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Concise Review

Exploring mesenchymal stem cells homing mechanisms and improvement strategies

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Abstract

Mesenchymal stem cells (MSCs) are multipotent cells with high self-renewal and multilineage differentiation abilities, playing an important role in tissue healing. Recent advancements in stem cell-based technologies have offered new and promising therapeutic options in regenerative medicine. Upon tissue damage, MSCs are immediately mobilized from the bone marrow and move to the injury site via blood circulation. Notably, allogenically transplanted MSCs can also home to the damaged tissue site. Therefore, MSCs hold great therapeutic potential for curing various diseases. However, one major obstacle to this approach is attracting MSCs specifically to the injury site following systemic administration. In this review, we describe the molecular pathways governing the homing mechanism of MSCs and various strategies for improving this process, including targeted stem cell administration, target tissue modification, in vitro priming, cell surface engineering, genetic modifications, and magnetic guidance. These strategies are crucial for directing MSCs precisely to the injury site and, consequently, enhancing their migration and local tissue repair properties. Specifically, our review provides a guide to improving the therapeutic efficacy of clinical applications of MSCs through optimized in vivo administration and homing capacities.

Key words: mesenchymal stem cells; homing; improvement strategies; administration; migration; target tissue modification; priming.

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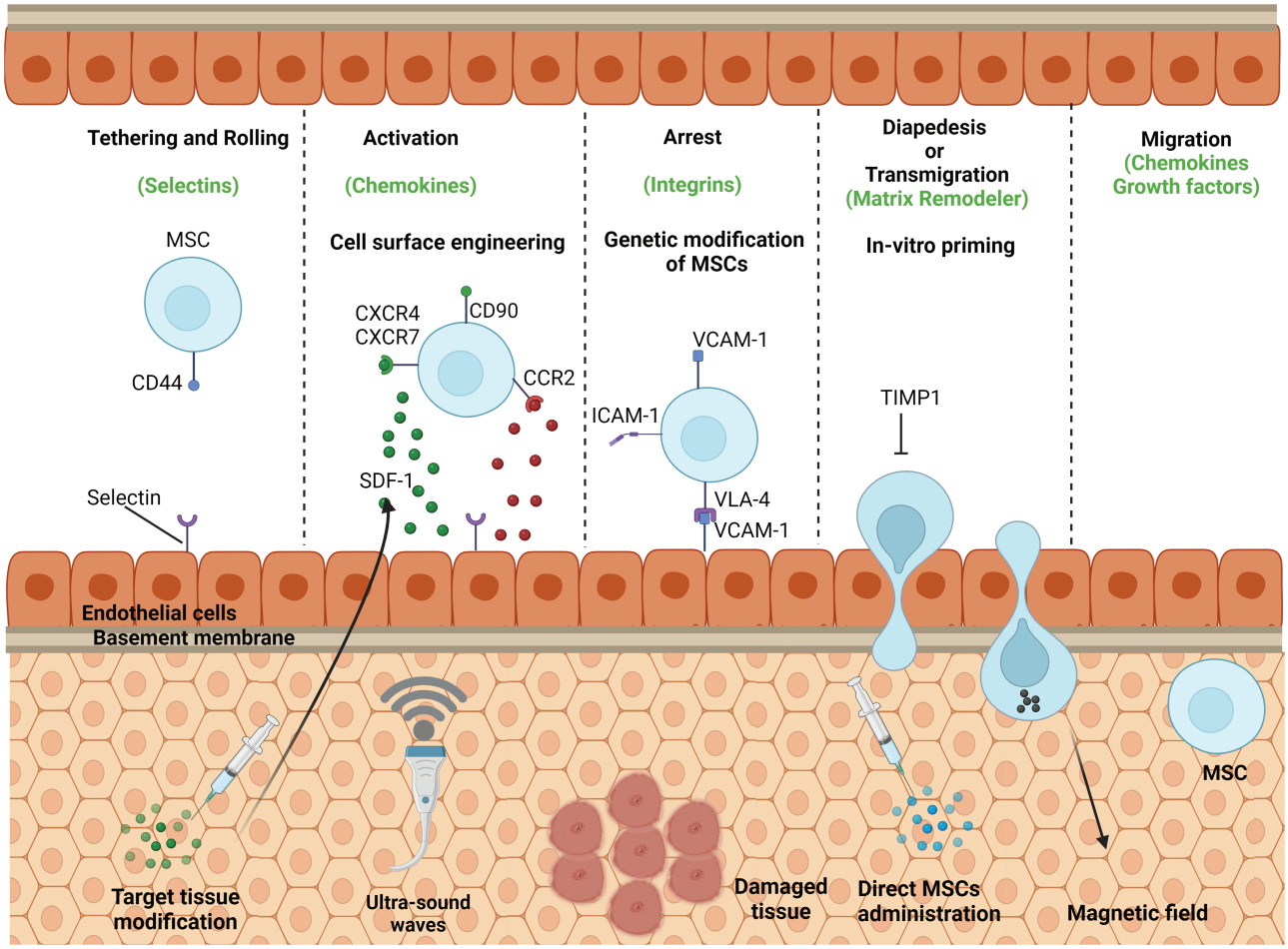
Graphical Abstract



Significance Statement

Mesenchymal stem cells (MSCs) hold tremendous potential for regenerative medicine and the treatment of currently incurable diseases. These adult multipotent progenitor cells are essential for tissue regeneration and wound repair due to their high capacity to differentiate into various tissues. Through paracrine effects, MSCs can regulate immune responses, enhance neovascularization, and improve cell survival. Moreover, MSCs have the ability to preferentially home to damaged tissues and serve as a reservoir of growth and proregenerative factors. Therefore, understanding and enhancing MSC homing efficiency at injury sites is crucial to maximizing their therapeutic effects. In this review, we analyze a variety of strategies to optimize MSC homing and foster the potential of MSC-based cell therapies in regenerative medicine.

Introduction

Adult stem cells such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) are 3 main types of stem cells. MSCs are adult multipotent progenitor cells that can differentiate into various tissues, including adipose, bone, and cartilage.[1] MSCs are characterized morphologically by a small cell body with a few cell processes that are long and thin. Importantly, those fibroblast-like cells were identified first by Friedenstein et al[1] in the 1960s. The observations of Friedenstein have laid a milestone for the later discovery of what is now known as MSCs. In 1974, Friedenstein et al[2] isolated MSCs from bone marrow for the first time. Since then, MSCs have been isolated from various other tissues, which include fetal tissue,[3] perivascular tissue,[4] muscle,[5] dermis,[5] adipose tissues,[6] and dental pulp.[7]

Based on the criteria of the International Society for Cellular Therapy MSCs show the following characteristics[8]: (1) plastic adherence; (2) positive expression of CD90, CD105, and CD73 surface markers; (3) negative expression of stem cell lineage markers including CD34, present on hematopoietic and endothelial cells, CD79a or CD19 present on B cells, and CD45 present on pan-leukocyte; (4) negative expression of myeloid markers including CD14 or CD11b; and (5) tri-lineage differentiation potential into chondrocytes, osteocytes, and adipocytes.[8] These minimal criteria must be met by MSCs isolated from any tissue. Furthermore, certain nonclassical differentiation potential of MSCs including neural,[9] hepatocytic,[10] and myoblastic[4] lineages has been demonstrated, although the neural differentiation remains controversial.

In contrast, ESCs are pluripotent stem cells that may differentiate into any mature cell of the 3 germlines after being isolated from the inner cell mass of a mouse early preimplantation blastocyst.[11] In general, stem cell-based research aims to improve therapies for currently untreatable diseases. Presently, tissues derived from stem cells, stem cell-based products, and biomaterials combined with stem cells offer a promising alternative in regenerative medicine.[12] MSCs have demonstrated superior therapeutic effects because of their ability to regulate many types of immune cells of the adaptive and innate immune systems. In particular, MSCs promote neovascularization, enhance angiogenesis, inhibit cell death, increase cell proliferation and viability, and regulate immune responses by exosomes, cell-to-cell contacts, and paracrine effects.[13,14]

Although MSC treatments have made significant advances in recent decades, several challenges remain. High levels of heterogeneity, issues regarding immune compatibility, differentiation capacity, phenotype stability, and migratory capabilities are the key points.[15] Upon tissue damage, MSCs are rapidly mobilized into the bloodstream,[16] moving to the injury site, where they create a proregenerative microenvironment for proper wound healing.[17,18] Importantly, allogenically transplanted MSCs can also home to the damaged tissue site and support the recovery process or act as activators for the regeneration of tissues. This concept underpins the therapeutic potential of the administration of MSCs for clinical purposes. Table 1 represents a summary of preclinical and clinical trials involving MSCs.[17]

Once localized at the target site, MSCs release various factors, which have angiogenic, immunomodulatory, and antiapoptotic effects.[24-26] Based on these characteristics, MSCs have been applied in clinical settings including regulation of immune response in autoimmune and inflammatory diseases, protection of tissue after injury, and regenerative medicine.[27] Therefore, the improvement of MSCs' homing efficiency is necessary since delivering MSCs to the injury site represents the key feature of their therapeutic efficacy. Hence, this review elaborates on different strategies for improving MSC homing efficiency at the molecular level.

