Mesenchymal stem cells’ homing and cardiac tissue repair*

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Nowadays, mesenchymal stem cells (MSCs) are essential players in cellular therapy and regenerative medicine. MSCs are used to treat cardiac disorders by intramyocardial injection or injection into the bloodstream. Therefore, a premise of successful MSC-based therapy is that the cells reach the site of injury and home the damaged tissue. In response to inflammatory conditions, MSCs can potentially move into the place of injury and colonize damaged tissues, where they participate in their regeneration. This review presents the current knowledge of the mechanisms of MSCs migration and target tissue homing in the field of cardiovascular therapies.

Key words: mesenchymal stem cell, cell migration, tissue repair, cardiovascular diseases, MSC-based therapy

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Abbreviations: AFM, Atomic Force Microscopy; BM-MSCs, Bone Marrow Mesenchymal Stem Cells; CCR, C-C chemokine receptor; CXCR, CXC chemokine receptor; ECM, extracellular matrix; EGF, epidermal growth factor; ERK, Extracellular Signal Regulated Kinase; FAK, Focal Adhesion Kinase; FGFR, fibroblast growth factor; FLT-1, fms-like tyrosine kinase 1; HGF, hepatocyte growth factor; HUC-MSC-EXO, Human Umbilical Cord Mesenchymal stem cells-Derived Exosomes; IGF-1, insulin-like growth factor 1; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; ISCT, International Society for Cellular Therapy; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein 1; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein; MMP, matrix metalloproteinase; MSC-EXO, Mesenchymal stem cells-Derived Exosomes; MSCs, Mesenchymal stem cells; MT1-MMP, membrane type 1 metalloproteinase; PDGF, platelet-derived growth factor; PDGFR, platelet derived growth factor receptor; PI3K, Phosphoinositide 3-kinase; SDF-1, stromal cell-derived factor-1; sFRP2, Secreted Frizzled Related Protein 2; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; VEGF, vascular endothelial growth factor; VLA-4, Very Late Antigen 4; WJ-MSCs, Wharton’s Jelly Mesenchymal Stem Cells

INTRODUCTION

Mesenchymal stem cells (MSCs) represent a population of undifferentiated cells, multipotent, with the ability to self-renew and differentiate into many cell types. They carry markers similar to those of tissue fibroblasts and are difficult to distinguish from them. For the first time, Friedenstein and others (Friedenstein et al., 1970) described bone marrow-derived fibroblast-like cells which later became the most extensively studied MSCs. Subsequently these cells were also found in the adipose tissue, muscle, dental pulp, periosteum, synovium, and synovial fluid, tendons, endometrium, skin, lungs, chorionic villi, peripheral blood, menstrual blood, breast milk, as well as in umbilical cord, Wharton’s jelly, placenta, and umbilical cord blood (Eleuteri & Fierabracci, 2019; Berbicchez-Fridman & Montero-Olvera, 2018; Kong et al., 2019).

The minimum criteria to be fulfilled by a cell to be classified as a mesenchymal stem cell were stated in a paper published by the International Society for Cellular Therapy (ISCT) in 2006 (Dominici et al., 2006). As per this statement, cells need to satisfy three conditions to be recognized as MSC (Table 1). Even though a wide range of selection markers defining MSCs were identified, no single marker specific only to them has been indicated.

In response to inflammatory conditions, MSCs can potentially move into the site of injury and colonize the damaged tissues, where they participate in their regeneration (Murphy et al., 2013; Rosenthal, 2003). The efficacy of MSC-based therapy depends on their homing ability and engraftment into the target tissue. The possibility of using MSCs in the therapy of many diseases needs to be preceded, though, by an in-depth analysis of their properties, especially by determining the mechanism of tissue homing, as well as the mechanism due to which the cells contribute to tissue regeneration.

This review presents the current knowledge of the mechanisms of MSCs migration, homing, and cardiac tissue regeneration, hoping to develop an effective treatment for cardiovascular diseases and many other clinical applications.

| Table 1. General characteristics of mesenchymal stem cells. |
|-----------------------------------------------|
| **Morphology** | Spindle-shaped, fibroblast-like |
| **Growth properties** | Adherent |
| **Surface markers** | CD73+, CD90+, CD105+, CD11b, CD14, CD19, CD45, CD79a, HLA-DR, MHC-II |
| **In vitro differentiation potential** | Osteogenic, chondrogenic, adipogenic |
WHY MSCs?

