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**Biological, chemical and mechanical factors regulating migration and homing of mesenchymal stem cells**

Szydlak R. Factors regulating migration and homing of MSCs

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**Abstract**

Mesenchymal stem cells (MSCs) are a population of primary and non-specialized cells, which can be isolated from various tissues. Currently, MSCs are key players in cellular therapy and regenerative medicine. However, the possibility of using MSCs in the treatment of many diseases needs to be preceded, though, by in-depth analysis of their properties, especially by determining the mechanism of tissue homing as well as the mechanism, due to which cells contribute to tissue regeneration. This review is intended to present information on recent findings regarding the mechanism of recruitment and tissue homing by MSCs and discuss current hypotheses for how MSCs can reach target tissues.

**Key Words:** Mesenchymal stem cell; Cell migration; Regenerative medicine; Mesenchymal stem cell-based therapy

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**Core Tip:** Mesenchymal stem cells (MSCs) have been extensively studied for their therapeutic potential in clinical practice and regenerative medicine. MSCs can migrate towards damaged tissue and act as reservoirs for regenerative molecules and growth factors. Consequently, MSC-based therapies rely on the successful migration of these cells into the damaged tissue following administration. Here we look at the factors influencing the migration and colonization of damaged tissues by MSCs.

**INTRODUCTION**

Mesenchymal stem cells (MSCs) are a population of primary and non-specialized cells, which can be isolated from various tissues. Friedenstein *et al*[1] described a bone marrow-derived fibroblast-like cell for the first time, which later became the most extensively studied MSC and are sometimes regarded as the “gold standard.” Later, these cells were identified in nearly every tissue type (peripheral blood, adipose tissue, bone marrow, dental pulp)[1-4]. The human umbilical cord (UC), cord blood, placenta, and amniotic fluid have been shown to contain MSCs[5,6].

Independently of the tissue source, the harvested cells must have common characteristics to be defined as the MSCs. Therefore, to organize the nomenclature and define the characteristics of human MSCs, the International Society for Cellular Therapy proposed three minimum criteria characterizing human MSCs[7]. Accordingly, to classify cells as MSCs cumulatively three conditions must be met by cells: (1) adhere to plastic during *in vitro* cultivation; (2) express a set of surface markers, CD73, CD90, and CD105, simultaneously lacking CD34, CD45, CD14, CD11b, CD79a, CD19 and the major histocompatibility complex class II; and (3) demonstrate multipotency and significant plasticity of trilinear differentiation to osteoblasts, adipocytes, and chondrocytes[7,8]. Even though a wide range of selection markers defining MSCs was identified, no single marker specific to them has been indicated.

Because of their unique properties, MSCs provide extraordinary therapeutic potential that is used to treat a wide range of disorders. MSCs show high proliferative potential and the ability to differentiate into derived cell lines from all germ leaves. Also, these cells have unique immunomodulatory properties and the ability of directional migration in response to inflammatory factors, and the ability to colonize damaged tissues, where they participate in their regeneration[9]. MSCs have a special ability to secrete many biological factors, including cytokines and growth factors, involved in various processes conducive to tissue remodeling, such as angiogenesis and immunomodulation, but these cells may stimulate endogenous repair mechanisms[10-12].

The success of MSC-based therapy depends on MSC homing efficiency, which here means the ability of these cells to reach the damaged tissue. This process is possible thanks to their ability to adhere, migrate, and implant in the target tissue. The homing process can be accomplished with both local and systemic injections (Figure 1)[13]. For local injection, MSCs are transplanted into the target tissue and then directed to the site of injury *via* a proinflammatory cytokine gradient. In systemic injection, MSCs are administered into the bloodstream and then have to go through a multistep process to leave the circulation and move to the site of the injury. In this case, it is assumed that MSCs exhibit migration mechanisms similar to leukocytes. However, it should be emphasized that they occur with the participation of other adhesion molecules, and MSCs are larger than leukocytes[13]. The therapeutic effectiveness and tissue colonization by MSCs are influenced by several factors that can be divided into biological (*e.g.,* the presence of adhesive molecules, cell source, donor age, doubling rate), biochemical (*e.g.,* cytokines, chemokines, growth factors), and biophysical (*e.g.,* cell size, cell deformability, shear force). There are also other factors such as cultivation conditions, method of cell administration, number of injected and implanted cells, general health of the host, and compliance of the recipient[14-18]. This review summarizes information about the factors influencing tissue migration and colonization by MSCs.