MSCs homing mechanism

The ability of MSCs to home to damaged tissues is a key benefit and a requirement for a successful stem cell-based therapy. Therefore, it is important to first define the homing mechanism, including both systemic and nonsystemic homing.[28] In nonsystemic homing, MSCs are implanted locally at the target site, and a chemokine gradient guides them to the injury.[29] In contrast, in systemic homing, MSCs are administered into the bloodstream and migrate through a multistep process to the injury site after leaving circulation.[30]

The systemic homing can be divided into 5 distinct steps (Figure 1):

1. tethering and rolling,
2. activation,
3. arrest,
4. diapedesis or transmigration, and
5. migration.[32]

Importantly, endothelial cells express selectins which facilitate initial tethering.[33] On the other hand, CD44 is expressed by MSCs, which bind to endothelial selectins, and upon this, MSCs begin to roll on the vasculature. Table 2 depicts all important cell surface markers and integrins expressed on distinct types of MSCs.

It is known that P-selectin glycoprotein ligand-1 (PSGL-1) and the hematopoietic cell E-/L-selectin ligand (HCELL) bind to specific selectins expressed by endothelial cells, triggering initial tethering. However, in the case of MSCs, it is still not completely understood which selectins bind to MSCs, as they express neither PSGL-1 nor HCELL.[34] Some in vitro models mimicking the homing of MSCs have been reported previously.[35] Interestingly, Rüster et al[35] reconstructed a model demonstrating a coordinated sequence of adhesion steps of human MSCs with human endothelium, initiated by tethering events in a parallel plate flow chamber. The authors confirmed that the binding of human MSCs to human endothelial cells could be suppressed by anti-P-selectin antibodies, while the rolling of MSCs increased when exposed to a P-selectin-containing plate in the chamber. Since MSCs do not express PSGL-1, a different ligand is used for binding with P-selectin. In one study, galectin-1 was identified as a possible ligand for P-selectin.[38] Moreover, Bailey et al[39] identified CD24 as another potential P-selectin ligand in stromal cells derived from human adipose tissue.

G protein-coupled chemokine receptors facilitate the second step, "activation," typically in response to inflammatory signals. Animal experiments, where either the entire body or a local area was irradiated, showed higher numbers of MSCs

Table 1. Summary of preclinical trials and clinical trials involving mesenchymal stem cells (MSCs).

Disease/condition	Clinical application	Status	References
Graft-versus-host disease (GVHD)	Immunomodulation	Clinical	Dominici et al[8], Chinnadurai et al[19]
Multiple sclerosis (MS)	Neuroregeneration	Clinical	Chinnadurai et al[19]
Crohn's disease (CD)	Tissue homeostasis	Clinical	Lotfy et al[20]
Amyotrophic lateral sclerosis (ALS)	Regeneration	Clinical	Lotfy et al[20], Rendra et al[21]
Myocardial infarction (MI)	Cardiac repair	Clinical	Kahrizi et al[22]
Acute respiratory distress syndrome (ARDS)	Anti-inflammatory effects	Clinical	Lotfy et al[20]
Heart failure	Cardiac repair	Preclinical	Kahrizi et al[22]
Lung injury	Anti-inflammatory effects	Preclinical	Galipeau[23]
Liver disease	Tissue regeneration	Preclinical	Chinnadurai et al[19]

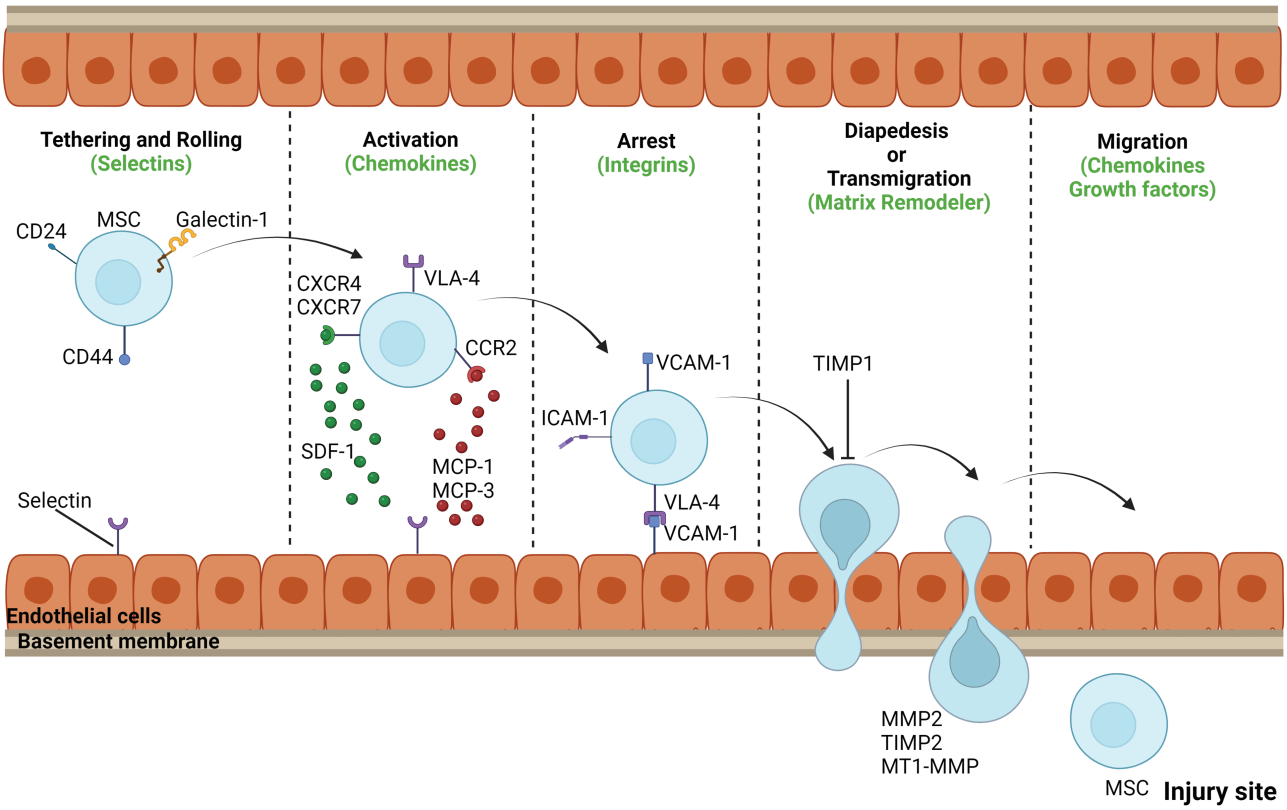


Figure 1. Overview of MSC homing mechanism. The systemic homing of MSCs comprises 5 distinct steps, including tethering and rolling, activation, arrest, diapedesis or transmigration, and migration. Tethering and rolling, which are the first steps of this mechanism, are facilitated by interactions of selectins and ligands. The second step activation is facilitated by G protein-coupled chemokine receptors, and the third step of cell arrest involves integrins. In the fourth step of diapedesis or transmigration, MSCs cross the endothelial cell layer and basement membrane by secreting matrix metalloproteinases (MMPs). In the final step, MSCs migrate to the injury site through the interstitium due to chemotactic signals released upon tissue damage. Modified from Ullah et al.[31]

Table 2. Summary of surface markers and integrins relevant to homing mechanisms and expressed on various types of MSCs.