MSCs can be of great significance for healing tissue damage owing to their distribution in a wide range of tissues, their differentiation potential, and the reparative effects noticed when MSCs are infused in pre-clinical and clinical models (Wei et al., 2013). It is widely accepted that there are roles for MSCs in tissue growth, wound healing, and maintenance of the cell supply to compensate for the cells’ lost due to apoptosis and pathology. Due to these roles, researchers and clinicians have used MSCs for treating tissue damage.

Numerous studies were performed, indicating the effectiveness of MSCs’ application to decrease the postinfarction myocardial scarring and restore regular systolic function in case of acute myocardial infarction (Afzal et al., 2015; Majka et al., 2017). MSCs exhibit high chemotaxis into damaged tissues, and areas embodied with inflammatory reaction and oxygen deficiency, thus conditions dominating in ischemic damaged tissue of cardiac muscle (Sohni & Verfaillie, 2013). However, the exact mechanism due to which the cells contribute to regeneration of the cardiac muscle is still unknown. Supposedly, this process depends on many factors and probably does rely on a direct ability of MSCs to diversify towards cardiomycocytes, but on their ability to release cytokines and growth factors with trophic properties (Gneecci & Cervio, 2013; Yamahara & Nagaya, 2007). Among fundamental mechanisms of mesenchymal stem cells action, the most important is secretion of the paracrine factors and integration at the cellular level (Markel et al., 2008; Mirotou et al., 2007; Karnatalis & Hare, 2015). MSCs can also contribute to attenuation of inflammatory conditions and stimulation of endogenous repair mechanisms through their immunosuppressive properties (Hamid & Prabhu, 2017; Kocher et al., 2001; Ward et al., 2018).

MSCs secrete TNF-α, IL-6, and IL-8 cytokines suggested as potential mediators of heart preservation (Hatzistergos et al., 2010; Molina et al., 2009). It was demonstrated that proinflammatory cytokines increase immunity of cardiomycocytes to ischemia (Molina et al., 2009). Additionally, IL-8 is known to influence cell proliferation and angiogenesis.MSCs also secrete growth factors, including granuloocyte and macrophage colony-stimulating factors, as well as the FMS-like tyrosine kinase 3 (Hodgkinson et al., 2016). Growth factors are capable of inducing myocardium by restraining apoptosis of cardiomycocytes in the implantation area, and further secreting antiapoptotic and angiogenic factors, such as the vascular endothelial growth factor (VEGF) that stimulates angiogenesis (Markel et al., 2008) and sFRP2 protein that modulates the Wnt signaling pathway (Mirotou et al., 2007). Secretion of angiogenic factors is crucial for neovascularization of the cardiac muscle after heart attack, as mesenchymal stem cells lacking VEGF are less efficient at myocardial regeneration after injury (Markel et al., 2008).

In addition to cytokines, mesenchymal stem cells also secrete metalloproteinases which reorganize the extracellular matrix (ECM) in the scar tissue (Molina et al., 2009). Reversed remodeling of the scar tissue and anti-fibrotic effects in the necrotic tissue of the heart muscle are essential for regeneration and functional restoration of the heart after myocardial infarction. Further, mesenchymal stem cells stimulate the proliferation and differentiation of endogenous cardiac stem cells, simultaneously contributing to the cardiac muscle regeneration (Hatzistergos et al., 2010).

Moreover, MSCs also immediately interact with other cell types through interactions at the cellular level. Owing to direct and intermediate cell communication and signaling with cells in the damaged areas, MSCs recruit other stem cells to facilitate regeneration of the damaged tissue. An excellent example of the mentioned type of interactions is the signaling pathway SDF-1α/CXCR4 that regulates cell migration of hematopoietic stem cells to the damaged myocardium (Elmadbough et al., 2007; Zhang et al., 2007).

