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*REVIEW*

# Role of the CXCR4-SDF1-HMGB1 pathway in the directional migration of cells and regeneration of affected organs

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## Abstract

In recent years, several studies have reported positive outcomes of cell-based therapies despite insufficient engraftment of transplanted cells. These findings have created a huge interest in the regenerative potential of paracrine factors released from transplanted stem or progenitor cells. Interestingly, this notion has also led scientists to question the role of proteins in the secretome produced by cells, tissues or organisms under certain conditions or at a particular time of regenerative therapy. Further studies have revealed that the secretomes derived from different cell types contain paracrine factors that could help to prevent apoptosis and induce proliferation of cells residing within the tissues of affected organs. This could also facilitate the migration of immune, progenitor and stem cells within the body to the site of inflammation. Of these different paracrine factors present within the secretome, researchers have given proper consideration to stromal cell-derived factor-1 (SDF1) that plays a vital role in tissue-specific migration of the cells needed for regeneration. Recently researchers recognized that SDF1 could facilitate site-specific migration of cells by regulating SDF1-

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CXCR4 and/or HMGB1-SDF1-CXCR4 pathways which is vital for tissue regeneration. Hence in this study, we have attempted to describe the role of different types of cells within the body in facilitating regeneration while emphasizing the HMGB1-SDF1-CXCR4 pathway that orchestrates the migration of cells to the site where regeneration is needed.

**Key Words:** C-X-C motif chemokine 12; Mesenchymal stem cells; Monocytes; Neutrophils; Peripheral blood mononuclear cells; Receptor for advanced glycation end products



**Core tip:** In the last few decades, cell-based regenerative therapy has received considerable attention for the treatment of degenerative diseases or the regeneration of injured organs. However, poor cell retention is considered a major drawback associated with the short-term regenerative benefits. Furthermore, the short-term regenerative benefits are linked to paracrine factors secreted by the transplanted stem cells. To improve regenerative outcomes, researchers have identified the role of stromal cell-derived factor-1 (SDF1) as a key chemotactic factor that can facilitate site-specific migration and retention of transplanted cells, and stem or progenitor cells within the body by activating the SDF1-CXCR4 or HMGB1-SFD1-CXCR4 pathways.

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## INTRODUCTION

Over the past decades, non-communicable diseases, especially degenerative diseases are becoming more prevalent worldwide, which also contributes to major morbidity. During the past two decades, stem cell-based regenerative therapy has been considered hopeful in addressing the unmet needs of treating degenerative diseases[1].

Among the different tools of regenerative medicine "stem cells" are considered the most promising due to their self-renewal capability and multi-differentiation potential. However, recent studies have shown that the positive outcomes of different types of stem cell-based regenerative therapies are not directly correlated to the engraftment of transplanted cells[2,3]. These findings have created a huge interest in the regenerative potential of paracrine factors and have led scientists to reveal the regenerative potential of proteins in the secretomes. Further studies have revealed the mitogenic, angiogenic, anti-apoptotic, anti-scarring and chemoattractant features of secretomes or cell culture supernatants that make them a potential tool for regenerative therapy[1,4]. Furthermore, the regenerative potential of the secretome from adult stem cells[5], freshly isolated healthy peripheral blood mononuclear cells (PBMC)[6] and apoptosis-induced PBMC[7,8] has been acknowledged by several researchers. Secretomes from stem and progenitor cells have been found to be favorable for regenerating tissues or treating several disorders including neuronal disorders[9], vascular diseases[10] and cutaneous wounds[11]. The growing evidence on the role of paracrine factors (cytokines, chemokines and growth factors) in the regeneration of affected organs has led to the introduction of cell culture supernatants or secretomes as a new therapeutic tool of regenerative medicine.

Regeneration is a complex process and several types of cells namely lymphocytes, monocytes, neutrophils, endothelial progenitor cells (EPCs), hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and tissue resident stem cells are involved in the process of regeneration. Recent studies reported that stromal cell-derived factor-1α (SDF1α) present in the secretome increases proliferation, viability, migration and homing of stem and progenitor cells; helps lymphoid tissue development and differentiation; and inhibits apoptosis of cells[4,12]. All these features are highly important for regeneration of damaged organs[13]. Furthermore, SDF1 and C-X-C-X-C

chemokine receptor type 4 (CXCR-4) play a vital role in the high mobility group box 1 (HMGB1)-mediated inflammatory cell recruitment to the site of damaged tissue which is also vital for tissue repair and regeneration[14]. Hence, in this review we have attempted to describe the role of different types of cells in regeneration while emphasizing activation of the HMGB1-SDF1-CXCR4 pathway which is considered a key pathway that regulates the directional migration of all cells and facilitates the process of regeneration.