Surface marker	Expression in MSCs	Function	MSC types	References
CD90 (Thy-1)	High expression	Associated with MSC identity and immunomodulation	Bone marrow-derived MSCs (BM-MSCs), adipose tissue-derived MSCs (AT-MSCs)	Dominici et al[8]
CD73	High expression	Involved in adenosine production and immunosuppression	BM-MSCs, AT-MSCs	Dominici et al[8]
CD105 (endoglin)	High expression	Regulates angiogenesis and tissue repair	BM-MSCs, AT-MSCs	Dominici et al[8]
CD44	High expression	Cell adhesion and migration	BM-MSCs, AT-MSCs	Sackstein et al[34]
CD273 (PD-L2)	Variable expression	Immunomodulatory role	BM-MSCs, AT-MSCs	Wu et al[29]
CD146	Variable expression	Associated with angiogenesis and tissue regeneration	BM-MSCs, AT-MSCs	Caplan et al,[13] Fan et al[14]
CD248 (endosialin)	Variable expression	Implicated in tissue remodeling and angiogenesis	BM-MSCs, AT-MSCs	Caplan et al,[13] Fan et al[14]
VLA-4 (α4β1 integrin)	Expressed by MSCs	Mediates binding to endothelial cells via its ligand VCAM-1	BM-MSCs, AT-MSCs	Rüster et al,[35] Segers et al,[36] Steingen et al[37]
VCAM-1 (vascular cell adhesion molecule-1)	Expressed by endothelial cells	Facilitates MSC binding to endothelial surfaces during inflammation		Rüster et al,[35] Segers et al,[36] Steingen et al[37]

in response to inflammation.[40] The critical factor for this step is stromal cell-derived factor-1 (SDF-1) expression on endothelial cells,[41] interacting with CXC chemokine receptors type 4 (CXCR4) expressed by MSCs.[42-44] Homing to the bone marrow was reported to increase with overexpression of CXCR4 on MSCs.[45] However, other receptors may be

involved in this process, as some studies reported that MSCs do not express CXCR4.[46]

In this regard, another receptor, CXC chemokine receptor type 7 (CXCR7), was identified to be expressed on MSCs. Like CXCR4, CXCR7 also binds to SDF-1.[47-49] Other receptors and chemokines also play crucial roles in the homing process. For example, monocyte chemoattractant protein-1 (MCP-1), an anti-inflammatory marker expressed in the myocardium of mice, enhances MSC homing by binding to its corresponding receptor, CC chemokine receptor type 2 (CCR2).[50] Mice expressing MCP-1 recruited MSCs expressing the CCR2 receptor through this interaction.[50] In another study, MSC homing was significantly increased by MCP-3 expression in the myocardium.[51] MSCs also express several other receptors, including CCR1, CCR4, CCR5, CCR6, CCR7, CXCR9, and CXCR10.[43,46] However, the roles of these receptors are not yet fully understood.

Furthermore, integrin affinity increases through conformational changes in their extracellular domains, a process also involved in the MSC activation step. Integrins are vital for cell adhesion to target tissues.[52,53] For example, Talin and Kindlin signaling molecules interact with the cytoplasmic domain of very late antigen-4 (VLA-4) upon SDF-1 stimulation, changing VLA-4 from an inactive to an active form, promoting MSC migration and binding to receptors.[54]

Integrins facilitate the third step, cell adherence. High integrin expression significantly enhances MSC adherence. Chemokines like SDF-1 activate VLA-4, an integrin expressed in MSCs. Upon activation, vascular cell adhesion molecule 1 (VCAM-1), expressed by endothelial cells, binds to activated VLA-4 integrin.[35-37] The homing of MSCs to bone marrow increases when VLA-4 integrin is overexpressed. VCAM-1 and other integrin ligands are also expressed by MSCs.[55,56]

In the final step, MSCs migrate to the injury site through the interstitium.[57] Chemotactic signals which are released upon tissue damage guide this step. MSCs move toward those specific signals which include insulin-like growth factor (IGF)-1 and platelet-derived growth factor-AB (PDGF-AB). Further, MSCs can be also attracted by chemokines like SDF-1, macrophage-derived chemokine, as well as RANTES.[57] MSCs migration toward chemokines can be increased by preincubating MSCs with tumor necrosis factor (TNF)-alpha, which upregulates their CCR2, CCR3, and CCR4 receptors.[57] MSCs migration toward sites of injury may also be promoted by inflammatory chemokines such as interleukin (IL)-8.[58,59] This chemokine also stimulates in MSCs the secretion of regenerative factors like vascular endothelial growth factor (VEGF).[60] Thus, comprehensive knowledge of molecular events that are involved in MSC homing provides different strategies for the optimization of the MSC homing process for therapeutic purposes.

Currently, MSC homing efficiency remains one of the key challenges in MSC therapies. Multiple reports suggest that only a small percentage of MSCs reach the target tissue when administered intravenously.[61-63] Several factors contribute to low MSC homing efficiency. One reason is that MSCs become trapped in the lung capillaries after intravenous administration. Anticoagulants like heparin and vasodilators have been shown to increase MSC homing to the liver and bone marrow by reducing lung trapping.[64,65] Another reason for low homing efficiency may be the reduced expression of specific homing molecules like CXCR4 on MSCs,[44,46] as homing molecule expression decreases with in vitro MSC expansion.[43,66]

Enhancing of MSCs homing efficiency

MSCs homing efficiency can be improved by a variety of approaches:

1. targeted administration,
2. target tissue modification,
3. in vitro priming,
4. cell surface engineering,
5. genetic modification,
6. magnetic guidance, and
7. radiotherapeutic techniques.

Targeted administration

Targeted administration represents a method, which can significantly improve MSCs' homing. In this method, cells are at a target site or near to it (Figure 2) instead of introducing

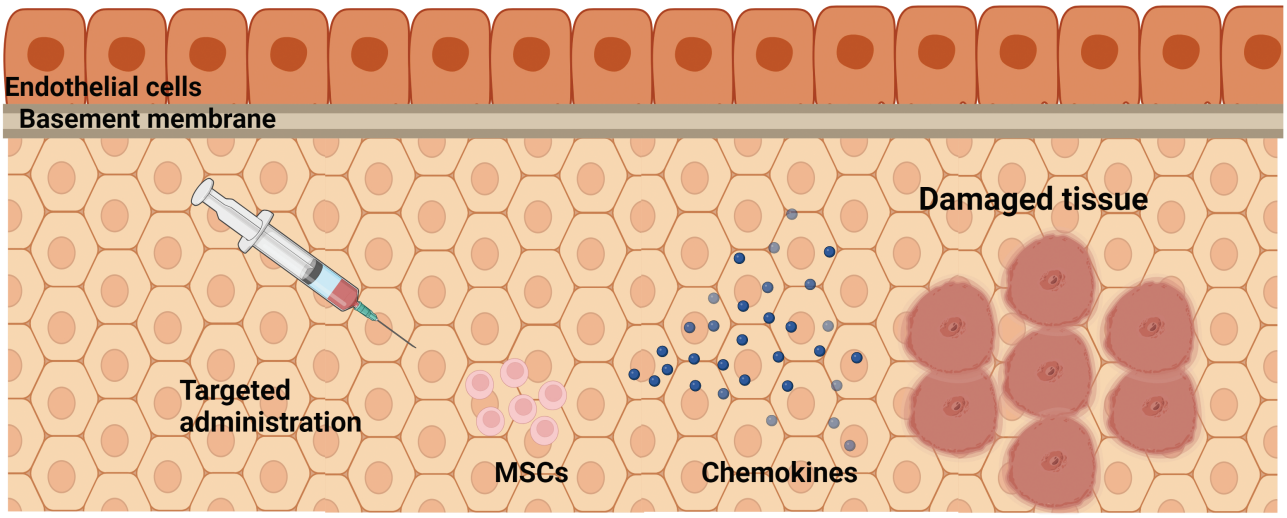


Figure 2. Targeted administration of MSCs at or near the damaged tissue. This process is called nonsystemic homing. It is the chemokines which guide the MSCs toward damaged tissue when administered near the damaged tissue. Modified from Ullah et al.[31]

them by intravenous routes. Retention of MSCs may increase by targeted administration, for example, by intracerebral application for neurological diseases, intratracheal application for lung disease, or intramyocardial injection for heart disease. A lot of research has been performed in the development of new medical technologies required for targeted administration. In particular, transcatheter injections into the myocardium have been used in several clinical trials of MSCs therapies for ischemic cardiomyopathy.[67,68]

In a porcine model, Dick et al[69]. identified infarct borders by utilizing magnetic resonance fluoroscopy. The authors delivered MSCs to the infarcted region by safely navigating the catheter to the target site. The applied MSCs were visible and detectable even after administration near the damaged tissue using MRI. This study confirmed the successful migration of MSCs into the infarct area; however, no quantification of MSCs retained in the target tissue was reported.