MSCs can also serve as an exosome provider (Lai et al., 2015). Exosomes play an essential role in cellular communication and change biochemical characteristics of the recipient cells by providing biomolecules (Wang et al., 2018). These bubbles are produced from body fluids and various cell types, such as MSCs (Zeringer et al., 2015). Evidence suggests that the mesenchymal stem cells-derived exosome (MSC-EXO) has MSC-like functions with low immunogenicity and no carcinogenic potential. Studies performed by Zhao et al. in a rat model of acute myocardial infarction have shown that the use of HUC-MSC-EXO and micro-vesicles can improve cardiac function after four weeks of HUC-MSC-EXO injection (Zhao et al., 2015). Also, reduced cardiac fibrosis was observed after Masson’s trichrome staining.

RECRUITMENT AND HOMING OF MSCs

Molecular factors involved in MSCs migration

A premise of successful MSC-based therapy is that the cells reach the site of injury and home the damaged tissue, which is possible due to their ability to reach the damaged places thanks to their ability to migrate, adhere, and get implanted into the target tissue. Therapeutic efficacy and target tissue homing by MSCs are influenced by several factors, such as the source of the cells, the age of the donor, breeding conditions, the number of passages, method of supplying cells, the number of cells implanted, general condition and susceptibility of the host (Beane et al., 2014; Siegel et al., 2013; Izadpanah et al., 2008; Zhuang et al., 2015). It has been proven that freshly isolated cells have higher engraftment in tissue and more efficient target tissue homing when compared to cells from long-term in vitro expansion (Rombouts & Ploemacher, 2003; Hong et al., 2019). This probably results from aging and differentiation of MSCs during in vitro cultivation (Trounson & McDonald, 2015). Culture conditions also have a significant impact on the MSCs homing, as they can modify expression of the surface markers involved in this process (Yang et al., 2018).

The site and method used for administration of MSCs for therapeutic purposes can influence the way taken by cells to reach the desired destination (Bolzce et al., 2015). Usually, MSCs are administrated systemically by injection into the bloodstream. Therefore, the necessary condition for an effective therapy based on MSCs is the capacity of the used cells to get to the site of injury and to occupy tissue affected by the disease. The remedial effect is most likely a result of increased migration of cells towards the damaged tissue, preceded by MSCs adhesion to vascular endothelial cells.

Many studies have shown that MSCs are capable of directional migration in response to inflammatory conditions (Nakajima et al., 2012; Zachar et al., 2016; Yagi et al., 2010). MSCs are thought to use the same mechanism of migration into a tissue as leukocytes (Nitsche et al., 2017). However, in contrast to the well-described
mechanisms of leukocyte adhesion and movement, the mechanism of tissue homing by MSCs is not yet fully understood, despite the fact that there are numerous studies assessing MSCs adhesive molecules and possible mechanisms of vascular wall adhesion and migration, as well as evaluating the role of chemokines in guiding MSCs to the target tissues (Kia et al., 2011; Ghaffari-Nazari et al., 2005; Lei et al., 2017). The interaction of integrins that are expressed in the MSCs’ cell membrane with adhesion molecules at the endothelial surface (VCAM and ICAM) can lead to formation of docking structures and transmigration wells that are rich in ICAM-1, VCAM-1, proteins, and cytoskeleton components (Nitzsche et al., 2017; De Becker & Van Riet, 2016).

Before MSCs migrate through the wall of a vessel, they are rolling on its surface, finding the best place for adhesion and then transmigrating through the endothelium (Fig. 1) (Nitzsche et al., 2017). The interaction of integrins that are expressed in the MSCs’ cell membrane with adhesion molecules at the endothelial surface (VCAM and ICAM) can lead to formation of docking structures and transmigration wells that are rich in ICAM-1, VCAM-1, proteins, and cytoskeleton components (Nitzsche et al., 2017; De Becker & Van Riet, 2016).