**ROUTES OF THERAPEUTIC CELL DELIVERY**

The site used for the administration of MSCs for therapeutic purposes can influence the route taken by cells to reach the desired destination[19]. For therapy, MSCs can be administered through intracardiac, intra-arterial (IA), intraperitoneal, or intravenous (IV) injection. Although intravenous administration is least invasive, more excellent engraftment rates were demonstrated by IA and intracardiac administration as compared to IV administration in models of myocardial infarction[20-22]. They administered radiolabeled cells in models with brain injury and found that IA injection in the extracranial right internal carotid artery (near target) led to greater homing of cells in the brain as compared to IV injection in the femoral vein. Walczak *et al*[22] demonstrated that the IA injection near the desired organ gave better results than IV injection at a distant point[22]. In cases of IV administration, MSCs accumulated in filtering parts of the body such as the spleen, liver, or lung, but this accumulation was reduced in cases of IA injection[20,23,24]. However, there was a higher chance of microvascular occlusions with IA injection, a condition known as passive entrapment[22]. In cases of IA and intracardiac administration, a significantly more MSCs were able to reach and engraft at an ischemic site as the cells bypassing the lungs.

The intraperitoneal administration of MSCs is occasionally used. It was used to administer MSCs to fetuses in mice with muscular dystrophy as IV injection was considered to be inappropriate for this particular case[25]. The donor cells were detected in muscular as well as non-muscular tissues. Finally, one can also use the method of local delivery by injection of MSCs directly into the target site. Beggs *et al*[26] administered Dil-labeled MSCs into baboons through IV injection but could not detect cells in limb muscles[26].

On the other hand, when they injected the cells directly into the muscle, DiO-labeled MSCs could be caught there[26]. However, Muschler *et al*[27] reported that this method is not feasible in most clinical cases because it is too invasive, particularly in the brain or heart[27]. Moreover, locally injected cells may die before their role in healing because of a limited supply of oxygen and nutrients.

Because intravascular infusion is the most common form of therapy, it is crucial to understand the mechanisms by which MSCs might be delivered to the microcirculation, become adherent to the walls of blood vessels and subsequently migrate through them. It is also useful to consider whether endogenous MSCs can circulate ‘normally’ in the blood.

**BIOLOGICAL FACTORS INVOLVED IN THE MIGRATION OF MSCs**

***Tissue origin and culture conditions***

Most research to date has focused on the behavior of exogenous bone marrow MSCs (BM-MSCs), which may differ from MSCs obtained from other sources. Recent work suggests that MSCs obtained from perinatal tissues for therapeutic purposes may have more advantages, such as better cell availability and ethical aspects. Sheriff *et al*[28] conducted a study comparing the adhesive properties of UC-MSCs and BM-MSCs and their interactions with platelets, which may be of particular importance for systemic injections[28]. This study showed that UC-MSCs had a greater ability to adhere to extracellular matrix proteins compared to BM-MSCs and that UC-MSCs also caused platelet activation[28]. In another comparative study by Alanazi *et al*[29], BM-MSCs, UC-MSCs, and tubercular-MSCs isolated from trabecular bone were tested. They showed that there were some differences in adhesive properties as well as in migration through the porous filter[29].

The migration properties of MSCs can also be influenced by cultivation conditions. Rombouts *et al*[30] showed that freshly isolated MSCs have higher tissue colonization capacity compared to *in vitro* cultured cells[30]. Probably this is the result of aging and differentiation of MSCs under *in vitro* culture conditions[31,32]. Culture conditions also have a significant impact on the homing capacity as they can modify the expression of surface markers involved in this process. For example, hypoxia and the presence of cytokines [*e.g.*, interleukin (IL)-6, hepatocyte growth factor] can regulate the expression of the chemokine receptor (CXCR)4 receptor, which is involved in the migration of MSCs[33,34].