Targeted administration of MSCs has been described in many studies, but very few compared standard intravenous injection with targeted administration. The optimal route of MSC administration can be determined by meta-analysis. In ischemic stroke, MSCs administered intracerebrally showed the highest efficacy, with intra-arterial administration ranking second and intravenous third in improving the neurological severity score.[70] In myocardial infarction, infarct size was significantly reduced by transendocardial administration of MSCs, while no significant results were obtained with intravenous, intracoronary, or intramyocardial administration in swine models.[71] However, results differed in human trials. The intracoronary route of MSC administration performed best, whereas the intravenous route showed some improvement, and the intramyocardial route demonstrated almost no positive effect.[72]

Therefore, it cannot be assumed that administering MSCs directly to the target tissue or organ would always yield the most promising results in vivo. For example, in a porcine model of emphysema, both intrathecal and intravenous routes reduced cell damage and lung inflammation.[73] However, cardiovascular function improved only with intravenous administration, which also shifted lung macrophage phenotypes from M1 to M2 due to MSCs being trapped in the lung capillaries when administered intravenously.

Some studies explored transplanting MSC sheets instead of using MSC suspensions. MSC sheets consist of single layers of cells grown on cell culture plastic that detach spontaneously when the temperature decreases. Ishikane et al[74] treated scarred myocardium in a rat model of chronic-stage myocardial infarction by direct transplantation of MSC sheets. Rats treated with such sheets demonstrated increased capillary density, reduced myocardial fibrosis, and improved cardiac function in the infarcted region compared to untreated control rats.

Another study examined the effectiveness of intramyocardial injection versus epicardial placement of MSC sheets in ischemic cardiomyopathy rat models.[75] The authors observed increased myocardial repair with MSC sheet transplantation compared to intramyocardial injection of MSC suspensions. Kaibuchi et al[76] evaluated MSC sheet transplantation for treating osteonecrosis of the jaw. They compared the results of MSC sheet transplantation with intravenous injection, finding that the MSC sheet group exhibited improved wound healing and enhanced vascularization compared to the intravenous injection group.

In general, there are 3 reasons favoring MSC sheet transplantation over MSC suspension injection: (a) improved survival of transplanted MSCs, (b) enhanced secretion of regenerative factors, and (c) no embolism risk. Although these studies highlight the significance of targeted administration, the results are highly dependent on the tissue and disease model.

Target tissue modification

Target tissue modifications can improve the homing efficiency of MSCs as shown in Figure 3. In particular, the target tissue modification aims to increase the concentration of homing factors at the target site that enhance the infiltration of MSCs.[77] The target tissue modification includes direct injection of the homing factor, target tissue genetic modification, and implantation of a scaffold containing homing factor.[77,78]

Direct injection of homing factors

Direct injection of SDF-1 into ischemic tissue has been reported to enhance neovascularization in both the myocardium[78,79] and skeletal muscle.[80] Although MSCs were not used in these studies, Sasaki et al[78] observed an increase in the homing of bone marrow MSCs after injecting SDF-1 directly into the ischemic myocardium. Similarly, Yamaguchi et al[80] observed a 1.8-fold increase in the endogenous homing of intravenously injected endothelial progenitor cells (EPCs) following SDF-1 injection into the ischemic hind limb muscle of mice. However, SDF-1 degrades quickly due to proteolytic enzymes. To address this, Segers et al bioengineered a protease-resistant version of SDF-1 that showed prolonged binding with CXCR4. The injection of this bioengineered SDF-1 improved blood flow in cases of peripheral artery disease and enhanced cardiac function in myocardial infarction.[81,82]

Target tissue genetic modification

Some studies performed genetic modification by applying targeted tissue transfection with chemokines encoding constructs.[77] Fujii et al[83] delivered SCF-containing plasmid into the myocardium by using the UMMD (ultrasound-mediated microbubble destruction) method. In this method, the plasmids with microbubbles are injected directly into the damaged tissue. The microbubbles, which are injected along with plasmids, cavitate and generate shear stress in response to the ultrasound. This shear stress also exerts many biological effects like alteration of vascular permeability of endothelial lining that improves uptake of plasmids. This technique enhanced the expression of SDF-1 in the myocardium, as well as the homing efficiency of endogenous CXCR4-expressing progenitor cells.[83] Similarly, improved cardiac function and angiogenesis were achieved by Sundararaman et al[84] by injecting SDF-1 plasmid into the heart tissue of mice without using the UMMD method. Phase I clinical trials of this therapy without a control group were carried out with SDF-1 plasmid being delivered directly into the infarcted region of 17 ischemic cardiomyopathy patients.[85] The patients showed quality of life and walk distance improvements after 12 months in a dose-dependent manner following the treatment. In phase II (placebo-controlled study) clinical trials of this therapy, no significant difference between treatment groups and placebo groups was observed after 6-minute walk distance.[86] However, significant improvements were observed when the analysis was limited to one-third of the most severe patients. However, there are some concerns regarding target

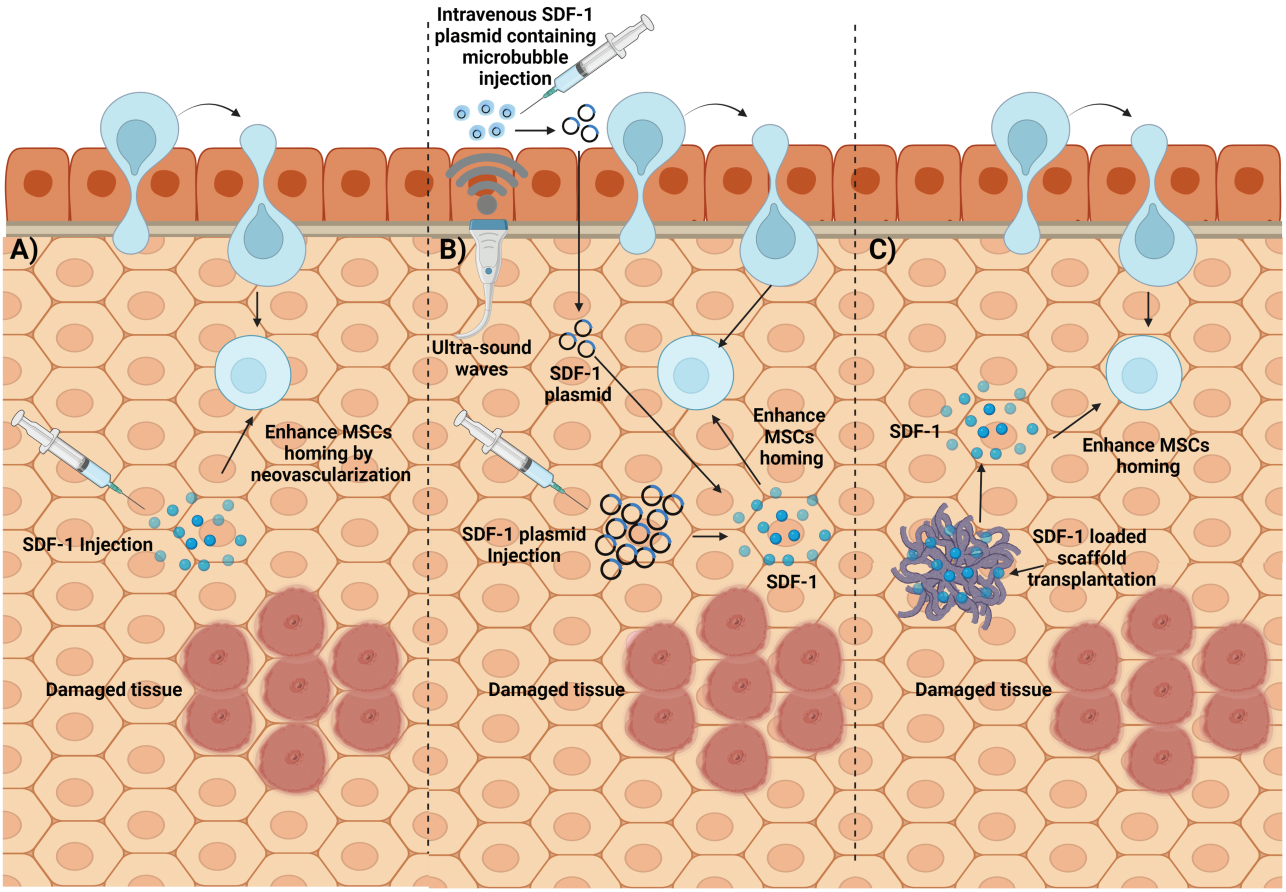


Figure 3. Target tissue modification for increasing MSCs homing efficiency. (A) Direct injection of homing factor, (B) target tissue genetic modification by direct injection of homing factor containing plasmid or by intravenous injection of homing factor containing microbubble injection followed by ultrasound-mediated microbubble destruction method, and (C) homing factor containing scaffold implantation. Modified from Ullah et al.[31]

tissue transfection due to high costs, intentional mutagenesis, and immunogenicity.