To date, several molecules involved in interactions between MSCs and endothelial cells were indicated, including VLA-4, VCAM-1, ICAM-1, and P-selectin. Adhesion molecules, such as selectins, integrins, and chemokine receptors, are committed to rolling, adhesion, and transmigration of MSCs. Mesenchymal stem cells have been shown to express various receptors associated with intercellular contacts and adherence to extracellular matrix proteins, such as α1, α2, α3, α4, α5, αv, β1, β3 and β4 integrins, and other adhesion molecules, e.g. VCAM-1, ICAM-1, ICAM-3, CD166 (ALCAM) (Rüster et al., 2006; Ip et al., 2007). Some studies have shown that MSCs adhesion to the endothelium occurs with participation of P-selectin. It has been observed that MSCs may use new carbohydrate ligands to interact with P-selectin on the endothelial surface (Rüster et al., 2006). Steigen et al. reported that MSCs could migrate through endothelium using the VLA-4/VCAM-1 complex, and that MSCs tend to integrate with the endothelial layer instead of passing full diapedesis (Steigen et al., 2008). Among the integrin family, a key role in adhesion, migration, and chemotaxis is played by integrin α4β1, which is a mediator in the cell-cell contact and cell-environment interactions. However, because the MSCs’ transendothelial migration has not been entirely blocked by the anti-VLA4 antibody and the anti-VCAM-1 antibody, it can be assumed that other integrins are also involved in this process (Steigen et al., 2008).

Although integrins and selectins play an essential role in transmigration of MSCs, chemokines released from the tissues and endothelial cells can promote activation of ligands involved in adhesion, migration, chemotaxis and homing of MSCs in the target tissues. Many reports suggest that the damaged tissue releases specific factors that act as chemoattractants to facilitate adhesion, movement, and homing of MSCs in the affected areas (Nakajima et al., 2012; Zachar et al., 2016; Yagi et al., 2010). Studies have shown that MSCs are capable of migrating to the inflamed tissues in response to factors that are regulated under inflammatory conditions. So far, many chemokines and growth factors have been identified that are involved in the migration process. These are pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and many growth factors, e.g., EGF, FGF, HGF, IGF-1, PDGF-AB, SDF-1α, TGF-β1, VEGF-A (Fox et al., 2007; Honczarenko et al., 2005; Kortesidis et al., 2005; Leibacher & Henschler, 2016; Guo et al., 2018). Some studies have shown expression of chemokine receptors by MSCs, including CXCR1–CXCR6, CCR1–CCR10, and have pointed to functional roles of some of them in the MSCs migration process (Honczarenko et al., 2005; Ringe et al., 2007; Lüttichau et al., 2005; Sordi et al., 2005). It has been proven that CXCR1, CXCR2, CXCR4, CCR1, CCR2, IL-8, MIP-1α, and MCP-1 are involved in migration of MSCs into the damaged tissue (Escone & De Bar, 2015). Other studies have shown that the SDF-1/CXCR4 axis plays a vital role in the movement of MSCs isolated from the bone marrow (Su et al., 2017; Kitaori et al., 2009). Therefore, it is likely that chemokines released from tissues cause expression of the CXCR4 receptor, which contributes to migration of MSCs to their final destination. It has also been shown that an increase in IL-8 concentration in the damaged tissues can activate the MSCs migration (Ringe et al., 2007). An active role of IL-6, PDGF, PDGFR-α PDGFR-β, vascular endothelial growth factor receptor 1 (FLT-1), and IGF-1 was indicated in the BM-MSCs migration studies (Escone & De Bar, 2015). PDGFR has been highly expressed in the BM-MSCs, and PDGF induces BM-MSCs migration. A migration test through a porous filter also showed that PDGF has a stronger effect on MSCs chemotaxis than SDF-1 and MCP-1 (Lee et al., 2012). According to those studies, numerous chemokines play a role in induction of MSCs migration, but details, including mechanisms of colonization by MSCs, require further in vitro and in vivo studies.

An important role played by proteolytic enzymes – metalloproteinasies which regulate the extracellular matrix degradation, has been also confirmed (Steigen et al., 2008; De Becker et al., 2007; Ries et al., 2007). Different MMPs and their signaling pathways have been shown to affect MSCs differentiation, migration, angiogenesis, and proliferation. Migration and invasion of MSCs into damaged tissues are facilitated by expression of CXCR4, MMP-2, and MT1-MMP (Almalki & Agrawal, 2016). Inflammatory cytokines, such as IL-1β and TNF-α, stimulate production of MMPs by MSCs and activate chemotactic migration through the extracellular matrix (Sohni & Verfaillie, 2013).