## PBMC IN REGENERATION

PBMC are widely used in preclinical research and applications in vaccine trials, source of biomarkers in various infectious and chronic diseases, and are a useful tool in studying various aspects of pathology and biology *in vitro*[15]. In addition, PBMC are an easily accessible source of different types of adult stem and progenitor cells, such as HSCs, MSCs, osteoclast precursor cells, and EPCs[16]. Due to the content of different types of adult stem cells, in a favorable microenvironment the potential to differentiate into several tissue specific cells including mature blood cells, endothelial cells, hepatocytes, cardiomyocytes, smooth muscle cells, epithelial cells, neural cells, osteoblasts, osteoclasts, and myofibroblasts has been shown[16-18]. Furthermore, compared to bone marrow (BM) or other multipotent cells sources, the isolation of PBMC is less invasive. However, a series of standard procedures for PBMC collection, isolation, cryopreservation and preparation are crucial for their use in cell-based regenerative therapy[15]. PBMC contain terminally differentiated immune cells, namely monocytes and lymphocytes that also a play vital role in tissue remodeling and regeneration[19-21].

### *Monocytes*

Monocytes that contribute approximately 4%-10% of leukocytes in our bloodstream are highly plastic in nature[22]. Monocytes and macrophages are the largest types of white blood cells and are involved in inflammation and elimination of harmful foreign substances[23,24]. As part of the innate immunity they are involved in tissue homeostasis and facilitate wound healing by removing apoptotic and necrotic cells[24].

In regenerative tissues, macrophages are highly plastic and play a decisive role in tissue repair and regeneration[25]. In response to injury and subsequent healing, macrophages are capable of polarization towards a spectrum of phenotypes. Based on the environmental cues and molecular mediators, these cells will differentiate into either pro-inflammatory type I macrophage (M1) or anti-inflammatory type II macrophage (M2) phenotypes[25-27].

Studies have reported that M1 macrophages infiltrate tissues at the earlier stages of acute injury to promote the clearance of necrotic cells or tissue debris. Moreover, following activation M1 macrophages secrete a wide range of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12, IL-18, IL-23, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1[28]. Whereas, M2 macrophages appear within the injured tissue at later stages and release high amounts of anti-inflammatory paracrine factors such as IL-10 and transforming growth factor-β (TGF-β)[25,29]. They are also capable of secreting extracellular matrix (ECM) remodeling components such as fibronectin, osteopontin, fibrin cross-linker transglutaminase and promote tissue healing[30,31]. Although there are controversies regarding the sequential presence of the two different macrophages within tissues, this is because of the dynamic shift in macrophage polarization or the recruitment of new monocytes which do not invalidate the role of macrophages in tissue regeneration.

### *Lymphocytes*

Among the different types of lymphocytes, the regulatory T-cells (Treg) are involved in the repair and regeneration of affected tissues and organ systems. Following injury, Treg are recruited to the site to regulate inflammation and modulate the process of regeneration[32]. Following the initiation of inflammation, Treg inhibit recruitment of neutrophils by secreting IL-10 which in turn helps to minimize the secretion of inflammatory cytokines namely IL-1β, IL-6, interferon (IFN)-γ, and TNF-α. Moreover, Treg induce apoptosis of neutrophils and clear debris by activation of M1 macrophages. In addition, they play a vital role in macrophage polarization towards the M2 phenotype by secreting anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 which eventually support tissue repair and regeneration[32,33]. However, the

regenerative function of Treg follows a tissue specific manner. For instance, in skeletal muscle, Treg infiltrate the tissues in response to IL-33 following activation of the M1 population and removal of necrotic tissues by these cells. Following infiltration, Treg inhibit M1-mediated inflammation and shift the polarization of macrophages towards the M2 population[32]. Whereas, in heart tissues, recruitment of the higher number of Treg induces polarization of macrophages towards the M2 phenotype that help to inhibit inflammation, excessive matrix degradation, and adverse remodeling which eventually reduce ventricular ruptures and increases the rate of survival[34].