***Adhesion molecules supporting MSCs migration***

Exogenous MSCs injected into the body can bind non-specifically in microvessels or with adhesion molecules such as integrins, bind to endothelial cells or extracellular matrix proteins (*i.e.* collagen, fibronectin, laminin), and then transmigrate through the endothelium and basal membrane to tissues[35-39]. MSCs are thought to use the same migration mechanism as leukocytes[13]. However, in contrast to the well-described mechanisms of leukocyte adhesion and migration, the mechanism of tissue homing by MSCs has not yet been fully understood, even though many studies are assessing MSC adhesive molecules and possible mechanisms of vascular wall adhesion and migration (Table 1) as well as the role of chemokines in guiding MSCs to target tissues[40].

Before MSCs migrate through the vessel wall, they “crawl” on its surface, looking for the best place for adhesion and then transmigration through the endothelium (Figure 1)[13]. Interactions of integrins that are expressed in the MSC cell membrane and adhesion molecules on the endothelial surface [(vascular cell adhesion molecule (VCAM)-1) and intercellular adhesion molecule (ICAM)] can lead to the formation of so-called docking structures and transmigration wells that are sites rich in ICAM-1, VCAM-1 molecules, proteins, and cytoskeleton components (*e.g.*, α-actinin).

If the homing concept is correct, tissues would need to recruit circulating MSCs from the flow to ensure effective delivery to damaged sites. For this purpose, MSCs have on their surface many different adhesion molecules shared by leukocytes. These adhesion molecules include CD24, CD29 (β1-integrin), CD44, and CD49a-f (α1-α6-integrin), although other studies found no CD24[41,42]. Adhesion molecules that are found on endothelial cells are also expressed by MSCs. These molecules include VCAM-1, ICAM-1, and ICAM-2[43].

It seems that the number and type of adhesion molecules found to be present on MSCs may be influenced by the source of MSCs and the method used for their isolation and culture. For example, adhesion molecules expressed by MSCs at passage four and passage six were found to be different[44]. There was a linear relationship between passage number and the expression of CD49, but a decrease in the expression of CD44 was noted at passage six. However, other reports indicated no difference between the molecules expressed by MSCs at passages 3, 5, and 7 (*e.g.*, CD73, CD90, and CD105)[45]. Concerning the origin of MSCs, it was found that adhesion molecules expressed by MSCs isolated from bone marrow and those isolated from adipose tissue differed. Differences in expression were noted for cell adhesion molecules CD49d (integrin α4), CD54 (ICAM-1), CD34, and CD106 (VCAM-1) with large variation in CD106 (VCAM‑1) and CD54 (ICAM-1)[45]. It is therefore likely that the source and methods of isolation and expansion must be taken into consideration when evaluating adhesive properties of MSC adhesion.

Several mechanisms involving different adhesion molecules have been proposed for recruiting flowing MSCs to the vasculature. During a study on MSC recruitment to the vasculature in mice, Rüster *et al*[42] found that P-selectin and α4β1-integrin/VCAM-1 played a significant role in recruitment in venules[42]. In comparison with the wild-type controls, the P‑selectin-/- mice demonstrated a lesser degree of MSCs rolling in the ear venules. The function of other adhesion molecules was also investigated through *in vitro* studies that made use of endothelial cells as a substrate for the adhesion. During a flow-based assay, the number of MSCs demonstrating adherence decreased considerably when P-selectin was blocked on the tumor necrosis factor-α (TNF-α)-treated endothelial cells[42]. However, it was found that MSCs neither expressed P‑selectin glycoprotein ligand-1 (CD162) nor the alternative P-selectin ligand, CD24, on their surface[42]. In the same study, adherence of MSCs to the TNF-α-treated endothelial cells was found to be reduced after blocking α4β1-integrin or VCAM-1 to a similar degree to each other, showing a role for this pathway[42]. It should be highlighted that in these studies the flow was reduced to very low shear stress to allow attachment followed by an increase in flow to “washout.” In another study, small numbers of MSCs adhered to cytokine-treated endothelial cells after prolonged perfusion at 0.1 Pa, also through VCAM-1[46].

In the studies conducted by Luu *et al*[47], MSCs were also perfused over endothelial cells treated with TNF-α[47]. It was found that MSC adhesion was negligible at a wall shear stress of 0.05 Pa, which resembles the low end of venular shear. If the flow was decreased to 0.01 Pa to allow attachment, then washed out at 0.05 Pa, adhesion could be detected on stimulated but not unstimulated endothelial cells[47]. MSCs adhered in large numbers if allowed to remain stationary and in contact with endothelial cells for 30 min before washout at 0.05 Pa. Chamberlain *et al*[48] also found little adhesion of perfused MSCs to endothelial cells unless flow was stopped, and the cells were allowed to settle before washing out[48]. These data suggested that attachment of flowing MSCs in intact vessels would be rare under normal circulatory conditions, but that MSCs could adhere to endothelium only if already arrested or trapped[48].

