Summary. Human bone marrow is a reservoir containing cells with different self-renewal capabilities, such as mesenchymal stem cells (MSC) and hematopoietic stem cells (HSC). MSC in particular have been increasingly used in preclinical and clinical treatment of tissue regenerative disorder. Understanding the molecular mechanisms underlying MSC homing and mobilization is critical to the design of rational cell therapy approaches. In this review, we will discuss the key molecular mechanisms that govern the homing of MSC to bone marrow, the mobilization of MSC to tumors and injured sites via circulation, and strategies that enhance MSC migration.

Key words: Mesenchymal stem cells, Migration, Tumor tropism

Introduction

Mesenchymal stem cells (MSC), also known as mesenchymal stromal cells, are non-hematopoietic stem cells that can be isolated from various tissues, such as bone marrow, adipose tissue, umbilical cord, cord blood and Wharton’s jelly. Thus far, MSC are identified according to the criteria set forth by the International Society for Cell Therapy that described MSC as plastic adherent cells that express CD73, CD90 and CD105; are immunonegative for the monocyte and macrophage marker CD14, hematopoietic markers CD34 and CD45, and the Major Histocompatibility Complex (MHC) class II surface receptor HLA-DR; can be differentiated into osteoblasts, adipocytes and chondrocytes when cultured in defined medium (Dominici et al., 2006). Besides mesodermal lineage-specific differentiation, neuronal and astrocytic-lineage differentiation were also observed (Wislet-Gendebien et al., 2005; Li et al., 2011). The multipotent potential of MSC renders it an excellent cell source for regenerative medicine. MSC have been used in clinical trials for the treatment of myocardial infarction (Behfar et al., 2010; Jorgensen et al., 2010; Trachtenberg et al., 2011), spinal cord injury (Bhanot et al., 2011; Park et al., 2012), cartilage and bone injury (Qi et al., 2012). Moreover, MSC are poorly immunogenic due to low expressions of MHC class I and absence of MSC class II (Barry et al., 2005), rendering it ideal for treating inflammation-associated disorders such as graft-versus-host disease (GVHD) (reviewed by Sato et al. (2010)) and Crohn’s disease (Duijvestein et al., 2010; Ciccocioppo et al., 2011). To date, the most impressive effect of MSC in regeneration and tissue repair was observed in the treatment of GVHD after allogeneic transplantation of HSC, whereby infusion of MSC into patients with steroid resistant grade III and IV disease markedly improved clinical response with no side effects or toxicity (Le Blanc et al., 2008; Prasad et al., 2011).

In the laboratory, MSC have been shown to migrate to and stimulate repair of pancreatic islet and renal glomeruli in a model of diabetes in NOD/SCID mice (Lee et al., 2006). In addition, MSC migrated to coronary artery occlusion-induced ischemic brain following intrathecal administration promoted neurological recovery and reduced ischemic damage (Lim et al., 2011). MSC also supported hematopoietic stem cells (HSC) transplantation in the bone marrow microenvironment and hematopoietic recovery after myeloablative therapy (Koc et al., 2000). Because a tumor is known as a “wound that never heals,” it was hypothesized that the tumor milieu may be an ideal environment for the engraftment of exogenous MSC. Indeed, MSC were found to specifically home to and
integrate into melanoma and orthotopic glioma when administered systemically (Studeny et al., 2002, 2004; Nakamizo et al., 2005). Although local or systemic transplantation of MSC has proven to be beneficial and suggests a potential for clinical use, the migration of MSC towards the target region is not well elucidated. In this article, we will review the signaling cascade that has been implicated in the mobilization of MSC to and from bone marrow with emphasis on its tumor tropism properties (Fig. 1).