## PERIPHERAL BLOOD POLYMORPHONUCLEAR CELLS IN REGENERATION

Neutrophils are the most abundantly found white blood cells in the human peripheral circulation and contribute approximately 50%-70% to all circulatory white blood cells. They are the first leukocyte population recruited to the site of injury and regulate the process of tissue regeneration positively or negatively[32]. However, the role of neutrophils in the process of regeneration is microenvironment-dependent and context-specific.

For example, in the case of skeletal muscle injury, neutrophils impair the restoration and function of muscles by releasing hypochlorous acid, nicotinamide adenine dinucleotide phosphate oxidase, and other cytokines[32,35,36]. Downregulation of lung regeneration following ischemia-reperfusion by neutrophils has also been reported[37]. It is noteworthy that neutrophils have also shown positive effects on the repair of lung epithelium and nerve cells[38,39].

## MESENCHYMAL AND OTHER TISSUE-SPECIFIC STEM CELLS IN REGENERATION

Apart from HSCs, other adult stem cells or tissue-specific progenitor cells such as MSCs, EPCs, mammary stem cells, intestinal stem cells, and neural stem cells are found in adult tissues[40]. Tissue-specific stem cells maintain tissue homeostasis, while MSCs can differentiate into a variety of cell types. MSCs, in particular, have promising cell sources, as they can be harvested from various sources, such as BM, umbilical cord (UC), adipose tissue, and dental tissues[41-43]. Unlike embryonic stem cells (ES cells or ESCs), which are pluripotent, MSCs are multipotent cells which possess limited differentiation potential. Nevertheless, their potential to differentiate into osteoblasts and osteocytes is very well known. There is also accumulating evidence regarding their robust potential in tissue healing and regenerative medicine, in both preclinical and clinical studies[44-46]. According to a recent PubMed search conducted on November 2019, there were 110 MSC-based human clinical trials exploring the safety and efficacy of stem cells for tissue healing and the treatment of degenerative diseases. However, most of these trials were phase I and phase II, or a mixture of phase I/II studies. Whereas, phase III or phase II/III trials which investigate the long-term safety of MSC-based therapies prior to full establishment of MSCs in clinical practice are poorly documented. Thus, BM-derived MSCs (BMSCs) have been the most studied stem cells in cell therapy and tissue repair for the last 5 years, due to their multi-lineage differentiation potential[47].

However, it is worthwhile noting that different MSC populations exhibit tissue-specific characteristics such as the expression of specific cell surface markers and transcription factors. In response to injury signals, these MSCs can potentially migrate from their niche to reach target tissues through vessel walls in the peripheral circulation[48]. Many studies have been conducted to investigate both the chemical and mechanical factors that influence the homing mechanism and engraftment of MSCs into local areas of damaged sites. The chemical factors that affect the trafficking process are the presence of a variety of chemokines, growth factors and cytokines, whereas the mechanical factors involved in the process include ECM stiffness, vascular cyclic stretching and hemodynamic forces or shear stress on the vessel walls[49]. These factors make up the vital characteristics of MSCs and result in their promising effect in tissue healing and differentiation.

The first characteristic of MSCs is their multi-lineage differentiation potential. MSCs are capable of differentiating into several mesoderm lineages, including adipogenic, osteogenic, chondrogenic and myogenic lineages, depending on the multitude of

stimuli and inhibitors present in the tissue microenvironment[50]. The microenvironment plays an important role in the activation or downregulation of transcription factors that regulate the expression of genes responsible for the induction and progression of tissue-specific differentiation[51]. MSCs can also generate neural cells in the ectodermal layer, and hepatic cells and pancreatic cells in the endodermal layer[52]. The study by Chen *et al*[53] was among the first to explore the ability of MSCs to differentiate into functional islet-like cells that might play an important role in the future treatment of diabetes. MSCs cultured in stiff scaffolds can easily differentiate into osteoblasts, and showed the potential for myogenic, adipogenic and neurogenic differentiation, respectively, but with a decrease in elasticity. Recently, Jung *et al*[54] demonstrated that ECM proteins in 3D composites were able to trigger differentiation of BMSCs into mesodermal lineages with enhanced adipogenic differentiation and IL-6 expression compared to that in 2D ECM proteins.