MSC engraftment rate is higher in the irradiated target tissues.[18,87] This increase is due to upregulated SDF-1 expression hence enhancing the activation stage of the homing process.[88] However, radiation therapy in human patients raises safety concerns and thus, it cannot be used clinically. Therefore, alternatives of radiation therapy showing similar improvements in the homing process of MSCs can be used as shown in Figure 4.

Ultrasound has various therapeutic applications along with its usage as a diagnostic tool.[89] Therapeutic ultrasound mainly focuses on the modifications of a target tissue. In particular, sound waves exert mechanical pressure at the target site, which induces many biological effects leveraging tissue regeneration. For example, ultrasound-mediated microbubble destruction techniques improve MSC homing as shown in Figure 3. Many studies applied this technique for increasing cardiac recovery in case of myocardial infarction.[90-92] For example, Li et al[93] observed that the ultrasound-mediated microbubble destruction (UMMMD) technique increases the proportion of CXCR4-expressing cells and enhances SDF-1 secretion in the target site. Further, the same technique promoted the homing of MSCs in the kidney by upregulating the expression of selectins, integrins, cytokines, and other trophic factors.[94] In addition, the UMMD technique was shown to induce an inflammatory response in the brain that, in turn, upregulated several trophic and inflammatory factors.[95] However, improper application of UTMD may produce undesired complications since previous studies reported the presence of erythrocyte extravasations, inflammation, and intracerebral hemorrhage within sonicated areas as the most common side effects.[96-98] Therefore, some studies started the investigation of focused ultrasound without microbubbles. In this modified method, focused pulses of highly intense sound waves are administered by pulsed focused ultrasound (pFUS) that prevents tissue damage and high temperatures.[99] Burks e al.[100] demonstrated that pFUS generated a chemical gradient in the muscle leading to upregulated expression of proinflammatory cytokines and chemokines, which play a crucial role in tissue remodeling and repair processes. For example, cell adhesion molecules such as VCAM-1 and ICAM-1, growth factors, and cytokines show increased expression upon treatment. pFUS establishes a local chemical gradient by activating TNF-alpha, which further triggers the signaling cascade of cyclooxygenase-2 (Cox2) leading to upregulation of many homing factors and cytokines.[101] pFUS enhanced homing of MSCs by 4-fold in limb ischemia mouse models compared to MSCs alone, hence improving clinical outcomes.[102] Similar results were obtained in the kidney by using pFUS,[103] which activated IL-1α and TNF-alpha in the kidney upregulating Cox2 and the NF-κB pathways.[104] Moreover, Jang et al[105] observed that pFUS initially increases TNF-alpha, which causes upregulation of growth factors and cytokines in the heart. However, further studies are required to determine the long-term effects of pFUS, but the research

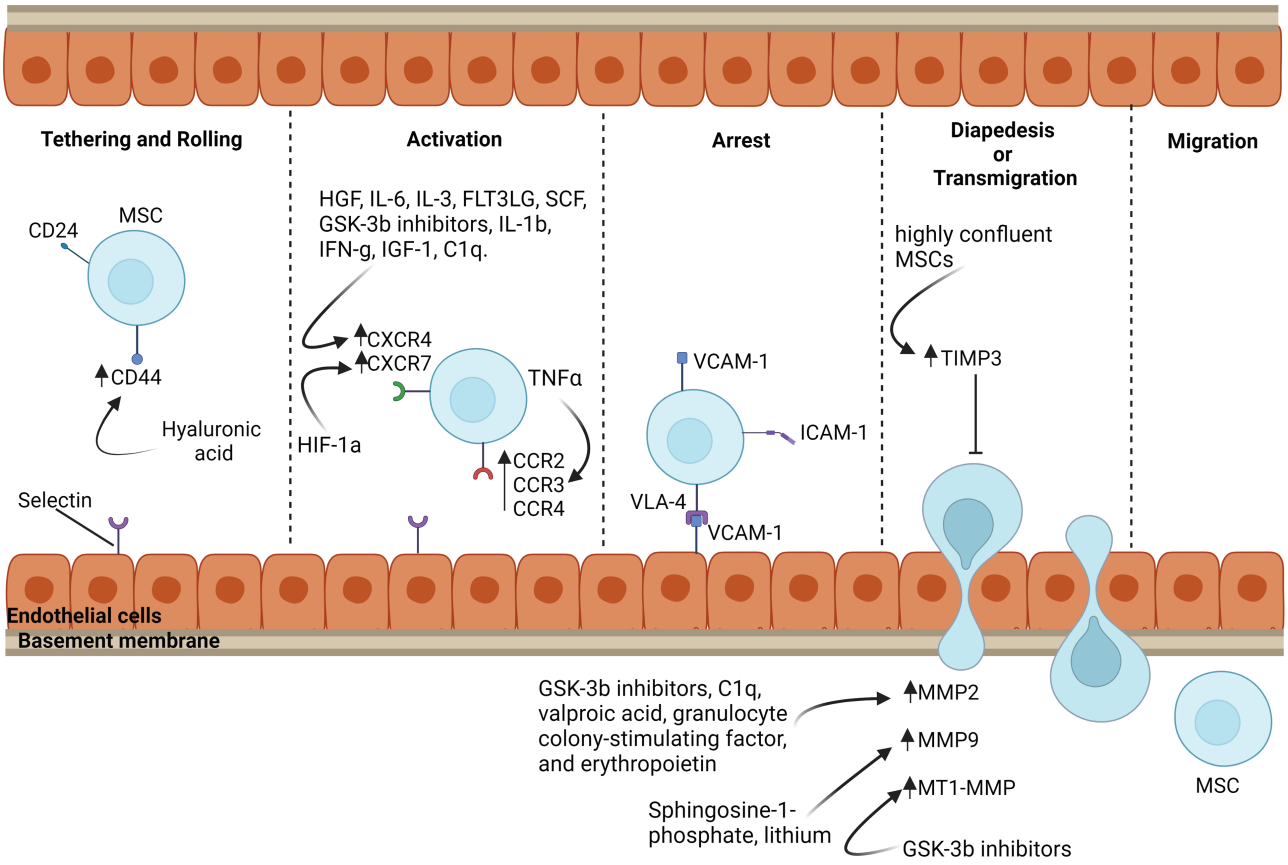


Figure 4. Overview of cell surface engineering, genetic modifications, magnetic guidance, and radiotherapeutic (ultrasound) techniques for improving MSCs homing at the target tissue. Modified from Ullah et al.[31]

performed until now demonstrated a promising avenue for increasing the homing efficiency of MSCs by using pFUS.

