han Q, Chen B, Shi M, Li J, Li B, You S, Shi Y, Zhao RC. Effects of human mesenchymal stem cells on the differentiation of dendritic cells from CD34+ cells. Stem Cells Dev 2007;16(5):719–731. [PubMed: 17999594]
13. Crisan M, Yap S, Casteilla L, Chen CW, Corselli M, Park TS, Andriolo G, Sun B, Zheng B, Zhang L, Norotte C, Teng PN, Traas J, Schugar R, Deasy BM, Badylak S, Buhring HJ, Giacobino JP, Lazzari L, Huard J, Peault B. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell 2008;3(3):301–313. [PubMed: 18786417]
14. Crisostomo PR, Wang M, Herring CM, Markel TA, Meldrum KK, Lillemoe KD, Meldrum DR. Gender differences in injury induced mesenchymal stem cell apoptosis and VEGF, TNF, IL-6 expression: role of the 55 kDa TNF receptor (TNFR1). J Mol Cell Cardiol 2007;42(1):142–149. [PubMed: 17070836]
15. Dazzi F, Ramasamy R, Glennie S, Jones SP, Roberts I. The role of mesenchymal stem cells in haemopoiesis. Blood Rev 2006;20(3):161–171. [PubMed: 16364518]
16. De Becker A, Van Hummelen P, Bakkus M, Vande Broek I, De Wever J, De Waele M, Van Riet I. Migration of culture-expanded human mesenchymal stem cells through bone marrow endothelium is regulated by matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-3. Haematologica 2007;92(4):440–449. [PubMed: 17488654]
17. De Ugarte DA, Alfonso Z, Zuk PA, Elbarbary A, Zhu M, Ashjian P, Benhaim P, Hedrick MH, Fraser JK. Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow. Immunol Lett 2003;89(2–3):267–270. [PubMed: 14556988]
18. Devine SM, Bartholomew AM, Mahmud N, Nelson M, Patil S, Hardy W, Sturgeon C, Hewett T, Chung T, Stock W, Sher D, Weissman S, Ferrer K, Mosca J, Deans R, Moseley A, Hoffman R.

Mesenchymal stem cells are capable of homing to the bone marrow of non-human primates following systemic infusion. Exp Hematol 2001;29(2):244–255. [PubMed: 11166464]

19. Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, Gianni AM. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99(10):3838–3843. [PubMed: 11986244]
20. Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, Apparailly F, Cantos C, Jorgensen C, Noel D. Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells 2007;25(8):2025–2032. [PubMed: 17510220]
21. Dwyer RM, Potter-Beirne SM, Harrington KA, Lowery AJ, Hennessy E, Murphy JM, Barry FP, O'Brien T, Kerin MJ. Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. Clin Cancer Res 2007;13(17):5020–5027. [PubMed: 17785552]
22. Eliopoulos N, Stagg J, Lejeune L, Pommey S, Galipeau J. Allogeneic marrow stromal cells are immune rejected by MHC class I- and class II-mismatched recipient mice. Blood 2005;106(13): 4057–4065. [PubMed: 16118325]
23. English K, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. Immunol Lett 2007;110(2):91–100. [PubMed: 17507101]
24. English K, Barry FP, Mahon BP. Murine mesenchymal stem cells suppress dendritic cell migration, maturation and antigen presentation. Immunol Lett 2008;115(1):50–58. [PubMed: 18022251]
25. English K, Ryan JM, Tobin L, Murphy MJ, Barry FP, Mahon BP. Cell contact, prostaglandin E(2) and transforming growth factor beta 1 play non-redundant roles in human mesenchymal stem cell induction of CD4+CD25(High) forkhead box P3+ regulatory T cells. Clin Exp Immunol 2009;156 (1):149–160. [PubMed: 19210524]
26. Ermert L, Ermert M, Goppelt-Struebe M, Walmrath D, Grimminger F, Steudel W, Ghofrani HA, Homberger C, Duncker H, Seeger W. Cyclooxygenase isoenzyme localization and mRNA expression in rat lungs. Am J Respir Cell Mol Biol 1998;18(4):479–488. [PubMed: 9533935]
27. Fedyk ER, Jones D, Critchley HO, Phipps RP, Blieden TM, Springer TA. Expression of stromal-derived factor-1 is decreased by IL-1 and TNF and in dermal wound healing. J Immunol 2001;166 (9):5749–5754. [PubMed: 11313418]
28. Fox JM, Chamberlain G, Ashton BA, Middleton J. Recent advances into the understanding of mesenchymal stem cell trafficking. Br J Haematol 2007;137(6):491–502. [PubMed: 17539772]
29. Garcia-Olmo D, Garcia-Arranz M, Herreros D, Pascual I, Peiro C, Rodriguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis Colon Rectum 2005;48(7):1416–1423. [PubMed: 15933795]
30. Gnecchi M, He H, Liang OD, Melo LG, Morello F, Mu H, Noiseux N, Zhang L, Pratt RE, Ingwall JS, Dzau VJ. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. Nat Med 2005;11(4):367–368. [PubMed: 15812508]
31. Guan JL, Hynes RO. Lymphoid cells recognize an alternatively spliced segment of fibronectin via the integrin receptor alpha 4 beta 1. Cell 1990;60(1):53–61. [PubMed: 2295088]
32. Hall B, Dembinski J, Sasser AK, Studeny M, Andreeff M, Marini F. Mesenchymal stem cells in cancer: tumor-associated fibroblasts and cell-based delivery vehicles. Int J Hematol 2007;86(1):8–16. [PubMed: 17675260]
33. Hardjo M, Miyazaki M, Sakaguchi M, Masaka T, Ibrahim S, Kataoka K, Huh NH. Suppression of carbon tetrachloride-induced liver fibrosis by transplantation of a clonal mesenchymal stem cell line derived from rat bone marrow. Cell Transplant 2009;18(1):89–99. [PubMed: 19476212]
34. Hwu P, Du MX, Lapointe R, Do M, Taylor MW, Young HA. Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation. J Immunol 2000;164(7): 3596–3599. [PubMed: 10725715]
35. Imhof BA, Aurrand-Lions M. Adhesion mechanisms regulating the migration of monocytes. Nat Rev Immunol 2004;4(6):432–444. [PubMed: 15173832]
36. Ip JE, Wu Y, Huang J, Zhang L, Pratt RE, Dzau VJ. Mesenchymal stem cells use integrin beta1 not CXC chemokine receptor 4 for myocardial migration and engraftment. Mol Biol Cell 2007;18(8): 2873–2882. [PubMed: 17507648]