Secondly, MSCs are capable of dynamic interactions with their microenvironment and secrete a wide variety of paracrine factors that are required for tissue recovery or wound healing. Several studies refuted the hypothesis that direct trans-differentiation or cell fusion of MSCs was the principal mechanism underlying their therapeutic action in tissue regeneration[55]. Indeed, MSCs transplantation regulated released factors in experimental models of tissue injury, which was largely associated with suppression of immune and inflammatory reactions, inhibition of apoptosis, and enhancement of cell proliferation and angiogenesis, thereby promoting regeneration of the tissue[56]. Apart of MSCs-mediated secretion of these paracrine and autocrine factors, extracellular vesicles such as exosomes and microvesicles may also regulate these functional roles[57,58]. The MSC-mediated factors released at high levels include the following: (1) Growth factors and their receptors [*i.e.*, granulocyte-macrophage colony-stimulating factor (GM-CSF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-binding proteins (IGFBP3, IGFBP4, IGFBP7) and bone morphogenetic protein 2 (BMP-2)]; (2) Extracellular matrix remodelers/mediators [*i.e.*, periostin, fibronectin, collagen, TIMP metallopeptidase inhibitor 2 (TIMP-2), metalloproteinase inhibitors, and decorin]; and (3) Immune system signaling regulatory proteins (*i.e.*, TGF-β, MCP-1, IL-6, and IL-8)[49,59]. Various studies have demonstrated that the released pro-inflammatory cytokines up-regulate the efficacy of MSC-mediated immunomodulation and functional improvement in microvascular injury[60], inflammatory liver disease[61], osteoarthritis[62], spinal cord injury[63], brain cancer[64], ischemic limb regeneration[65], and asthmatic[66] models. Taken together, it is well accepted that the combination of MSCs with these trophic factors can modulate their behavior during inflammation and tissue injury. Research should now focus on the strategies to manipulate and modulate the secretion of these molecules in the infused or implanted MSCs microenvironment to enhance their functional role[1].

Finally, MSCs exhibit immunomodulatory properties[67-69]. The immunomodulatory properties of MSCs proved effective in treating various immune disorders in both *in vivo* and human studies. MSCs modulate the functions of almost all cells of both the innate and adaptive immune systems and induce an anti-inflammatory phenotype[59]. MSCs interact with a variety of immune cells and have the capacity to inhibit the excessive response of B cells, T cells, macrophages, dendritic cells, and natural killer cells[68]. Nevertheless, the underlying molecular and cellular mechanisms behind MSC-mediated immunomodulation have not been fully elucidated. MSCs have been shown to modulate the immune response by secreting soluble factors [*e.g.*, IL-6, M-CSF, IL-10, TGF-β, HGF, and prostaglandin E2 (PGE2)] in the presence of adhesion molecules [*i.e.*, vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and lymphocyte function-associated antigen (LFA)-3][70-72]. Through a synergy of cell contact-dependent mechanisms and these soluble factors, MSCs are able to initiate the T-cell interactions that play a prominent role in their immunomodulatory potential[71,73]. Furthermore, anti-inflammatory monocytes/macrophages and Tregs are also important in MSC-mediated immunosuppression[69,74]. Studies also linked the low immunogenic properties of MSCs to the lower level of expression of major histocompatibility complex (MHC) class I antigens, and lack of MHC class II and co-stimulatory molecules such as CD80, CD86, and CD40[75,76]. Although the immunomodulatory effect of MSCs is hypothesized to be *via* MSC-secreted cytokines in many studies, most studies documented that MSCs act differently depending on the local microenvironment and the presence of inflammatory cytokines during the pre-treatment of MSCs. An understanding of the immune suppressive role of MSCs would enhance prospective clinical applications of these cells.