**Mechanical cues regulating MSCs movement**

During migration through peripheral blood circulation towards the damaged tissue, exogenous MSCs injected into the body 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 migration of MSCs. Studies by Zhang and others (Zhang et al., 2015) have shown that

![Figure 1](https://periobasics.com/mechanisms-of-transendothelial-migration-of-leukocytes.html)
cyclic mechanical stretching (10%, 8 hours) promotes MSCs migration through the FAK-ERK1/2 pathway, but leads to a decrease in the invasive potential of MSCs by downregulating MT1 – MMP via the PI3K/Act signaling pathway (Zhang et al., 2015; Fu et al., 2019).

Shear stress is another type of force inside the blood vessels. However, so far only a few studies have focused on the effects of shear stress on MSCs movement. It was observed that shear stress (~0.2 Pa) promoted MSCs migration in the wound healing test, while a higher shear stress (> 2 Pa) had significantly inhibited MSCs migration by regulating the JNK and p38 MAPK pathways (Yuan et al., 2012).

The ability of the cell to dynamically reshape is essential for migratory behavior due to physical limitations in the tissue (Rudzka et al., 2019; Xu et al., 2012). How a given cell remodels its shape is related to the cell deformability, and cell elasticity depends on the structure of the cytoskeleton ( Olson & Sahai, 2009). Our recent studies have proven that the elasticity of MSCs observed by atomic force microscopy (AFM) is an important factor that determines the ability of MSCs to migrate across a porous filter (Szydlak et al., 2019). The results have shown that MSCs with the potential of transendothelial migration and invasion were characterized by higher deformability (Szydlak et al., 2019). Previous studies performed by McGrail et al. have demonstrated that loss of MSCs elasticity leads to a decrease in MSCs motility in the wound healing assay and transmigration tests (McGrail et al., 2013).

Furthermore, mechanical properties of the microenvironment, such as the extracellular matrix elasticity, and mechanical and shear stresses occurring in the blood vessels, are crucial in MSCs migration. Biophysical signals that reach MSCs play an essential role in regulating their behavior.

Previous studies focused on the effect of extracellular matrix rigidity on MSCs migration. The research conducted by Raab et al. showed that MSCs migrated from a soft substrate (1 kPa) towards the rigid surface (34 kPa) by cytoskeleton polarization and myosin-IIIB heavy chain phosphorylation (myosin-IIIB) (Raab et al., 2012), which suggests that mechanical properties of the substrate are regulating the MSCs polarization and migration. Other studies, conducted by Vincent et al., constructed substrates with a stiffness gradient that was intended to simulate natural changes in the tissue stiffness, pathological changes, and tissues showing abrupt changes in stiffness. The results of this experiment showed that MSCs migrated towards stiffer fragments, using the actin cytoskeleton for this purpose, and directional migration was carried out using microtubes (Vincent et al., 2013).

The studies of the mechanism of MSCs’ migration are crucial for the development of MSC-based therapies because their ability to reach target tissue is a key factor in achieving therapeutic effectiveness. After recruitment and migration into the damaged tissues, MSCs will play their role and promote damaged tissue repair and organ regeneration, as well as reverse progression of the disease.

FUTURE DIRECTIONS

Despite promising results of clinical trials involving MSCs, there are ongoing efforts to increase the effectiveness of MSCs, primarily because effects observed in the preclinical studies are stronger than in the clinical ones. Standardization of stem cell acquisition and culture methods is one of the fundamental challenges of modern cell therapy, and MSCs cell isolation and culture protocols to enhance safety of their in vivo use still require refinement. In addition, various methods are tested to increase the effectiveness of MSCs in vivo. They include a combination of MSCs therapy with standard pharmacotherapy (Ascheim et al., 2014), genetic engineering techniques (Bobis-Wozowicz et al., 2011), biomaterials engineering (Sekula et al., 2017), MSCs pre-conditioning, e.g. by reducing oxygen availability (Ejtehadifar et al., 2015) or using an inflammatory factor (Hahn et al., 2008).