**Signals that govern the homing of MSC to the bone marrow versus mobilization into the circulation**

MSC mobilization has been postulated to be similar to the migration of leukocytes and HSC. Leukocyte migration is well documented and involves the activation and presentation of selectins on the cell surface, which initiates leukocyte rolling. This is followed by cell adhesion that involves molecules such as vascular cell adhesion molecule (V-CAM) and its interacting protein, very late antigen (VLA)-4, and hyaluronic acid/CD44, followed by transendothelial migration that is facilitated by matrix metalloproteinases (MMP) (Ley et al., 2007; Woodfin et al., 2010; Hess and Allan, 2011). HSC migration involves the interaction of chemokine (C-X-C) receptor (CXCR)-4 with its ligand, stromal cell-derived factor (SDF)-1 (also known as chemokine (C-X-C motif) ligand (CXCL)-12) (Peled et al., 1999; Brxmeyer et al., 2005; Dar et al., 2006), which not only directs migration of HSC, is also implicated in regulating survival and engraftment of the cells. Activation of SDF-1 has been shown to stimulate the migration of stem cells from the bone marrow reservoir into circulation (Dar et al., 2006). Furthermore, SDF-1-induced migration of MSC could be effectively inhibited by CXCR4-specific antagonist AMD 3100 (Ryu et al., 2010; Song et al., 2010; Park et al., 2011). However, only a small fraction of MSC has been shown to express functional cell surface CXCR4 receptors, although intracellular CXCR4 could be detected (Wynn et al., 2004; Brooke et al., 2008). Findings from Ip and
Molecules involved in MSC migration

co-workers suggested that MSC do not require CXCR4 for myocardial migration and engraftment (Ip et al., 2007). At present, it is difficult to conclude the precise role of CXCR4 in MSC migration due to the transient cell surface expression of CXCR4. Even though CXCR4 may be present in the bone marrow (Wynn et al., 2004) and ischemic tissues (Kubo et al., 2009), it is often absent on the surface of culture-expanded MSC, especially during late cell passage (Honczarenko et al., 2006). Thus, further studies are required to delineate the role of CXCR4/SDF1 axis in MSC migration.

Apart from CXCR4, MSC also respond to growth factors, chemokines and cytokines released from injury sites. MSC are known to express a broad range of chemokine receptors including CXCR1, CXCR3, CXCR4, CXCR5, CXCR6, chemokine (C-C motif) receptor (CCR)-1, CCR2, CCR3, CCR4, CCR5, CCR9 and others. Recent results from Middleton lab suggested that chemokines such as CXCL12, CXCL13, CXCL16, chemokine (C-C motif) ligand (CCL)-11 and CCL22 and their receptors can enhance the bidirectional migration of MSC to and from the bone marrow niche (Smith et al., 2012). There is evidence to suggest that specific chemokines are involved in the unidirectional migration of MSC. For example, CXCL16 (ligand for CXCR6) was most effective in the homing of MSC into the bone marrow, while CCL22 (ligand for CCR4) has the strongest chemotactic effect in mobilizing MSC from the bone marrow into the circulation (Smith et al., 2012). CXCL16 is present in most organs and inflammation-associated cancers such as prostate cancer cells, lung carcinoma, hepatocellular carcinoma and colorectal cancer (Darash-Yahana et al., 2009). In normal physiological conditions, CCL22 are expressed in macrophage, monocyte-derived dendritic cells and thymus (Katou et al., 2001). CCL22 expression could also be detected in malignant brain and ovarian cancers, and are found closely associated with infiltrated regulatory T cells (Tregs) (Curiel et al., 2004; Jacobs et al., 2010), suggesting that CCL22/CXCR4 signaling may be involved in mobilization of monocytes and T lymphocytes to pathological lesions. Given that CXCL16 and CCL22 are detectable in tumors, it is plausible that the mobilization cues to injury site and tumor are similar to those that direct MSC into the bone marrow.