Thus, the fate of MSCs is vastly influenced by their environment which includes mechanical or physical stimulation, growth factors, cell density, and cell-cell

attachment or interactions. However, this multipotency of MSCs could also be due to another reason which has been widely discussed. In fact, a debate is currently ongoing regarding the 'stem cell' status of MSCs[77]. It is postulated that MSCs are purely specific adult stem cells, which contradicts findings that MSCs are a diverse mixture of many specific lineage progenitor cells. However, these shortcomings provide a good reason for the continuous research on MSCs in stem-cell based therapy.

## CELL MIGRATION IS ESSENTIAL FOR TISSUE REGENERATION

Progenitors and MSCs migrate and initiate the homing mechanism in response to inflammatory signaling molecules and corresponding receptors around the injured tissue. MSCs are therapeutically capable of reaching and homing to sites of inflammation by various routes such as intravenous (IV), intra-arterial (IA), intraparenchymal, intracoronary (IC) local administration and into the subarachnoid and epidural spaces[48]. From the systemic circulation, MSCs migrate specifically to damaged tissue sites and exert their functional effects locally under a variety of pathologic conditions. Luger *et al*[78] demonstrated that intravenously administered fluorescent and radiolabeled MSCs homed to regions of myocardial injury to suppress the progressive deterioration in left ventricular function and adverse remodeling in mice, and it is thought to be a feasible and effective therapeutic strategy for the treatment of patients with large infarcts and ischemic cardiomyopathy. MSCs homing involves various chemokines and their receptors (*i.e.*, SDF1, CCL5, CXCR4, CXCR5, CXCR6, CCR2, CCR3, and CCR4), matrix metalloproteinases (MMPs) [MMP-2 and membrane type 1 MMP (MT1-MMP)], receptor tyrosine kinase dependent growth factors [*e.g.*, hepatocyte growth factor-Mesenchymal Epithelial Transition Factor (c-Met) proto-oncogene/receptor tyrosine kinase (HGF/c-Met) axes, platelet-derived growth factor (PDGF) and insulin-like growth factor 1 (IGF-1)] and some other adhesion molecules (*i.e.*, integrin β1, integrin α4, and VCAM)[79-82]. These homing signals are released by injured cells and/or respondent immune cells. Besides these homing signals, other molecules are implicated in different steps of the homing process such as PGE2 and hematopoietic cell E-/L-selectin ligand (HCELL) that are functionally involved in cell migration to the injured tissue[83]. These factors could be a feasible strategy to facilitate therapeutic delivery of MSCs to targeted injured tissue.

Of the different chemokines and chemokine-mediated pathways, the SDF1-CXCR4 and HMGB1-SDF1-CXCR4 axis have received considerable attention due to their potential in-site specific directional migration of stem and progenitor cells. The role of HMGB1-SDF1-CXCR4 in regeneration of injured tissues or organs is discussed further below.

## HMGB1-SDF1-CXCR4 AXIS IN FACILITATING TISSUE-SPECIFIC MIGRATION

### *HMGB1 in orchestrating the process of migration and regeneration*

HMGB1 protein is a highly conserved non-histone nuclear protein that binds to DNA and regulates the expression of genes and the chromosomal architecture[84]. Extracellular HMGB1 is actively secreted from activated or stressed immune cells, while passively secreted from necrotic tissues[85,86]. Following secretion into the extracellular space, HMGB1 exerts chemotactic activity or acts as a damage-associated molecular pattern molecule[87]. Indeed, the overall signaling mechanism by HMGB1 interacting with target cells needs to be elucidated for future therapeutic intervention[88].

Wound healing is a complex process that involves the ECM, cytokines, growth factors and several types of cells. The steps involved in the process of wound healing include hemostasis, inflammation, cell migration and proliferation, wound contraction, and remodeling[89,90]. During the inflammatory phase, vasodilation followed by early vasoconstriction which is mediated by histamine, leukotrienes, and prostaglandins, increases capillary permeability and cell migration into the wound site[91]. Neutrophils are the first among the infiltrated cells to the site of injury followed by monocytes and lymphocytes. Initiation of leukocyte migration is mediated by several autocrine and paracrine factors. In addition, proteases are involved in the elimination of denatured ECM components. Following infiltration into the site of injury, monocytes transform into macrophages and clear debris from the area, release

cytokines and growth factors, such as FGF, TGF-β, PDGF, and EGF that help to initiate the formation of granulation tissue[92]. HMGB1 also acts as an important chemotactic factor that regulates the directional migration of monocytes and neutrophils[93]. Following injury or inflammation, HMGB1 is released into the extracellular space and triggers the secretion of TNF, IL-1α, IL-6, and IL-8 from monocytes, macrophages and neutrophils[94-96].