Implantation of a scaffold containing chemokines increasing homing

Another method of increasing homing is to deliver chemokines in a scaffold releasing chemoattractants such as SDF-1 to the injured target site. For example, Kimura and Tabata[106] generated a hydrogel showing a slow release of SDF-1. Similarly, a subcutaneous implantation of gelatin hydrogel containing SDF-1 showed improved results than SDF-1 injection alone.[106] Similarly, He et al[107] engineered SDF-1-loaded hydrogel, which increased the migration of bone marrow stromal cells upon implantation. Further, Goncalves et al[108] engineered SDF-1 containing a chitosan/poly(g-glutamic acid) complex, which enhanced the in vitro MSCs migration. Moreover, Shen et al[109] developed a silk-collagen sponge scaffold releasing SDF-1. This scaffold increased the endogenous progenitor cell migration and tendon regeneration in rat Achilles tendon injury models after implantation. Using a complex system, Thevenot et al[110] engineered an SDF-1-releasing scaffold by applying a mini osmotic pump. Subcutaneous implantation of these scaffolds in mice increased the homing effect of MSCs by 3-fold.[110]

In vitro priming

Priming methods affect gene expression by altering the culture conditions and thus, various steps of systematic homing (tethering, activation, and transmigration) in various studies as shown in Figure 5. For example, it was shown that CD44 is upregulated at the tethering stage when MSCs are coated with hyaluronic acid.[111] Further, many different soluble factors can increase the expression of CXCR4, CXCR7, CCR2, CCR3, and CCR4 during the activation step.[57,112-123] The cell culture confluence also affects the migration ability of MSCs.[124] Several treatments increased matrix metalloproteinase (MMP) expression, which improved the transmigration of MSCs.[116] These methods aim to promote MSC's ability to migrate toward the site of tissue damage or inflammation, which is essential for the potential therapeutic use of these cells.

In conclusion, in vitro priming methods include CD44 upregulation at the tethering stage, increased expression of CXCR4, CXCR7, CCR2, CCR3, and CCR4 at the activation step, and increased matrix metalloproteinases (MMPs) expression at transmigration stage.

Supplementation of culture media

Some specific treatments like supplementation of culture media with HIF-1a (hypoxia-inducible factor) or coating MSCs with some specific factors can increase the expression of certain markers or genes, which increases MSC homing. For example, the selectin ligand CD44 is upregulated at the tethering stage when MSCs are coated with hyaluronic acid.[111] Indeed, the CD44 upregulation increased the invasion and homing of MSCs by 2-fold, which resulted in a reduced in inflammation at the target site.[111] It has been found that different soluble factors can increase the expression of CXCR4, which is linked with the activation step of the

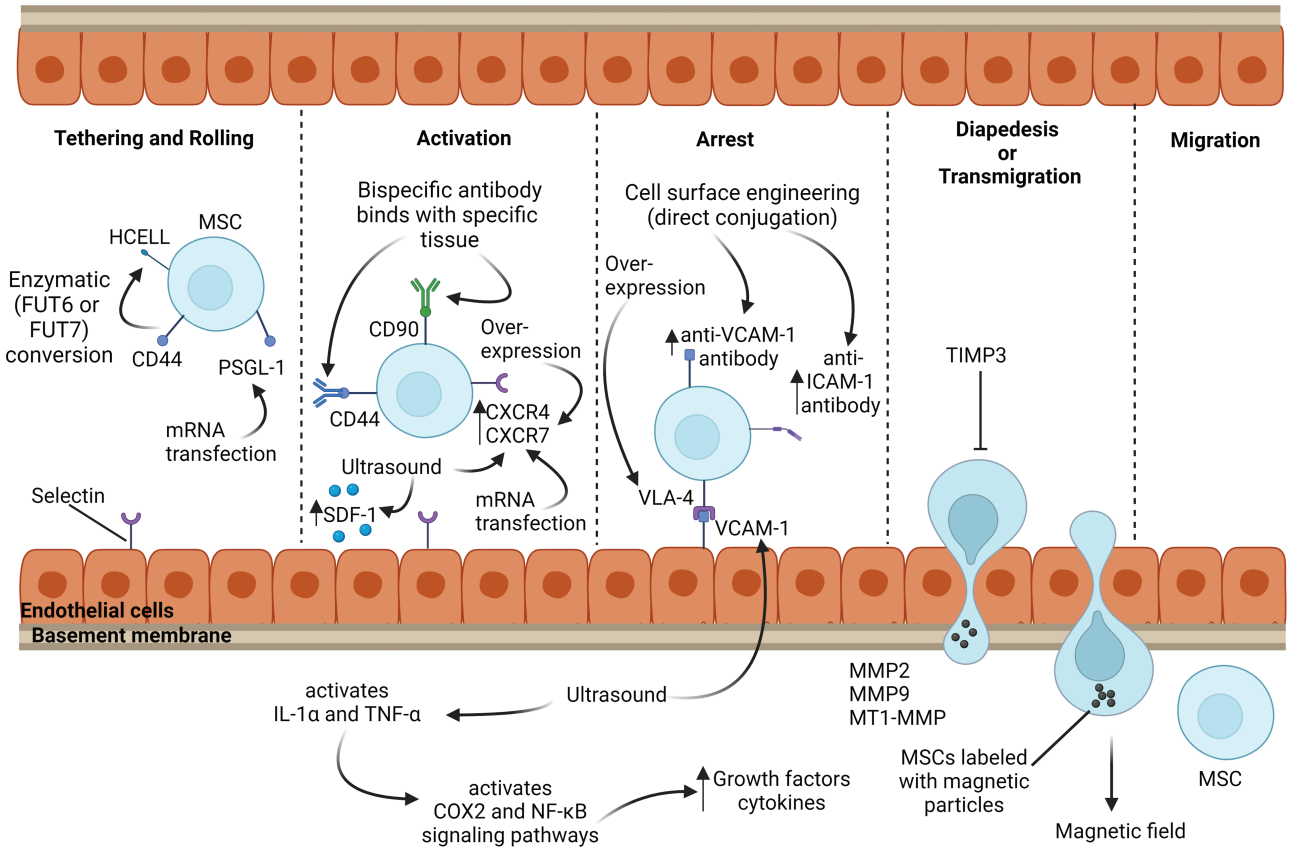


Figure 5. Overview of in vitro priming methods to enhance homing of MSCs modified from Ullah et al.[31] These methods include CD44 upregulation at tethering stage, an increase in the expression of CXCR4, CXCR7, CCR2, CCR3, and CCR4 at activation step, an increase in matrix metalloproteinases (MMPs) expression at transmigration stage.

homing process. The specific combinations of soluble factors include (1) HGF, IL-6, IL-3, FLT3LG, and stem cell factor (SCF)[112]; (2) iron chelator deferoxamine[113]; (3) valproic acid (the mood stabilizer drug)[114,115]; (4) glycogen synthase kinase (GSK)-3b inhibitors[116]; (5) IL-1b[117]; (6) interferon (IFN)-g[118]; and (7) IGF-1.[119]

Furthermore, HIF-1a induced under hypoxic cell culture conditions, increased expression of CX3CR1,[120] as well as CXCR7,[121,122] and CXCR4.[123] It seems that deferoxamine stabilizes HIF-1a even at the normal level of oxygen,[125] that finally increases the expression of many homing genes.[113] MSCs exposure to C1q (complement 1q) results in an increase in the expression of CXCR4, which enhances the migration of MSCs toward SDF-1.[126] Furthermore, culture conditions can upregulate other homing receptors as well. For example, migration of MSCs toward chemokines increases when MSCs are treated with TNF-alpha because this treatment upregulates the expression of CCR2, CCR3, and CCR4.[57] Other treatments can increase MMP expression, which have a role in the transmigration of MSCs. The inhibition of GSK-3 is known to induce increased expression of MMP2, a membrane-type MMP1.[116] Interestingly, complement 1q treatment also enhances MMP2 secretion.[126] Further, valproic acid and lithium, both drugs used to treat bipolar disease were demonstrated to enhance MMP9 activity, while valproic acid further increases the activity of MMP2.[114] The combination of erythropoietin and GCSF also enhances the expression of MMP2, which improves the migration of MSCs.[127] Further, sphingosine-1-phosphate-treated MSCs migration demonstrated significantly improved migration in in vitro trans well assays.[128] This treatment upregulates specifically MMP9 expression, which was shown to increase the homing capacity of MSCs to the infarcted myocardium.[129]

The impact of culture confluence on MSC migration

The cell culture confluence can affect the migration ability of MSCs. Indeed, a study reported that highly confluent MSCs secrete a higher amount of tissue inhibitor of metalloproteinase 3 (TIMP3), an MMP inhibitor decreasing the migration of MSCs as compared to the low confluence of cultured MSCs.[124] In another work, complete gene expression profiling of low and high-confluent MSCs was compared. The study demonstrated that proliferation-related genes were expressed higher levels in low-confluence MSCs, whereas genes involved in migration and regeneration (GDF15, A2M, MDK, PDFGD, VEGFA, FGF9, and WISP2), immune modulation (IL-6 and IL-1B), and activation (CXCL5, CXCL2, CXCL1, CXCL8, CXCL6, and CXCL16) related genes showed higher expression in high-confluence MSCs.[130]