Mobilization of MSC to tumor

The tumor microenvironment resembles an inflamed site, with a repertoire of macrophages, mast cells, myeloid progenitors and endothelial cells et cetera that orchestrate tumor metastasis, growth and neo-vascularization. Changes in the tumor microenvironment will thus affect MSC migration. Solid tumors are often hypoxic as a result of inadequate oxygen supply, and tumors with increased hypoxia are known to express elevated levels of pro-inflammatory mediators, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1. Most of these factors and cytokines act in a paracrine fashion on MSC to activate signaling pathways involved in cell motility. For instance, recruitment of MSC to breast cancer cells is enhanced via the binding of IL-6 secreted by the tumor cells to the corresponding receptors on the MSC (Rattigan et al., 2010). Likewise, hypoxia upregulates hypoxia-inducible factor (HIF)-1α expression and enhances the promoter activity of hepatocyte growth factor (HGF) (Rosova et al., 2008), TNF-α (Teo et al., 2012) and platelet-derived growth factor (PDGF) (Bos et al., 2005). In this section, we will briefly introduce these factors, their receptors and their role in mediating tumor-specific MSC migration.

TNF-α

TNF-α is a pro-inflammatory cytokine that binds to TNF- Receptor 1 (TNF receptor superfamily member 1A (TNFRSF1A); CD120a; p55TNFR) and TNF-β (TNFRSF1B; CD120b; p75TNFR) and is secreted by macrophages (Verma et al., 2012). Furthermore, TNF-α regulates the expression of various cytokines, chemokines, soluble factors and MMPs that may play a role in MSC migration. Pre-treatment of MSC with TNF-α was shown to upregulate HGF (Zhang et al., 2010), CXCR4 (Egea et al., 2011), MMP-2, MT1-MMP and other MMPs (Ries et al., 2007) expression and activity. Increased transcriptions of these proteases are associated with enhanced invasive potential of MSC. TNF-α also increased the expression of cytokines and chemokines such as IL-8, MCP-1 and IL-6 (Lee et al., 2010), which mediate MSC migration through the activation of urokinase plasminogen activator (uPA) and its receptors (uPAR) on human tumor cells (Gutova et al., 2008). TNF-α may also increase the adherence properties of MSC to endothelial cells during extravasation (Segers et al., 2006) by upregulation of cell adhesion molecules such as intercellular cell adhesion protein (ICAM-1, CD54) (Fu et al., 2009), VCAM-1 (Xiao et al., 2012) and neural CAM (N-CAM) (Shi et al., 2012). High resolution imaging techniques showed that the adhesion of MSC to endothelial cells is VCAM dependent; blocking antibodies to VCAM-1 and its ligand VLA-4 inhibited TNF-α-mediated MSC adhesion and transmigration through the endothelial cells (Teo et al., 2012). Other molecules that are known to be upregulated by TNF-α include CCR4, a receptor for CCL22 that has been shown to attract MSC.

HGF/c-Met

HGF, also known as scattered factor, is secreted by stromal fibroblast and smooth muscle cells while its receptor c-Met is expressed on MSC (Neuss et al., 2004). HGF/c-Met signaling has been shown to promote hepatocytes and endothelial cell proliferation, and to regulate the interaction between epithelial and mesenchymal cells during development (Morishita et al., 2012).
1998). Because HGF/c-Met signaling also plays a role in angiogenesis (Morishita et al., 1998), and HGF expression has been shown to be activated by tissue injury, it has been suggested that HGF/c-Met signaling may facilitate wound healing and tissue regeneration through the recruitment of stem cells (Neuss et al., 2004). Indeed, intramuscular injection of MSC overexpressing HGF into dilated myocardium improved ventricular function, enhanced angiogenesis, suppressed fibrosis and increased recruitment of cardiac progenitor cells (Shabbir et al., 2009). Furthermore, Janowska-Wieczorek and colleagues found that MSC from either bone marrow or umbilical cord migrated towards HGF-rich environment (Son et al., 2006), thus confirming the role of HGF/c-Met signaling in MSC migration. The migration of MSC to injured tissues is well established, although not much has been reported regarding its role in MSC migration toward tumors. It was recently found that HGF expression in MSC is upregulated by the pro-inflammatory molecule TNF-α (Zhang et al., 2010). Since tumor cells express a high level of TNF-α, it is reasonable to speculate that MSC will migrate toward the tumor areas in response to HGF stimuli. HGF directed MSC migration was recently shown in a glioma model, whereby elevated HGF expression induced by aminolaevulinic acid-mediated photodynamic therapy (ALA/PDT) facilitated the migration of MSC toward U87 and U251 glioblastoma spheroids (Vogel et al., 2013).