Upon interaction of HMGB1 with the advanced glycation products (RAGE), toll-like receptor (TLR) 2, TLR4, and TLR9, activate pro-inflammatory responses thereby facilitating cell migration and the release of pro-inflammatory cytokines (Figure 1)[97-99]. In 2018, Xue *et al*[100] showed that the HMGB1/RAGE axis mediated migration of neural stem cells (NSCs) by the formation of filopodia which was further linked to the activation of RAGE/Rac and CDC42 or the RAGE/MAPK signaling cascade.

### *SDF1 in upregulation of the HMGB1-SDF1-CXCR4 axis*

SDF1α, known as C-X-C motif chemokine 12 (CXCL12), is a chemotactic factor encoded by the CXCL12 gene on chromosome 10[101]. Studies have reported the therapeutic potential of the SDF1-CXCR4 axis in tissue regeneration. SDF1 is capable of activation, mobilization, homing and retention of HSCs, MSCs and several progenitor cells[80,102-104]. SDF1 is able to bind to CXCR4 and CXCR7. However, the SDF1-CXCR4 axis induces the homing process by regulating the cellular secretion and cell adhesion molecules, while SDF1-CXCR7 is involved in angiogenesis and tumor development[105].

Principally, the binding of chemokine SDF1 to the chemokine receptor CXCR4 plays an important role in homeostatic regulation of leukocyte trafficking, hematopoiesis, organogenesis, cell differentiation and tissue regeneration in response to other molecules that are involved in triggering inflammation[14,106]. The mechanism of MSCs mobilization mediated by HMGB1 is analogous to the recruitment of inflammatory cells to injured tissues for leukocyte trafficking and homing (Figure 1). As mentioned above, HMGB1 acts as a damage-associated molecular pattern which is released either from necrotic cells or by secretion from activated immune cells, hepatocytes, enterocytes, and possibly several other types of cells under distress[107]. Stress conditions that promote HMGB1 secretion include hypoxia[108], lethal irradiation[109], treatment with specific antitumor drugs[110] or through regulation of autophagy[111]. HMGB1-induced cell migration requires both IκB kinase (IKK)-β and IKKα-dependent nuclear factor-κB (NF-κB) activation. IKKβ-mediated activation of NF-κB maintains expression of RAGE, while continuous production of SDF1 is ensured by IKKα-dependent NF-κB activation[112,113]. Moreover, HMGB1 induces both physical and functional interactions between molecules that prevent the degradation of SDF1[114].

In 2012, Kew *et al*[115] proposed that the SDF1-CXCR4 axis works as a co-receptor signal for RAGE receptor-dependent HMGB1 migration responses. Furthermore, SDF1 binding to CXCR4 can also induce CXCR4-TCR heterodimerization, which in turn can enhance gene transcription, cytokine production, increased calcium ion concentrations, and could facilitate cell migration. However, it is possible that the SDF1-CXCR4 axis might have other indirect effects on the regulation of cell migration such as enhancing HMGB1 binding to RAGE, which require further investigation.

### *TLR and RAGE dependent or independent activation of the HMGB1-SDF1-CXCR4 axis*

There is ample evidence of the capability of stem cells to regulate numerous growth factors, cytokines and chemokines. Chemokines, specifically, regulate cell locomotion and integrin function by binding to seven transmembrane domain receptors coupled to G-protein-coupled receptors (GPCR)s, which are heterotrimeric GTP-binding proteins, that are differentially expressed in various cell types[48,107]. In addition, there is always a need to assess the consequences of the combined activity of these chemokines and other inflammatory molecules to control appropriate tissue distribution of distinct leukocyte subsets under normal and pathological conditions. One of the interesting insights in stem cell research is the effect of such paracrine factors in the HMGB1-SDF1-CXCR4 signaling pathway during tissue regeneration.