The effect of cocultures on MSC migration

Culturing of MSCs with other cells (coculture) also affects the migration of MSCs. For example, coculturing Sertoli cells (from the testes) with MSCs upregulates homing-related factors such as CXCR4 and proliferation genes[131] as well as MMP2 expression in MSCs.[132] Furthermore, amniotic epithelial cells and amniotic MSCs coculturing upregulate the expression of CXCR4 and thus, increase MSCs proliferation.[133]

Further, the coculture of MSCs with melanoma cells dramatically improved the migratory and invasion potential of SK-Mel-5, G-361, MeWo, and A2058 melanoma cells. Furthermore, in an angiogenesis experiment in vitro, conditioned medium from all MSCs-melanoma cell cocultures stimulated tube formation.[134] In addition, treatment of MSCs with endothelial cell conditioned medium promotes their migration in vitro, presumably due to the presence of cytokines such as IL-6 and IL-8.[135] Interestingly, cocultures of nucleus pulposus cells and MSCs contributed to increased ECM synthesis and cell migration.[136]

Cell surface engineering

Many studies have performed chemical cell surface engineering of MSCs as shown in Figure 5 to enhance MSC homing. These specific modifications are temporary, but they are sufficient to improve the MSC homing because transmigration takes place within a few hours after MSC administration.[137] Importantly, CD44 is the selectin ligand naturally expressed on MSCs, whereas HCELL acts as a ligand for L- and E-selectin, and the hematopoietic stem cells utilize the HCELL ligand for bone marrow homing. Sackstein et al[137] converted CD44 to HCELL enzymatically by sugar modifications allowing MSCs to use L- and E-selectin for homing toward bone marrow. In the case of a diabetic mouse model, this modification increased the homing of MSCs to pancreatic islets by 3-fold after their intravenous administration and reversed the hyperglycemia condition.[138] These specific modifications of sugar molecules can also occur by genetic engineering. For example, CD44 to HCELL conversion in MSCs can be triggered by a (1,3)-fucosyltransferase (FUT6 or FUT7) expression.[139-141]

Another method of cell surface engineering is a direct conjugation of the desired ligand on the MSCs surface instead of modifying surface glycoproteins already present on MSCs. A platform developed by Sarkar et al[142] allows for any ligand attachment to the surface of MSCs. For coating MSCs in biotin, the group used biotinylated lipid vehicles. In particular, then streptavidin adaptor was attached, followed by the attachment of biotinylated SleX, which is an active site present in PSGL-1[142] Moreover, Cheng et al[143] used an NHS-PEG2-maleimide linker molecule for E-selectin-binding peptide conjugation with MSCs.

Moreover, the attachment of compounds the cell surface of MSCs is another popular strategy. For example, the palmityl group of palmitate protein can act as a cell membrane anchor, whereas the protein G is the site where antibody attachment occurs. Lo et al[144] used this method for attaching PSGL-1 fragment bound to the tail of IgG, which helped MSCs for rolling and tethering during shear stress. Further, Ko et al[145] attached anti-intercellular adhesion molecule (ICAM)-1 antibodies with MSCs by using the same system. This attachment

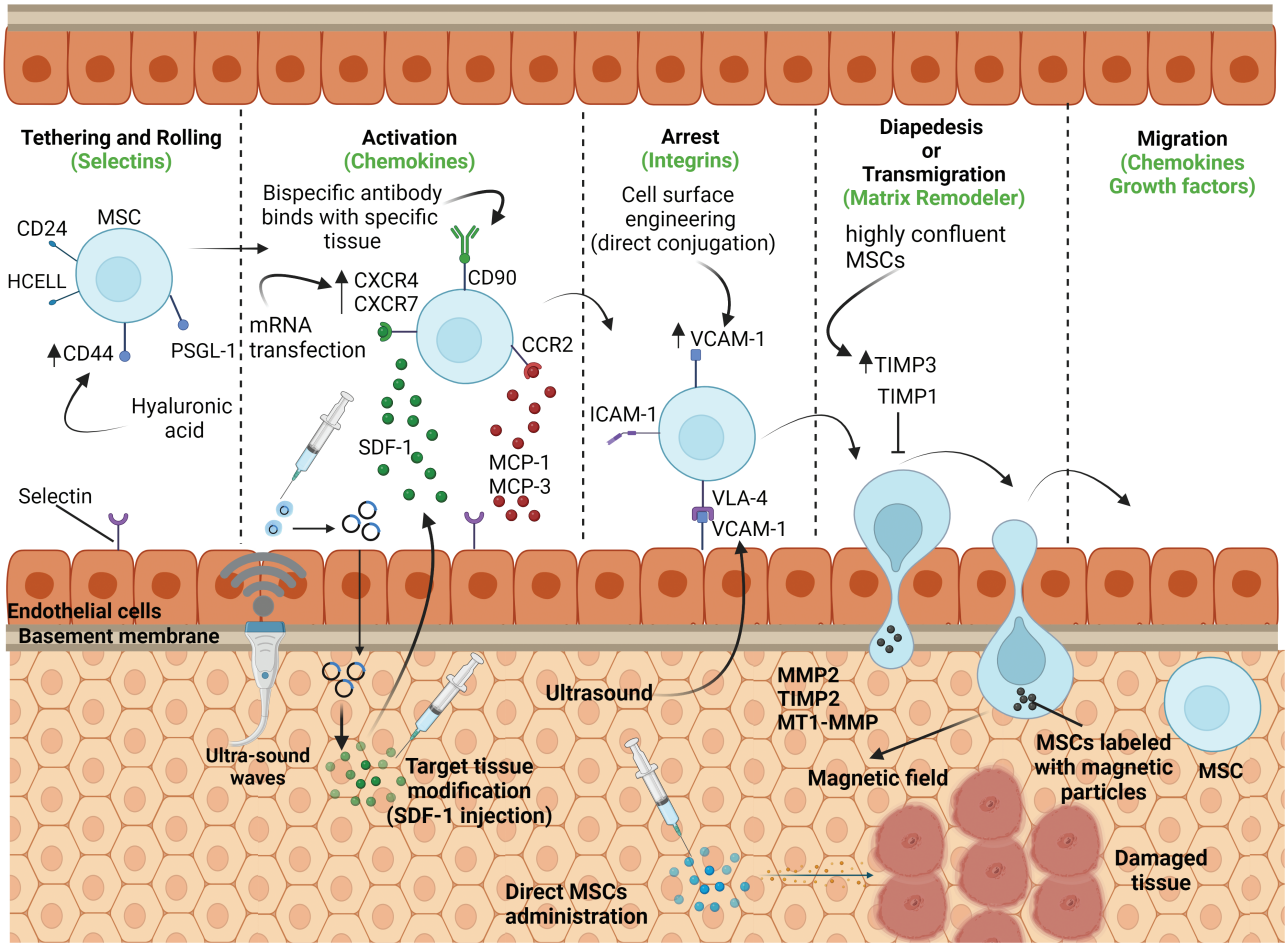


Figure 6. Explaining MSCs homing mechanism along with various strategies used for enhancing homing efficiency of MSCs at the target site. This includes both systemic homing and nonsystemic homing mechanism improvement strategies.

increased MSCs' arrest in a flow chamber. The group also attached another antibody VCAM-1 (antivascular cell adhesion molecule) on the surface of MSCs. This attachment showed a 1.3-fold improved homing efficiency of MSCs in the swollen lymph node and 1.8-fold higher MSC homing in the colon.[146]

Lee et al[147] created bispecific antibodies, where one side bound to CD44 present on MSCs surface, while the second side recognized the light chain of myosin (MLC), expressed by infracted myocardium. The bispecific antibodies bound MSCs localized specifically to the area of the heart.[147] Similarly, Gundlach et al[148] also created bispecific antibodies with one part recognizing CD90 present on the surface of MSCs, while the second end recognized MLC, expressed by ischemic myocardium. Those bispecific antibodies bound MSCs became attached to the immobilized MLC in vitro. Both these studies improved the MSCs' migration to the target tissue by targeting injury markers.