A wide range of different cells express the glycoprotein CD44 on their surface, which can act as a ligand to allow adhesion *via* several other molecules, including hyaluronan[49]. Its role as a ligand for P-selectin has also been reported, and it may be the ligand for P‑selectin expressed by MSCs. Studies indicate that hematopoietic cells E-/L-selectin ligand is capable of binding with E-selectin[50,51]. While MSCs have a high expression of CD44 molecules on their surface, it was found that MSC adhesion was not decreased by blocking E-selectin on endothelial cells[42]. However, other researchers have found CD44 on MSCs to interact with E-selectin[52].

The molecular mechanisms involved in mouse MSC recruitment to the heart were investigated in animals suffering myocardial infarction[53]. Upregulation of several genes was recorded in the heart after infarct, and these included the genes for *VCAM-1* , *ICAM-1-1*, and *E‑selectin*. Recruitment of murine MSCs in the infracted myocardium decreased when MSCs were treated with the antibody against β1-integrin. Blockade of α4β1-integrin (CD49d/CD29) did not affect recruitment, and the particular α-integrin subunit working in this process was not identified, although the presence of α9-, α6- and α8-integrins were demonstrated[53].

So far, several adhesion molecules have been identified to be involved in MSC transendothelial migration. These include very late antigen-4 (VLA-4), VCAM-1, ICAM-1, and P-selectin[42,53]. Adhesive particles, including integrins, selectins, and chemokine receptors, are involved in the rolling, adhesion, and transmigration of MSCs. MSCs have been shown to express a diversity of receptors associated with intercellular contacts and adherence to extracellular matrix proteins, such as integrins α1, α2, α3, α4, α5, αv, β1, β3 and β4, and other adhesive molecules, *i.e.* VCAM-1, ICAM-1, ICAM-3, and CD166. Some studies have shown that the interaction of MSCs with the endothelium is mediated by P-selectin. Other studies have shown that E-selectin and L-selectin are not expressed in the MSC cell membrane. and their involvement in the interaction with the wall of blood vessels is not significant[42]. It has also been reported that, if present, this mechanism only has an indirect function due to the strong interaction of VLA-4/VCAM-1 particles, which are crucial receptors for MSC transendothelial migration. Steingen *et al*[54] reported that MSCs can migrate through non-activated endothelium using VLA-4/VCAM-1 molecules and tend to integrate with the endothelial layer instead of undergoing full diapedesis. Among the integrin family, integrin α4β1, which is a cell surface heterodimer and mediates cell-cell and cell-environment contact, plays an essential role in migration and chemotaxis. However, because transendothelial migration of MSCs has not been entirely blocked by anti-VLA-4 and anti-VCAM-1 antibodies, it can be assumed that other integrins are also involved in this process[54].

***Participation of platelets in the migration of MSCs***

Platelets have been reported to be involved in the recruitment of MSCs in both *in vitro* and *in vivo* models. In a flow-based adhesion assay, Langer *et al*[55] noticed an increase in the recruitment of MSCs to human arterial endothelial cells when the endothelial cells were preincubated with platelets[55]. In particular, preincubation with platelets caused more excellent MSC adhesion in comparison with the activation of endothelial cells with IL-1β. *In vivo* studies generated results that followed these findings. MSC adhesion was found to be decreased considerably in a murine model with carotid artery injury after treatment with anti-GPIb and platelet-depleting antibody. It was also demonstrated that αvβ3-integrin blockade reduced the adhesion of platelets to immobilized MSCs[55]. In a model of pulmonary arterial hypertension, infused rat MSCs protected a rise in right-sided blood pressure and cardiac hypertrophy[56]. MSCs were found in the lung, and their adhesion there was reduced by blockade of P-selectin and GpIIbIIIa. The same receptors were found to support the attachment of MSCs along with platelets to collagen in an *in vitro* flow assay. It was concluded that platelets mediated MSC homing to the lung. In a recent study, there was preferential trafficking of infused MSCs to an inflamed *vs* control ear, but this was decreased if platelets were depleted from the blood[57]. Direct observation of microvessels showed MSCs were adherent along with platelets and neutrophils. The above studies strongly suggest that MSCs will interact with platelets in the blood and that this interaction will modify their behavior *in vivo*.