Extracellular HMGB1 can interact with different molecules to dictate their biologic effects. The role of HMGB1 as a chemokine or cytokine is determined by its oxidative state (Figure 1). The role of extracellular HMGB1 to promote cell migration was first reported in smooth muscle cells in 2010[116]. Similar involvement was also reported in different cell types in the same year by Rauvala and Rouhiainen[117]. Studies showed that HMGB1-induced cell migration requires the formation of a heterocomplex with

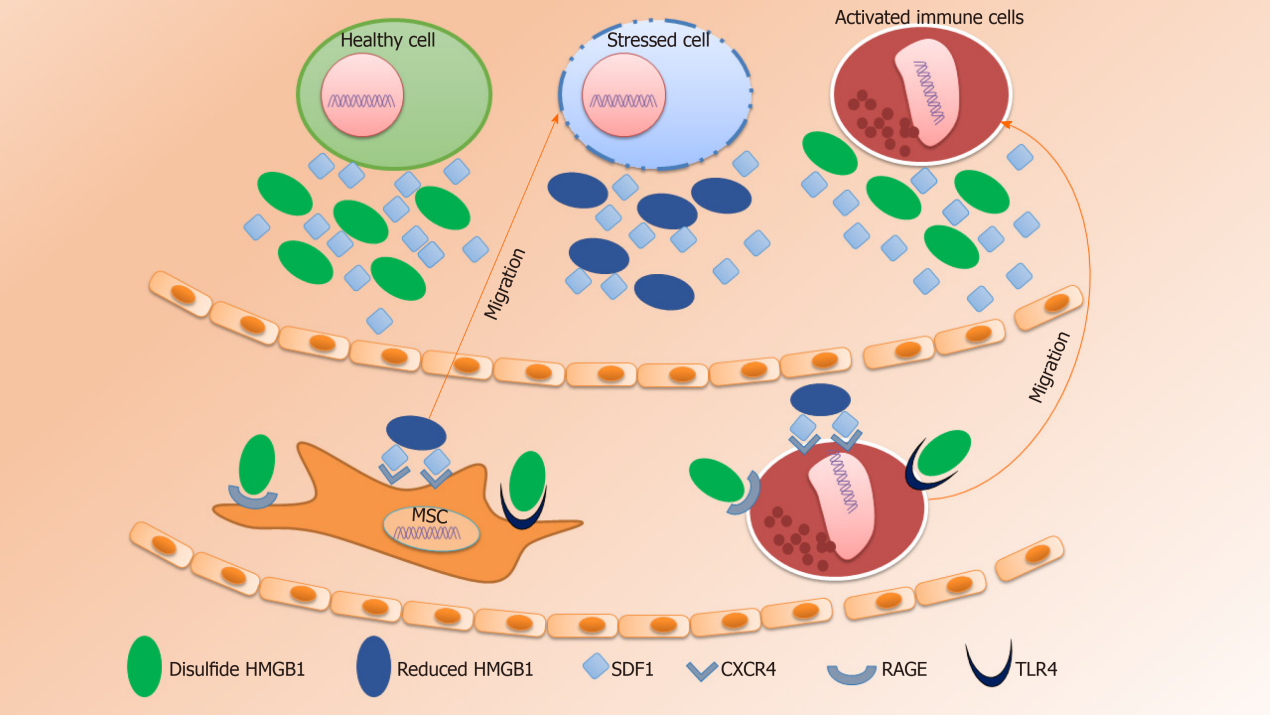


**Figure 1 Schematic diagram of the dynamic HMGB1–CXCL12–SDF1 axis for accelerated tissue regeneration.** Disulfide (oxidized) HMGB1 usually binds to RAGE and TLR and regulates the expression of genes with pro- or anti-inflammatory properties and partial chemotactic properties. Whereas, fully reduced HMGB1 released from necrotic or stressed cells forms a heterocomplex with SDF1 secreted from activated immune cells or from cells within the injured tissues. Later, this heterocomplex binds to the CXCR4 receptors on the cells and facilitates site-specific migration[123-125]. MSC: Mesenchymal stem cells.

SDF1 and further binding with CXCR4, and not with RAGE, TLR2, or TLR4. Furthermore, it was also reported that HMGB1 does not affect migration by other chemokines such as CXCL8, CCL2, CCL7, CCL19, and CCL21[14].