Although many studies (both preclinical and clinical) show more and more evidence of the therapeutic effectiveness of MSCs, the main problem that remains is the low degree of retention of MSCs in the tissues due to their short-lived viability after implantation into the recipient’s body (Von Bahr et al., 2012). The immune status of the patient before and after injection determines survival of the implanted allogeneic MSCs. In vivo experiments have shown that the time of MSCs transplantation decides on their therapeutic effect in a model of myocardial infarction (Hu et al., 2007). Rigol et al. observed that MSCs induce better neovascularization and better long-term prognosis when injected 15 minutes after reperfusion than those injected a week later (Rigol et al., 2014). It has been detected that less than 10% of MSCs are retained in the damaged tissue 24 hours after injection into the body, and only about 1% is still at the site of injury after four weeks (Lee et al., 2011). In addition, it has been shown that after MSCs transplantation, many of them become trapped in the capillaries of the lungs, which reduces the population of cells occupying the target tissue (Rigol et al., 2014), and only a part of MSCs population responds to inflammatory factors and reaches the damaged tissue, e.g. in the case of infarcted myocardium or ischemic damaged brain (Von Bahr et al., 2012; Barzegar et al., 2019). This problem was attempted to be solved by repeated MSCs injections. However, it was observed that such a repeated administration might cause production of immune alloantibodies (Cho et al., 2008). Therefore, one of the biggest challenges faced by MSC-based therapies is to improve engraftment efficiency.

An important factor is also the change in the expression of some adhesive molecules that occurs during long-term in vitro culture (Phinney & Procop, 2007; De Becker et al., 2007). It has been observed that the expansion of MSCs gradually leads to a loss of expression of homing molecules and, in consequence, to a loss of tissue homing capacity by MSCs (Honezarenko et al., 2005; Rombouts & Ploemacher, 2003).

The method of administration of MSCs can be an essential factor in achieving the intended destination. Researchers have tested many ways of providing MSCs that aim to ensure that these cells are successfully homed in the areas of ischemia, to prolong survival in the body in an inflammatory environment that will eventually lead to successful neovascularization. Also, non-invasive methods are considered due to the risks associated with operational procedures. For example, in the treatment of brain damage, injecting MSCs directly into a damaged brain can bring high efficacy in therapy, but involves the risk of surgical complications that can be minimized by using less invasive or non-invasive techniques, or by systemic administration. New methods of stem cell delivery are currently being tested. These include such techniques as genetic modification of MSCs and cell surface engineering, in vitro pre-conditioning, and target tissue modification, as well as biomaterial engineering and cell scaffolding construction (Chen et al., 2018). In addition,
methods such as targeted administration, magnetic and ultrasound guidance, and radiotherapy techniques are being tested (Fakoya, 2017). The advantage of selective injection of these cells is reduced cell loss during cell delivery and migration, when compared to systemic administration (Kim et al., 2014).

On the other hand, the methods for labeling and detection of MSCs in vitro after transplantation still need improvement. Despite promising results of in vitro studies, there is lack of data about the behavior of MSCs after transplantation. That is why it is so important to be able to monitor the distribution, survival, and function of MSCs after in vitro transplantation, especially in patients. These needs have led to remarkable advances in molecular imaging, including magnetic resonance imaging, scintigraphy, PET, optical imaging, and ultrasound, as well as multimodal imaging (Bose & Mattrey, 2019).

Stem cell labeling with reporter genes or reporters to enable their detection and evaluation of their in vivo function was achieved using all current imaging methods with promising results in preclinical results and with some success in clinical trials as well (Wang & Jokser, 2016). However, currently there is no ideal approach to MSC imaging, each having advantages and limitations.

CONCLING REMARKS

The magical ability to regenerate damaged parts of the body to regain a lost function has been a dream of humanity for a long time. MSC-based therapy is still an innovative and clinically needed therapeutic concept. The three properties of MSC make them optimal for tissue regeneration: (1) immunoregulatory ability is beneficial in alleviating abnormal immune responses, (2) paracrine or autocrine functions that generate growth factors, and (3) the ability to differentiate into target cells. Despite promising results of many studies, the biggest challenge of MSC-based therapies is to increase the target tissue retention. There is still need for basic research that will allow us to fully understand the in vivo mechanisms of MSCs in the future. The proposed scheme of the relationship between MSC migration and tissue repair is based on a chemotactic hypothesis. In response to inflammatory conditions, MSCs can potentially move into the site of injury and colonize the damaged tissues, where they participate in their regeneration. To date, many variables factors have been recognized that affect MSC migration, but the detailed mechanism involved in this process is not yet fully understood. Answers to these questions would provide valuable information for further research and effective cellular therapy.

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Conflicts of Interest

The author declares no conflict of interest.

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