**BIOCHEMICAL FACTORS INVOLVED IN THE MIGRATION OF MSCS**

***Cytokines, chemokines, and growth factors controlling trafficking of MSCs***

In MSC trafficking, chemokines released from tissues and endothelial cells can promote the activation of ligands involved in adhesion, migration, chemotaxis, and homing of MSCs in target tissues. Many reports suggest that damaged tissue releases specific factors that act as chemoattractants to facilitate the adhesion, migration, and homing of MSCs in affected areas. Studies have shown that MSCs are capable of migrating to inflamed tissues in response to factors that are regulated under inflammation[4,58,59]. To date, many chemokines and growth factors have been identified that are involved in the migration process. These include inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL‑8 and many growth factors, *e.g.*, epidermal growth factor, vascular endothelial-derived growth factor-A, fibroblast growth factor, platelet-derived growth factor (PDGF-AB), hepatocyte growth factor, transforming growth factor-β1, stromal cell-derived factor, and insulin-like growth factor (IGF‑1)[39,59-62].

Some studies have shown the expression of chemokine receptors by MSCs, including CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CCR1, CCR2, CCR4, CCR6, CCR7, CCR8, CCR9, and CCR10, and indicated the functional roles of some of them in the migration process of MSCs[60,63-65]. It has been proved that CXCR1, CXCR2, CXCR4, CCR1, CCR2, IL-8, macrophage inflammatory protein-1α, and monocyte chemoattractant protein-1 are involved in the migration of MSCs to damaged tissue[66]. Other studies have shown that the stromal cell-derived factor-1/CXCR4 axis plays an essential role in the movement of MSCs isolated from the bone marrow[67,68]. Thus, it is likely that the chemokines released from the tissues cause the intracellular CXCR4 receptor to move to the cell surface, which contributes to the migration of MSCs to the destination.

It has also been shown that an increase in IL-8 concentration in damaged tissues can activate MSC migration[63]. The active role of IL-6, PDGF, PDGFR-α, PDGFR-β, vascular endothelial growth factor receptor 1, and insulin-like growth factor-1 have been indicated in BM-MSC migration studies[66]. PDGFR is strongly expressed on the surface of BM-MSCs, and PDGF induces BM-MSCs migration. The migration test through a porous filter also showed that PDGF had a stronger effect on MSC chemotaxis than stromal cell-derived factor-1 and monocyte chemoattractant protein-1[69]. Inflammatory cytokines such as IL‑1β and TNF-α stimulate the production of matrix metalloproteinase (MMPs) by MSCs and trigger the activation of chemotactic migration through the extracellular matrix[35]. According to studies, many chemokines play a role in the induction of MSC migration, but characteristics including the settlement of MSCs require further *in vitro* and *in vivo* studies.

***Extracellular matrix remodeling enzymes***

It has also been confirmed that an essential role of MSC migration is played by proteolytic enzymes-MMPs, which regulate the degradation of the extracellular matrix[36,70]. Different MMPs and their signaling pathways have been shown to affect MSC differentiation, migration, angiogenesis, and proliferation. The migration and invasion of MSCs into damaged tissues are facilitated by the expression of CXCR4, MMP-2, and MT1-MMP[71,72].

**BIOPHYSICAL FACTORS INVOLVED IN THE MIGRATION OF MSCS**

***Influence of hemodynamic forces***

Exogenous MSCs injected into the body during migration through peripheral blood circulation towards the damaged tissue are exposed to various hemodynamic forces applied to the vessel walls, including shear stress and cyclic mechanical load. It has been observed that mechanical loads affect the migration of MSCs. As an example, studies have shown that cyclic mechanical stretching (10%, 8 h) promoted MSC migration but led to a decrease in the invasive potential of MSCs[73,74].

Shear stress is another type of force inside the blood vessels. However, few studies have focused on the effects of shear stress on MSC migration. It was observed that shear stress (approximately 0.2 Pa) promoted MSC migration in the wound healing test while higher shear stress (> 2 Pa) significantly inhibited MSC migration[75].