**PDGF/PDGFR signaling**

The PDGF family of proteins comprises four different polypeptide chains encoded by different genes: PDGF-A, PDGF-B, PDGF-C and PDGF-D. Dimerization of PDGFs facilitates their binding to their corresponding homo- and hetero-dimeric receptors, PDGFR-α and PDGFR-β, which in turn activates downstream signaling that includes the activation of phosphoinositide-3-kinase (PI3K), Akt and extracellular signal-regulated kinases (ERK). MSC migration toward tumor has been suggested to be mediated by PDGF-AA, -BB and -AB (Fiedler et al., 2004; Hata et al., 2010) and PDGF-D (Gondi et al., 2010) via the interaction with PDGF receptors expressed on MSC (Hata et al., 2010), and can be abolished upon treatment with PDGF inhibitor (Beckermann et al., 2008). PDGFR-mediated MSC migration could also involve the interaction between activated PDGFs with integrin α5β1 (Veevers-Lowe et al., 2011) or neuropilin (Nrp-1) (Ball et al., 2010a); the complex (PDGF/α5β1 and PDGFR/Nrp-1) leads to enhanced PI3K and Akt activity, membrane ruffling, network reorganization and increased cell migration towards PDGF-BB. In fact, PDGFRα+/Lin- bone marrow MSC can be mobilized into the circulation by extracellular high mobility group box 1 (HMGB1) protein secreted by injured tissues (Tamai et al., 2011), confirming the chemotactic effect of recombinant HMGB1 on MSC as observed by Meng et al. (2008). The mechanism of HMGB1-mediated MSC mobilization maybe similar to the recruitment of inflammatory cells to injured tissues. At the injury site, heterocomplex formed between HMGB1 and SDF-1 acts through CXCR4 to enhance the recruitment of monocytes (Schiraldi et al., 2012). Alternatively, HMGB1 interaction with Toll-like receptor 4 may also promote MSC migration (Pevsner-Fischer et al., 2007; Waterman et al., 2010). In a similar fashion, PDGF-BB stimulated MSC migration may involve transforming growth factor (TGF)-β signaling, which was recently demonstrated to mediate the homing of MSC toward gliomas through its interaction with TGFβ-receptor III expressed on MSC (Shinojima et al., 2013). Interaction of other angiogenic molecules that are secreted under hypoxic stress, such as vascular endothelial growth factor (VEGF) (Schichor et al., 2006; Beckermann et al., 2008; Liu et al., 2011) and basic fibroblast growth factor (bFGF) (Langer et al., 2009), with their receptors also regulate MSC migration toward areas of neovascularization (Ritter et al., 2008).

**Chemokine signaling**

A number of chemokine and cytokine signaling pathways have been associated with migratory activities of MSC. In particular, MCP-1/CCR2, Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES)/CCR5, thymus expressed chemokine (TECK)/CCR9, and SDF-1/CXCR4 have been implicated in tumor mediated migration (as summarized in Table 1).