The bonding chemistry between SDF1 and HMGB1 was analyzed by NMR chemical shift mapping and revealed that most of the amino acids present in SDF1 have the ability to bind HMGB1 or its individual HMG boxes[14]. Each HMGB1 molecule has two HMG boxes and thereby can attach two SDF1 molecules at a time. Interestingly, the first few N-terminal residues of the SDF1 molecule do not attach to the HMGB1 molecule and remain free. These free residues can access deep inside the CXCR4 transmembrane domain to initiate signaling cascades[118]. As the HMGB1-SDF1 heterocomplex can present two SDF1 ligand molecules to dimers of the CXCR4 receptor, this heterocomplex would be more efficient than SDF1 alone in inducing cellular migration[119]. Alternatively, the HMGB1-SDF1 heterocomplex may help to unlock the CXCR4 binding site to promote SDF1 binding, or help lock in SDF1 into the CXCR4 transmembrane domain by providing direct HMGB1-CXCR4 contacts.

HMGB1 induces changes in SDF1 residues that are responsible for the activation of CXCR4, the SDF1 receptor. An analysis using fluorescence resonance energy transfer (FRET) demonstrated that there are different conformational rearrangements of CXCR4 homodimers triggered by SDF1 alone or in complex with HMGB1[14]. It has also been hypothesized that the formation of a heterocomplex between HMGB1 and SDF1 acts through CXCR4 which promotes the recruitment of monocytes to the injury site[14]. The interaction of locally produced SDF1 and its receptor CXCR4 expressed on the surface of MSCs plays an important role in the homing of transplanted cells. The binding of SDF1 to both CXCR4 and CXCR7 is also responsible for the production of paracrine mediators, including VEGF, IGF-1, β-FGF and HGF that exert mitogenic, pro-angiogenic, anti-apoptotic, and anti-inflammatory effects[120]. Hypoxia has been shown to enhance the expression of both SDF1 receptors, CXCR4 and CXCR7, in MSCs. Liu *et al*[121] demonstrated that SDF1α is upregulated in ischemic kidneys during reduced oxygen tension. Hypoxia induces expression of CXCR4 and CXCR7 while promoting the role of both SDF1 receptors for enhanced migration, adhesion and survival of hypoxia preconditioned (HP)-MSCs and thus improves homing of systemically delivered MSCs to the ischemic kidney. In addition, in normal culture-expanded MSCs, CXCR4 expression will alleviate progressively and thus could affect its ability to migrate toward the SDF1 gradient in the ischemic tissue.

The intracellular signaling cascades have not yet been clearly demonstrated. In the case of SDF1-CXCR4 bonding, activation and coordination of focal adhesion kinase (FAK) and phosphoinositide 3-kinase (PI3K) were reported in the migration of human dental pulp stem cells[122]. Subsequently, increased β-catenin expression by phosphorylation of protein kinase B (Akt) at ser473 that inhibits the activation of glycogen synthase kinase 3 beta (GSK3β) was also reported. All these results indicate that the SDF1-CXCR4 axis activates the FAK/PI3K/Akt and GSK3β/β-catenin pathways that could facilitate the migration of human dental pulp stem cells. Whereas in the HMGB1-SDF1-CXCR4 axis, elevated extracellular signal-regulated kinase (ERK) phosphorylation and $Ca^{2+}$ release from stores were reported[14]. Elevated ERK phosphorylation was observed in the presence of the SDF1-HMGB1 heterocomplex but not observed in the presence of SDF1 and HMGB1 alone. In the presence of HMGB1 a suboptimal SDF1 concentration was reported with a rapid increase in intracellular $Ca^{2+}$.

## CONCLUSION

Until now, the migration and retention of transplanted cells have been considered a major drawback of cell-based regenerative therapy. SDF1 and its receptor CXCR4 play an important role in maintaining homeostasis by facilitating the homing of progenitor or other adult multipotent stem cells in the BM and regulating their mobilization into peripheral tissues during injury or stress. Studies have shown the potential of the SDF1-CXCR4 axis and/or HMGB1-SDF1-CXCR4 signaling pathways in regulating the process of directional migration followed by retention which are vital for the regeneration of injured tissues or organs. In addition, these pathways could play a major role in regulating the inflammatory conditions at the site of injury. Further studies concentrating on these pathways could make cell-based regenerative therapy more efficient and fruitful.

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