37. Jacobsen K, Kravitz J, Kincade PW, Osmond DG. Adhesion receptors on bone marrow stromal cells: in vivo expression of vascular cell adhesion molecule-1 by reticular cells and sinusoidal endothelium in normal and gamma-irradiated mice. Blood 1996;87(1):73–82. [PubMed: 8547679]
38. Jarvinen L, Badri L, Wettlaufer S, Ohtsuka T, Standiford TJ, Toews GB, Pinsky DJ, Peters-Golden M, Lama VN. Lung resident mesenchymal stem cells isolated from human lung allografts inhibit T cell proliferation via a soluble mediator. J Immunol 2008;181(6):4389–4396. [PubMed: 18768898]
39. Jiang XX, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, Mao N. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 2005;105(10):4120–4126. [PubMed: 15692068]
40. Johansson U, Rasmusson I, Niclou SP, Forslund N, Gustavsson L, Nilsson B, Korsgren O, Magnusson PU. Formation of composite endothelial cell-mesenchymal stem cell islets: a novel approach to promote islet revascularization. Diabetes 2008;57(9):2393–2401. [PubMed: 18519803]
41. Johnson GB, Brunn GJ, Platt JL. Cutting edge: an endogenous pathway to systemic inflammatory response syndrome (SIRS)-like reactions through Toll-like receptor 4. J Immunol 2004;172(1):20–24. [PubMed: 14688304]
42. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 2007;449(7162):557–563. [PubMed: 17914389]
43. Kollet O, Petit I, Kahn J, Samira S, Dar A, Peled A, Deutsch V, Gunetti M, Piacibello W, Nagler A, Lapidot T. Human CD34(+)CXCR4(-) sorted cells harbor intracellular CXCR4, which can be functionally expressed and provide NOD/SCID repopulation. Blood 2002;100(8):2778–2786. [PubMed: 12351385]
44. Krampera M, Glennie S, Dyson J, Scott D, Laylor R, Simpson E, Dazzi F. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 2003;101(9):3722–3729. [PubMed: 12506037]
45. Kunter U, Rong S, Djuric Z, Boor P, Muller-Newen G, Yu D, Floege J. Transplanted mesenchymal stem cells accelerate glomerular healing in experimental glomerulonephritis. J Am Soc Nephrol 2006;17(8):2202–2212. [PubMed: 16790513]
46. Kuo TK, Hung SP, Chuang CH, Chen CT, Shih YR, Fang SC, Yang VW, Lee OK. Stem cell therapy for liver disease: parameters governing the success of using bone marrow mesenchymal stem cells. Gastroenterology 2008;134(7):2111–2121. [PubMed: 18455168]
47. Lama VN, Smith L, Badri L, Flint A, Andrei AC, Murray S, Wang Z, Liao H, Toews GB, Krebsbach PH, Peters-Golden M, Pinsky DJ, Martinez FJ, Thannickal VJ. Evidence for tissue-resident mesenchymal stem cells in human adult lung from studies of transplanted allografts. J Clin Invest 2007;117(4):989–996. [PubMed: 17347686]
48. Lauffenburger DA, Horwitz AF. Cell migration: a physically integrated molecular process. Cell 1996;84(3):359–369. [PubMed: 8608589]
49. Le Blanc K, Rasmusson I, Sundberg B, Gotherstrom C, Hassan M, Uzunel M, Ringden O. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 2004;363(9419):1439–1441. [PubMed: 15121408]
50. Li H, Fan X, Houghton J. Tumor microenvironment: the role of the tumor stroma in cancer. J Cell Biochem 2007;101(4):805–815. [PubMed: 17226777]
51. Li H, Guo Z, Jiang X, Zhu H, Li X, Mao N. Mesenchymal stem cells alter migratory property of T and dendritic cells to delay the development of murine lethal acute graft-versus-host disease. Stem Cells 2008;26(10):2531–2541. [PubMed: 18635870]
52. Liechty KW, MacKenzie TC, Shaaban AF, Radu A, Moseley AM, Deans R, Marshak DR, Flake AW. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. Nat Med 2000;6(11):1282–1286. [PubMed: 11062543]
53. Liotta F, Angeli R, Cosmi L, Fili L, Manuelli C, Frosali F, Mazzinghi B, Maggi L, Pasini A, Lisi V, Santarlasci V, Consoloni L, Angelotti ML, Romagnani P, Parronchi P, Krampera M, Maggi E, Romagnani S, Annunziato F. Toll-like receptors 3 and 4 are expressed by human bone marrow-derived mesenchymal stem cells and can inhibit their T-cell modulatory activity by impairing Notch signaling. Stem Cells 2008;26(1):279–289. [PubMed: 17962701]