CCL2, also known as MCP-1, is a 76-amino acids chemokine that mediates the recruitment of monocytes and macrophages during inflammation by binding to CCR2 (Strieter et al., 1996). CCL2 modulates angiogenesis, metastasis, and the establishment of pre-metastatic niche for circulating cancer cells (Ueno et al., 2000; Lu et al., 2006). Human MSC, which expresses CCR2, have been shown to migrate toward MCP-1-containing medium derived from primary cultures of various cancer patient tissues (Dwyer et al., 2007; Huang et al., 2007; Klopp et al., 2007). The role of MCP-1 is exemplified in a mouse model of breast carcinoma treated with low dose irradiation, whereby a high level of MCP-1 expression enhanced the tropism and engraftment of MSC to the tumor region (Dwyer et al., 2007; Klopp et al., 2007). The level of MCP-1 expression not only correlates with the level of MMPs (MT1-MMP/MMP14) and the angiogenic factor thymidine phosphorylase, it also correlates with the extent of breast cancer progression and macrophage accumulation (Saji et al., 2001). The finding that secretion of MCP-1 was enhanced in co-culture of MSC with breast cancer cells when compared with those grown individually (Molloy et al., 2009) suggested that MCP-1/CCR signaling may play a role beyond tumor tropism of MSC, of which the precise function of MSC inside the tumor has yet to be elucidated.
CCL25 is expressed predominantly in the thymus and epithelium of the small intestine, and is known to mediate chemotaxis of T cells through its receptor CCR9 (Papadakis et al., 2001). In some tumor models, the expression and activation of CCR9 has been shown to influence the migration and invasiveness of tumor cells such as melanoma (Amerisi et al., 2008), prostate carcinoma (Singh et al., 2004), breast carcinoma (Johnson-Holiday et al., 2011) and ovarian cancers (Johnson et al., 2010). In human MSC, CCR9 is expressed at high levels (~64%) by flow cytometry analysis (Chamberlain et al., 2008). The ligand, CCL25, is expressed in primary human multiple myeloma cells (Xu et al., 2012) and has been shown to act as chemotactants for MSC and periosteal progenitor cells (Stich et al., 2008; Binger et al., 2009). Targeted knockdown of CCR9 in murine MSC was shown to significantly affect its migratory activity toward multiple myeloma cells when compared with the CCR9 wildtype MSC, although the presence of wildtype MSC has been suggested to favor myeloma growth in vivo (Xu et al., 2012).

MMPs in MSC migration

Successful homing of MSC to their target tissue implies that MSC are able to extravasate from the circulation and intravasate into the target tissues, survive during the migration process and finally interact with cells in the target microenvironment. The extravasation and intravasation entail degradation of the extracellular matrix (ECM) that requires the action of proteolytic enzymes such as MMPs, which are zinc-dependent endopeptidases (Ravanti and Kahari, 2000). All MMPs have a common domain structure that includes a propeptide region and a furin cleavage site, a catalytic domain with a zinc-binding region, and a hemopexin-like C-terminal domain. To date, there are 23 MMPs, and these MMPs are classified into several subgroups.