Previous studies focused mostly on the step of initial tethering; however, Won et al[149] aimed to optimize the activation step by cell surface engineering. In almost all the abovecited studies, cell differentiation, adhesion, proliferation, and viability of MSCs were unaffected; however, the methods of engineering cell surfaces are very complex in clinical setting.

Genetic modification of MSC surface receptors

Homing factors can be permanently overexpressed using viral transduction, mRNA transfection, and MSCs genetic modification techniques as shown in Figure 4. For example, the expression of the SDF-1 ligand is enhanced in the ischemic myocardium can bind to CXCR4 receptors and hence enhances the homing of MSCs.[150,151] Therefore, the elevated expression of CXCR4 in MSCs leads to increased MSC engraftment to ischemic myocardium due to enhanced MSC homing efficiency.[150,151] Another study reported that the homing of MSCs to bone marrow in mice was improved with increased expression of CXCR4 on MSCs.[152] Similarly, in the mouse model of colitis, the homing of MSCs to damaged intestinal mucosa also increased with the enhanced expression of CXCR4 on MSCs.[153] Furthermore, the increase in expression of CXCR7 on MSCs promoted the homing of MSCs to injured lung tissue.[48] However, in the mouse models of acute kidney injury, the homing efficiency of MSCs to the kidney did not change with the increased expression of CXCR4 or CXCR7 or both.[154] The increase in expression of a4-integrin (VLA-4 integrin component) at the cell arrest stage increased the homing efficiency of MSCs to the bone marrow.[155] However, in the rat model of stroke, the homing efficiency of MSCs to the heart was not increased with enhanced expression of a4-integrin, but harmful cell aggregates formation decreased.[156] However, such gene raises safety concerns. For example, oncogenesis can occur during genetic modifications in case viral DNA integrates into the tumor suppressor gene.

In contrast, mRNA transfection will result in a transient protein expression while eliminating the risk of insertional mutagenesis. Therefore, several studies opted for mRNA transfection methods instead of the viral transduction. For example, Levy et al[157] used the mRNA transfection method to improve MSCs tethering. They transfected MSCs with PSGL-1 and SLeX mRNA, both being ligands for P-selectin and for E-/L-selectin, respectively. Transfected MSCs showed increased homing efficiency to inflamed ear and bone marrow in the mouse experimental model. Similarly, Liao et al[158] also used the same method for MSC modification. They showed that modified MSCs exhibited increased rolling, adherence, and homing to the inflamed spinal cord. Ryser et al[159] used the mRNA transfection method to transiently overexpress CXCR4 mRNA in MSCs that resulted in increased migration of MSCs toward an SDF-1 gradient in vitro. However, Wiehe et al[160] applying the same method, have not confirmed these results. They successfully increased the CXCR4 expression by mRNA nucleofection, but no improvement in MSCs migration was observed in vitro. Thus, the authors concluded that the possible expression of other factors may be crucial for the activation of MSCs.

Magnetic guidance for MSC targeting

Magnetic guidance is a physical approach used for MSC targeting as shown in Figure 5. In this approach, the MSCs are labeled with magnetic particles and then directed to a target tissue or organ with the help of a magnetic field provided externally. Arbab et al[161] used particles of iron oxide for MSCs labeling and then injected them intravenously into the rats with and without placing the external magnet on the liver. In those rats that carried external magnets over the liver, MSCs moved deeper into the parenchyma of the liver. In contrast, in rats that did not wear magnets during MSCs targeting, MSCs were present around the portal triad. Thus, external magnet-wearing rats demonstrated 2-fold increase in the number of iron oxide-labeled MSCs in their liver. As a limitation, this study has not investigated which steps of MSCs' homing mechanism were involved.

Further, Kobayashi et al[162] treated osteochondral defects in knee joints with magnetically labeled MSCs in an ex vivo system by using an external magnetic field. In 2012, Yanai et al[163] placed the external magnet within the rat orbit and targeted magnetically labeled MSCs to the retina of rats by both intravenous or intravitreal administration. A high level of growth factors and anti-inflammatory molecules was present in the retina of rats with external magnets as compared to the animal group without external magnets. Thus, the authors concluded that magnetic guidance showed a very beneficial therapeutic effect. Since then, a lot of research has been performed to explore various types of magnetic particles, which may affect MSC differentiation, gene expression, proliferation, and viability.[164] Importantly, so far, no harmful effects of magnetic labeling on the functions of MSCs were observed.[165,166]

Conclusion and perspectives

In conclusion, MSCs hold significant promise in regenerative medicine due to their multipotent nature and ability to promote tissue healing. The natural homing mechanism of MSCs, as well as their capacity to home to injured tissues following allogenic transplantation, forms the basis for their therapeutic potential. However, attracting MSCs to the specific site of injury remains a major challenge. To optimize the homing mechanism of MSCs, various strategies have been developed. These include targeted stem cell administration, target tissue modification, in vitro priming, cell surface engineering, genetic modifications, magnetic guidance, and radiotherapeutic techniques. The majority of techniques as shown in Figure 6 are focused on systemic homing. These approaches improve the migration and localization of MSCs to the injury site, thereby enhancing their regenerative properties. By understanding the molecular pathways involved in MSC homing

and utilizing these strategies, researchers can enhance the therapeutic efficacy of MSC-based therapies. Precisely guiding MSCs to the injury site will facilitate their interaction with the damaged tissue, promoting tissue repair and regeneration.

The homing mechanisms of MSCs are poorly understood over several stages, including tethering, transmigration, and migration. It is also not clearly demonstrated which of these stages has a key role in MSC homing and thus, it is the most crucial for future research. Each strategy has its own set of disadvantages. Depending upon the tissue, targeted administration could not be possible or could be extremely invasive. The majority of MSC modifications do not inhibit them from spreading to nontargeted tissues. Modification of target tissue through genetic or chemical means increases the safety concerns. Such constraints pose a serious challenge to their use in clinics. Although it is still a work in progress, ultrasound usage to enhance the homing of MSCs appears to be a promising opportunity, with easy targeting for both the deep and the superficial tissues and, as far as we know, no considerable safety concerns.

Although several surface markers and integrins as well as their role in the process of homing are well described, there are still additional limitations for MSCs-based therapies. For example, senescence may occur as a negative effect of intensive cell culture expansion of MSCs, which is required for clinical applications, and it reduces the therapeutic impact.[167] Further, MSCs were thought to be immune privileged; however, several studies have revealed that MScs may experience immune rejection as a result of HLA mismatches.[168,169] Finally, MSCs used in clinical trials are nearly always freshly thawed; however, cryopreservation tends to reduce MSCs' immunosuppressive characteristics and limit their in vivo survival.[19] These differences may yield conflicting outcomes in both basic research and clinical trials. Therefore, understanding the fundamental processes that underlie MSC biology is crucial for further improvements. Such studies will continue to advance the area of cell-based treatments, enhancing the therapeutic efficacy of MSC transplantation across a wide range of applications, from immune regulation to regeneration.

A major obstacle is to currently attract MSCs to the injury site where they are required in regenerative medicine. This MSCs' homing to injury site can be enhanced by various strategies to bring advancement in the field of regenerative medicine as summarized in Table 2. We described the molecular pathways involved in the homing of MSCs and different strategies for optimizing homing, which include targeted stem cell administration, target tissue modification, in vitro priming, cell surface engineering, genetic modifications, and magnetic guidance. We believe that all these strategies enhance MSC homing to target sites; however, every strategy has its limitations that need to be considered while using that strategy for improving MSC homing. The currently available technological advances allow to attract MSCs precisely to the injury site and hence improve their migration and local tissue repair properties.

Author contributions

Umar Sajjad, Muhammad Ahmed, and M. Zohaib Iqbal conceptualized and designed the review, and contributed to drafting and revising the manuscript. Mahrukh Riaz assisted with the literature search, data analysis, and drafting. Muhammad Mustafa contributed to the review's design, coordinated among coauthors, and helped write the manuscript. Thomas Biedermann contributed to the design, provided oversight and feedback, and assisted with final editing. Agnes S. Klar supervised the project, provided conceptual and editorial guidance, funding, and contributed to the final revision and approval of the manuscript.

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Conflicts of interest

The authors declared no potential conflicts of interest.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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