54. Luster AD, Alon R, von Andrian UH. Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol 2005;6(12):1182–1190. [PubMed: 16369557]
55. Lutz MB, Schuler G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? Trends Immunol 2002;23(9):445–449. [PubMed: 12200066]
56. Ma Q, Jones D, Borghesani PR, Segal RA, Nagasawa T, Kishimoto T, Bronson RT, Springer TA. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. Proc Natl Acad Sci USA 1998;95(16):9448–9453. [PubMed: 9689100]
57. Mackay F, Loetscher H, Stueber D, Gehr G, Lesslauer W. Tumor necrosis factor alpha (TNF-alpha)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55. J Exp Med 1993;177(5):1277–1286. [PubMed: 8386742]
58. Mansilla E, Marin GH, Sturla F, Drago HE, Gil MA, Salas E, Gardiner MC, Piccinelli G, Bossi S, Petrelli L, Iorio G, Ramos CA, Soratti C. Human mesenchymal stem cells are tolerized by mice and improve skin and spinal cord injuries. Transplant Proc 2005;37(1):292–294. [PubMed: 15808623]
59. Meisel R, Zibert A, Laryea M, Gobel U, Daubener W, Dilloo D. Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. Blood 2004;103(12):4619–4621. [PubMed: 15001472]
60. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. Cell 2001;106(3):255–258. [PubMed: 11509172]
61. Menon LG, Picinich S, Koneru R, Gao H, Lin SY, Koneru M, Mayer-Kuckuk P, Glod J, Banerjee D. Differential gene expression associated with migration of mesenchymal stem cells to conditioned medium from tumor cells or bone marrow cells. Stem Cells 2007;25(2):520–528. [PubMed: 17053212]
62. Moretta L, Bottino C, Pende D, Castriconi R, Mingari MC, Moretta A. Surface NK receptors and their ligands on tumor cells. Semin Immunol 2006;18(3):151–158. [PubMed: 16730454]
63. Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN, Barrera JL, Mohar A, Verastegui E, Zlotnik A. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001;410(6824):50–56. [PubMed: 11242036]
64. Nagai Y, Garrett KP, Ohta S, Bahrun U, Kouro T, Akira S, Takatsu K, Kincade PW. Toll-like receptors on hematopoietic progenitor cells stimulate innate immune system replenishment. Immunity 2006;24(6):801–812. [PubMed: 16782035]
65. Nauta AJ, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE. Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells. J Immunol 2006;177(4):2080–2087. [PubMed: 16887966]
66. Nemeth K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, Mezey E. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009;15(1):42–49. [PubMed: 19098906]
67. Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci USA 2001;98(18):10344–10349. [PubMed: 11504914]
68. Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, Phinney DG. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci USA 2003;100(14):8407–8411. [PubMed: 12815096]
69. Palecek SP, Loftus JC, Ginsberg MH, Lauffenburger DA, Horwitz AF. Integrin-ligand binding properties govern cell migration speed through cell-substratum adhesiveness. Nature 1997;385(6616):537–540. [PubMed: 9020360]
70. Peled A, Petit I, Kollet O, Magid M, Ponomaryov T, Byk T, Nagler A, Ben-Hur H, Many A, Shultz L, Lider O, Alon R, Zipori D, Lapidot T. Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. Science 1999;283(5403):845–848. [PubMed: 9933168]
71. Pevsner-Fischer M, Morad V, Cohen-Sfady M, Rousso-Noori L, Zanin-Zhorov A, Cohen S, Cohen IR, Zipori D. Toll-like receptors and their ligands control mesenchymal stem cell functions. Blood 2007;109(4):1422–1432. [PubMed: 17038530]

72. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284(5411):143–147. [PubMed: 10102814]
73. Ponte AL, Marais E, Gallay N, Langonne A, Delorme B, Herault O, Charbord P, Domenech J. The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities. Stem Cells 2007;25(7):1737–1745. [PubMed: 17395768]
74. Rameshwar P. IFNgamma and B7-H1 in the immunology of mesenchymal stem cells. Cell Res 2008;18(8):805–806. [PubMed: 18679174]
75. Ridger VC, Wagner BE, Wallace WA, Hellewell PG. Differential effects of CD18, CD29, and CD49 integrin subunit inhibition on neutrophil migration in pulmonary inflammation. J Immunol 2001;166 (5):3484–3490. [PubMed: 11207307]
76. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol 2005;33(2):145–152. [PubMed: 15891110]
77. Ruoslahti E. Fibronectin in cell adhesion and invasion. Cancer Metastasis Rev 1984;3(1):43–51. [PubMed: 6324988]
78. Ruster B, Gottig S, Ludwig RJ, Bistrian R, Muller S, Seifried E, Gille J, Henschler R. Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells. Blood 2006;108 (12):3938–3944. [PubMed: 16896152]
79. Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. Clin Exp Immunol 2007;149 (2):353–363. [PubMed: 17521318]
80. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm (Lond) 2005;2:8. [PubMed: 16045800]
81. Sackstein R. The lymphocyte homing receptors: gatekeepers of the multistep paradigm. Curr Opin Hematol 2005;12(6):444–450. [PubMed: 16217160]
82. Sackstein R, Merzaban JS, Cain DW, Dagia NM, Spencer JA, Lin CP, Wohlgemuth R. Ex vivo glycan engineering of CD44 programs human multipotent mesenchymal stromal cell trafficking to bone. Nat Med 2008;14(2):181–187. [PubMed: 18193058]
83. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, Muroi K, Ozawa K. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 2007;109(1): 228–234. [PubMed: 16985180]
84. Schmidt A, Ladage D, Schinkothe T, Klausmann U, Ulrichs C, Klinz FJ, Brixius K, Arnhold S, Desai B, Mehlhorn U, Schwinger RH, Staib P, Addicks K, Bloch W. Basic fibroblast growth factor controls migration in human mesenchymal stem cells. Stem Cells 2006;24(7):1750–1758. [PubMed: 16822883]
85. Segers VF, Van Riet I, Andries LJ, Lemmens K, Demolder MJ, De Becker AJ, Kockx MM, De Keulenaer GW. Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms. Am J Physiol Heart Circ Physiol 2006;290(4):H1370–1377. [PubMed: 16243916]
86. Sheng H, Wang Y, Jin Y, Zhang Q, Zhang Y, Wang L, Shen B, Yin S, Liu W, Cui L, Li N. A critical role of IFNgamma in priming MSC-mediated suppression of T cell proliferation through up-regulation of B7-H1. Cell Res 2008;18(8):846–857. [PubMed: 18607390]
87. Sivori S, Pende D, Bottino C, Marcenaro E, Pessino A, Biassoni R, Moretta L, Moretta A. NKp46 is the major triggering receptor involved in the natural cytotoxicity of fresh or cultured human NK cells. Correlation between surface density of NKp46 and natural cytotoxicity against autologous, allogeneic or xenogeneic target cells. Eur J Immunol 1999;29(5):1656–1666. [PubMed: 10359120]
88. Sordi V, Malosio ML, Marchesi F, Mercalli A, Melzi R, Giordano T, Belmonte N, Ferrari G, Leone BE, Bertuzzi F, Zerbini G, Allavena P, Bonifacio E, Piemonti L. Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. Blood 2005;106(2):419–427. [PubMed: 15784733]
89. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells 2006;24(1):74–85. [PubMed: 16099998]

90. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood 2008;111(3):1327–1333. [PubMed: 17951526]
91. Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. Blood 2006;107(4):1484–1490. [PubMed: 16239427]
92. Springer TA. Adhesion receptors of the immune system. Nature 1990;346(6283):425–434. [PubMed: 1974032]
93. Standeven KF, Ariens RA, Grant PJ. The molecular physiology and pathology of fibrin structure/function. Blood Rev 2005;19(5):275–288. [PubMed: 15963835]
94. Steingen C, Brenig F, Baumgartner L, Schmidt J, Schmidt A, Bloch W. Characterization of key mechanisms in transmigration and invasion of mesenchymal stem cells. J Mol Cell Cardiol 2008;44(6):1072–1084. [PubMed: 18462748]
95. Terness P, Bauer TM, Rose L, Dufter C, Watzlik A, Simon H, Opelz G. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: mediation of suppression by tryptophan metabolites. J Exp Med 2002;196(4):447–457. [PubMed: 12186837]
96. Terry RW, Kwee L, Levine JF, Labow MA. Cytokine induction of an alternatively spliced murine vascular cell adhesion molecule (VCAM) mRNA encoding a glycosylphosphatidylinositol-anchored VCAM protein. Proc Natl Acad Sci USA 1993;90(13):5919–5923. [PubMed: 7687058]
97. Tomchuck SL, Zwezdaryk KJ, Coffelt SB, Waterman RS, Danka ES, Scandurro AB. Toll-like receptors on human mesenchymal stem cells drive their migration and immunomodulating responses. Stem Cells 2008;26(1):99–107. [PubMed: 17916800]
98. Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. Transplantation 2003;75(3):389–397. [PubMed: 12589164]
99. Valenick LV, Hsia HC, Schwarzbauer JE. Fibronectin fragmentation promotes alpha4beta1 integrin-mediated contraction of a fibrin-fibronectin provisional matrix. Exp Cell Res 2005;309(1):48–55. [PubMed: 15992798]
100. van Poll D, Parekkadan B, Cho CH, Berthiaume F, Nahmias Y, Tilles AW, Yarmush ML. Mesenchymal stem cell-derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. Hepatology 2008;47(5):1634–1643. [PubMed: 18395843]
101. Wang J, Guan E, Roderiquez G, Calvert V, Alvarez R, Norcross MA. Role of tyrosine phosphorylation in ligand-independent sequestration of CXCR4 in human primary monocytes-macrophages. J Biol Chem 2001;276(52):49236–49243. [PubMed: 11668182]
102. Werr J, Xie X, Hedqvist P, Ruoslahti E, Lindbom L. beta1 integrins are critically involved in neutrophil locomotion in extravascular tissue In vivo. J Exp Med 1998;187(12):2091–2096. [PubMed: 9625769]
103. Woodside DG, Kram RM, Mitchell JS, Belsom T, Billard MJ, McIntyre BW, Vanderslice P. Contrasting roles for domain 4 of VCAM-1 in the regulation of cell adhesion and soluble VCAM-1 binding to integrin alpha4beta1. J Immunol 2006;176(8):5041–5049. [PubMed: 16585601]
104. Wright SD. Toll, a new piece in the puzzle of innate immunity. J Exp Med 1999;189(4):605–609. [PubMed: 9989974]
105. Wu TC. The role of vascular cell adhesion molecule-1 in tumor immune evasion. Cancer Res 2007;67(13):6003–6006. [PubMed: 17616653]
106. Wynn RF, Hart CA, Corradi-Perini C, O'Neill L, Evans CA, Wraith JE, Fairbairn LJ, Bellantuono I. A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 2004;104(9):2643–2645. [PubMed: 15251986]
107. Yokokawa M, Ohnishi S, Ishibashi-Ueda H, Obata H, Otani K, Miyahara Y, Tanaka K, Shimizu W, Nakazawa K, Kangawa K, Kamakura S, Kitamura S, Nagaya N. Transplantation of mesenchymal stem cells improves atrioventricular conduction in a rat model of complete atrioventricular block. Cell Transplant 2008;17(10–11):1145–1155. [PubMed: 19181209]

108. Zanjani ED, Flake AW, Almeida-Porada G, Tran N, Papayannopoulou T. Homing of human cells in the fetal sheep model: modulation by antibodies activating or inhibiting very late activation antigen-4-dependent function. Blood 1999;94(7):2515–2522. [PubMed: 10498625]

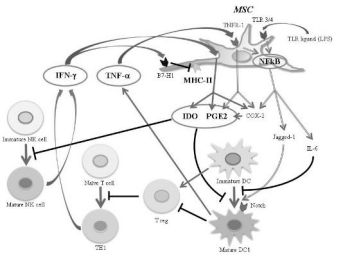

Figure 1. Mechanism of antigen presentation and immunomodulation

At low levels of IFN-γ, MSC express MHC-II as APCs and at high levels of IFN-γ, MHC-II is downregulated and B7-H1 is upregulated. IFN-γ, and TNF-α individually stimulate MSCs to upregulate PGE2, COX-2 and/or IDO. These mediators can inhibit T-cell, NK-cell, and DC function. MSC expresses TNFR and TLR which regulates NFkB activation. This pathway modulates the cytokine secretion from MSCs and the inhibition of T-cell proliferation.

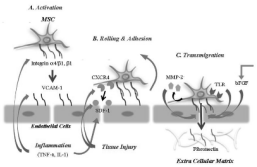

Figure 2. Mechanism of homing

A) MSCs express integrin β1 and/or integrin α4/β1 complex stimulated by cytokines such as TNFα and IL-1. They home to VCAM-1 expressed endothelial cells that are primed by local inflammation. B) MSCs can express CXCR4 stimulate by tissue injury and modulate cell-cell contact and rolling with endothelial cells that upregulate SDF-1 due to tissue injury, such as hypoxia. C) Finally, MSCs transmigrate into extracellular matrix by interactions with integrins and fibronectin which is modulated by bFGF, TLR signaling, or MMP-2 expressed by MSCs.