<table>
<thead>
<tr>
<th>Types</th>
<th>Molecules involved in tumor tropism of MSC.</th>
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<tbody>
<tr>
<td>Angiogenic factors</td>
<td>c-Met HGF PDGF-AA; PDGF-BB; PDGF-D</td>
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<tr>
<td>Angiogenic factors</td>
<td>PDGFR/integrin α5β1/Neuropilin-1</td>
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<tr>
<td>VEGFR-1</td>
<td>VEGF; Placental growth factor (PIGF)</td>
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<tr>
<td>FGFR</td>
<td>Basic fibroblast growth factor</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR1 CCL2/MIP-1alpha; CCL7/MCP-3; CCL14/HCC-1; CCL15/MIP-1delta; CCL16/HCC-4; CCL23/MPIF-1</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR2 CCL2 (MCP-1/MCAF); IL-8; GRO-α</td>
</tr>
<tr>
<td>Chemokine/Cytokines</td>
<td>CCR3 CCL3 (MIP-1α)</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR4 CCL16 (TARC) &amp; CCL22 (MDC)</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR5 CCL5 (RANTES)</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR7 CCL19 (MIP-3) &amp; CCL21 (6CKine)</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CCR9 CCL25 (TECK)</td>
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<td>Chemokine/Cytokines</td>
<td>CXCR1 GCP-2; IL8</td>
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<tr>
<td>Chemokine/Cytokines</td>
<td>CXCR2 GRO-α/βγ; ENA-78; GCP-2; NAP-2; IL-8</td>
</tr>
<tr>
<td>Chemokine/Cytokines</td>
<td>CXCR4 CXCL12 (SDF-1)</td>
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including collagenases (MMP-1), stromelysin (MMP-3 and MMP-10), matrilysin (MMP-7 and MMP-26), gelatinase (MMP-2 and MMP-9) and membrane type MMP (MT-MMP). One of the main functions of MMPs is to cleave molecules in the ECM and the stromal environment leading to activation of the cleaved molecule in most instances. For example, cleavage of plasminogen by MMP-3, 7, 9 and 12 yield an anti-angiogenic molecule, angiotatin, which is otherwise inactive in the plasminogen state (Chakraborti et al., 2003).

Among the various MMPs, MSC have been shown to secrete MMP-2, MT1-MMP (Ries et al., 2007) and MMP-1 (Ho et al., 2009). Gene knockdown of MMP-2 and MT1-MMP inhibited MSC invasion through the ECM in vitro whereas inflammatory cytokines such as TGF-β, IL-1, and TNF-α upregulated MMP-2 and MT1-MMP-mediated migration (Ries et al., 2007). Wnt-mediated upregulation of MT1-MMP promotes the activation of pro-MMP-2, thus increasing the migratory activities of MSC. By contrast, the ternary complex of pro-MMP-2 with tissue inhibitors of metalloproteinase (TIMP)-2 facilitates the activation of the zymogen by the surface tethered-MT1-MMP. Along the same line, it is reasonable to speculate that MMP-1 synergizes with other MMPs to mobilize MSC because MMP activity is a necessary component of growth factor-mediated cell migration.

In an attempt to determine the molecular pathways involved in the differential migration between the highly migratory and poorly migratory MSC, we performed microarray analysis on representative MSC isolates and found that MMP-1 activity and protein expression was higher in the highly migratory MSC versus those that do not migrate well (Ho et al., 2009). Importantly, the migratory activity can be abolished by RNA interference-mediated knockdown of MMP-1. Results from our laboratory further suggested that MMP-1 mediates MSC migration through its interaction with its cognate receptor, protease activated receptor-1 (PAR-1), because blockade of MMP-1/PAR-1 interaction abolished the migration of both adult (Ho et al., 2009) and fetal (Newman et al., 2011) MSC. Our more recent result suggested that MMP-1 negatively regulates the level of CXCR4 in MSC (unpublished observation), which might provide another reason for the low response of MSC toward SDF-1 and why only a small population of MSC express functional CXCR4 receptors. However, activation of SDF-1/CXCR-4 axis regulates MMP-1 transcription through ERK signaling (Sun et al., 2010), thus suggesting that MMP-1/PAR-1 axis crosstalk with SDF-1/CXCR4 axis to mobilize MSC. Aside from MMP-1, SDF-1/CXCR4 was also shown to interact with other MMPs, such as MMP-2. In the context of lung alveolar epithelial cells, CXCR4 antagonist or knockdown of CXCR4 using small interference RNA markedly reduced cell migration and MMP-2 activities (Ghosh et al., 2012). Also, there is connectivity between MMP-2 and CXCR4 in the homing and engraftment of MSC to tumors. Song et al., showed that MMP-2 expression was elevated after 2 hours exposure to conditioned media from tumor cells and decreased after 24 hours, while the reverse was true for CXCR4 (Song and Li, 2011), demonstrating that MSC migration is a multistep process.