***Cell size, cell deformability, mechanical entrapment***

Although there is ample evidence that specific ligand-receptor pairs are involved in tissue homing MSCs, mechanical entrapment of MSCs at sites of injury or in a tumor occurs at least in part in limited environments. The key difference between MSCs and lymphocytes is their size, with cell diameters ranging from 15-30 μm to 4-12 μm, respectively[76,77]. This larger cell size, especially after *ex vivo* cultivation, can lead to the passive retention of MSCs in small diameter vessels such as terminal arterioles, capillaries, and extra-glomerular venules due to mechanical entrapment[78]. Indeed, the vast majority of MSCs administered intravenously are cleared rapidly from the blood and are found in the pulmonary capillaries within minutes of an injection[23,79,80]. In both, animal models and clinical trials, this rapid entrapment is followed by removal from the lungs and accumulation in the spleen and liver[23,79-81]. The mechanical entrapment in the lungs is because the pulmonary capillaries have a diameter of 10-15 μm[76,82-84]. Studies conducted by Dutly *et al*[84] with microspheres have shown that objects with a diameter greater than or equal to 10 μm are very susceptible to this phenomenon[84]. Importantly, endogenous MSCs in the bone marrow are smaller in size, about 10 µm, which allows efficient trade in the systemic circulation[78]. Like MSCs, it is believed that they increase in size when activated by inflammatory factors at sites of tissue damage.

It can be assumed that the ability of cells to deform may facilitate the movement of larger cells through smaller vessels[18,59,85]. Although cellular deformability may to some extent facilitate the traverse of larger cells through smaller vessels[85].

IA infusions can reduce the entrapment of MSCs in the lung by providing one pass through the systemic circulation and exposure to peripheral tissues before entering the lungs. However, mechanical confinement may still be the predominant driver of MSC biodistribution. To date, little research has been done to determine the importance of active and passive arrest in the lung or other tissues. However, it is likely that both mechanisms are important and can be manipulated to increase the efficiency of targeting MSCs.

The vast majority of exogenously injected MSCs have limited access to damaged target tissue due to mechanical entrapment. To partially overcome this barrier and improve targeting, preadministration of vasodilators such as sodium nitroprusside was used in mouse models[82,83] to reduce lung entrapment. In addition, many researchers have developed *ex vivo* expansion protocols by which MSC cultures with smaller mean cell diameters can be obtained[86,87].

**CONCLUSION**

In conclusion, although MSC-based therapies give hope for effective treatment of many incurable diseases, the low percentage of MSCs homing to damaged tissue remains a big challenge in regenerative medicine. Even though many factors have been identified to be involved in the MSC migration process, undoubtedly, one of the great needs of MSC-based therapy is the improvement of the effectiveness of MSC homing and obtaining high-grade target tissue uptake. To date, it has been observed that only a small percentage of the injected MSCs authentically reach and remain in the target tissue[88]. Why is the homing efficiency so low? Several factors are presumed to be involved. A lot of transplanted MSCs may be trapped in the lung capillaries[89,90]. Hence, to reduce lung entrapment, some research groups have taken an approach with vasodilators like heparin[76,91]. Moreover, some of the MSCs are distributed into the liver, spleen, and sites of inflammation or damage.

As discussed above, this migration of MSCs is regulated by a wide spectrum of factors. Essentially, the homing process is based on specific molecular interactions rather than passive distribution. Thus, effective migration of MSCs and implantation into the target tissue requires a high expression level of the appropriate adhesion molecules. For example, Wynn *et al*[92] observed that a small population of MSCs expressed the CXCR4 receptor and that only these cells can migrate specifically to the bone marrow[92]. Also, the expression of the surface markers involved in the homing process may be modified by culture conditions[31,60]. The methods of preparing the MSCs for injection as well as the methods of injecting these cells remain at the experimental level. Parallel studies on the biology of MSCs and clinical trials are still ongoing. While much remains to be done, addressing the basic biological mechanisms underlying tissue homing in MSCs *in vivo* will reveal new optimization pathways.