**Enhancement of MSC migration**

By further understanding the molecules and signaling pathway involved in MSC migration, we can potentially increase the migration activities of MSC through several methods. Genetic modification of MSC to express certain growth factors or chemokine/cytokine receptors on their surface could increase their migration to a specific target. For example, overexpression of CXCR4 in human umbilical cord blood-derived MSC (hUCB-MSC) and bone marrow-derived MSC enhanced its migration towards gliomas (Park et al., 2011) and infarcted heart (Freyman et al., 2006; Yu et al., 2010; Huang et al., 2012). Similarly, genetic modification of poorly migratory MSC with MMP-1 significantly enhanced their migration in vitro and in vivo (Ho et al., 2009). In the same vein, one could overexpress other receptors such as CCR2 (receptor for MCP-1, IL-8 and GRO-α) and CCR5 (receptor for CCL5, RANTES) to direct MSC migration specifically to ischemic brain, injured myocardium or wound (Table 1).

In addition to genetic modification of MSC, it has been suggested that preconditioning MSC with pro-inflammatory cytokines mentioned in the previous section could increase migration of MSC. Priming MSC with these molecules could lead to global changes in the proteome profile that may impact the expression of ECM-modifying proteins, enzymes etc. In a bilateral murine breast carcinoma mouse model, the hind limb that was irradiated recruited more migratory MSC when compared with the non-irradiated hind limb of the same animal. The enhancement in MSC engraftments seems to have been mediated by higher levels of paracrine factors secreted after irradiation and by an upregulation of CCR2 (Klopp et al., 2007). Along the same line, irradiated LoVo colorectal carcinoma recruited more MSC and had a higher level of MCP-1 expression when compared with the non-irradiated control group (Zielske et al., 2009); while Kim et al showed enhanced recruitment of MSC to the irradiated glioma xenograft through upregulation of IL-8 expression (Kim et al., 2010). Macrophage inhibitory factor (MIF) is a pleiotropic cytokine that induced the expression of pro-inflammatory molecules as well as MMPs (reviewed by Sanchez-Nino et al., 2013)) and was recently shown to inhibit MSC migration through its interaction with its receptor, CD74 (Barrilleaux et al., 2010; Fishe-Valuck et al., 2010). On the other hand, antagonizing CD74 eliminated its inhibitory effect on MSC migration. Thus, inhibiting CD74 prior to and during MSC infusion may allow accumulation of MSC in the target site. The examples illustrated above highlighted that manipulation

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of the inflammatory response may improve MSC mobilization. Alternatively, inhibiting SDF-1/CXCR4 axis using CXCR4 antagonist, AMD3100, in combination with VEGF facilitated egress of MSC from the bone marrow into the circulation (Pitchford et al., 2009; Pitchford and Rankin, 2012). Taken together, the ability to enhance the migration and engraftment of MSC suggested the usefulness of the above mentioned techniques in overcoming the issues of low percentage of engraftment of MSC in the clinics.

Concluding remarks

MSC are increasingly being used in clinical trials worldwide. Although these cells are easily obtainable and expandable, the varied homing efficiency of MSC restricts its therapeutic efficacy. Despite the many factors involved in MSC migration, multiple studies have shown that only a subset of MSC possesses strong migratory properties (Francois et al., 2006; Majenburg et al., 2010). Thus, it would be ideal if one could isolate the highly migratory subset of MSC based on cell surface markers, a task which is not feasible currently. Furthermore, because molecules that are expressed at the inflamed site resemble those expressed in the tumor, suppression of inflammation may inhibit MSC recruitment and affect the overall therapeutic efficacy (Kidd et al., 2010). Thus, understanding the mechanism of MSC migration will help to develop an ideal delivery protocol in the clinics, including the optimal route of delivery for a particular disease and the dosage of transplanted cells required.

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Molecules involved in MSC migration


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