To overcome the problems with a low level of retention of regenerative cells, various strategies have been taken to improve the MSC homing as discussed elsewhere recently[93]. In general, these approaches include targeted administration, genetic modification, *in vitro* stimulation, cell surface engineering, magnetic guidance, radiotherapeutic techniques, and target tissue modification[93,94]. Many of these approaches are still debatable because many of them have not been validated *in vivo* yet. For example, targeted administration may not always be feasible or may be a highly invasive procedure depending on the target tissue. In addition, modifying MSCs does not prevent their distribution to organs other than the target. Also, modifying target tissue by chemical or genetic methods raises patient safety concerns. While it is still an active area of study, these limitations pose huge barriers to their application in the clinic. It is expected that future research will disclose which of these approaches provide the most effective treatment. Such research is essential for advancing the field of cell-based therapies and increasing the efficacy of therapies in applications ranging from immune modulation to regeneration.

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**Footnotes**

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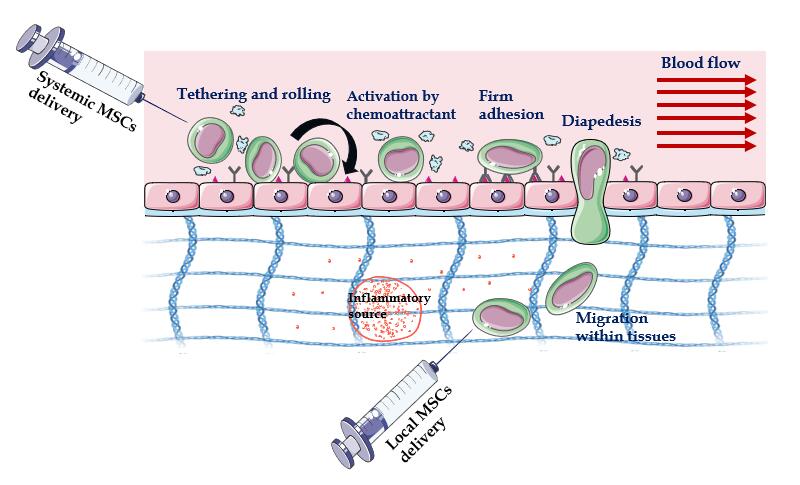
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**Figure Legends**



**Figure 1** **Mesenchymal stem cells migration cascade after injection.** MSCs: Mesenchymal stem cells.

**Table 1** **Molecules involved in migration and tissue homing by mesenchymal stem cells**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Molecules | Stage of homing | Ref. |
| Adhesion molecules | CD24, CD29, CD44, CD49a-f, CD51/61  VCAM-1, ICAM-1, ICAM-2, P‑selectin | Rolling, adhesion, transendothelial migration | Langer *et al*[55], 2009 |
| Eseonu and De Bari[66], 2015 |
| Chemokines receptors and chemokines | CXCR1/2/3/4/5/6, CCR1/2/4/6/8/9,  MIP-1α, MCP-1, SDF-1 | Chemotaxis | Kitaori *et al*[67], 2009 |
| Su*et al*[68], 2017 |
| Zhang *et al*[73], 2015 |
| Fu *et al*[74], 2019 |
| Proinflammatory cytokines and growth factors | TGF-β, IGF-1, TNF-α, IL-1β, IL-8, IL-6, IL-3, SCF, HGF, EGF, VEGF, FGF, PDGF, IGF | Chemotaxis | De Becker *et al*[70], 2007 |
| Yuan *et al*[75], 2012 |
| Gao *et al*[76], 2001 |
| Extracellular matrix metalloproteinases | MMP-1, MMP-2 | Invasion | Majumdar *et al*[43], 2003 |
| Schrepfer *et al*[82], 2007 |

VCAM: Vascular cell adhesion molecule-1; ICAM: Intercellular adhesion molecule; CXCR: Chemokine receptor; MIP-1α: Macrophage inflammatory protein-1α; MCP-1: Monocyte chemoattractant protein-1; SDF-1: Stromal cell-derived factor-1; TGF-β: Transforming growth factor-β; IGF-1: Insulin-like growth factor 1; TNF-α: Tumor necrosis factor-α; IL: Interleukin; SCF: Stem cell factor; HGF: Hepatocyte growth factor; EGF: Epidermal growth factor; VEGF: Vascular endothelial-derived growth factor; FGF: Fibroblast growth factor; PDGF: Platelet-derived growth factor; IGF: Insulin-like growth factor; MMP: Matrix metalloproteinase.