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REVIEW

Strategies to improve homing of mesenchymal stem cells for greater efficacy in stem cell therapy

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Abstract

Stem/progenitor cell-based therapeutic approach in clinical practice has been an elusive dream in medical sciences, and improvement of stem cell homing is one of major challenges in cell therapy programs. Stem/progenitor cells have a homing response to injured tissues/organs, mediated by interactions of chemokine receptors expressed on the cells and chemokines secreted by the injured tissue. For improvement of directed homing of the cells, many techniques have been developed either to engineer stem/progenitor cells with higher amount of chemokine receptors (stem cell-based strategies) or to modulate the target tissues to release higher level of the corresponding chemokines (target tissue-based strategies). This review discusses both of these strategies involved in the improvement of stem cell homing focusing on mesenchymal stem cells as most frequent studied model in cellular therapies.

Keywords: chemokine receptors; homing; mesenchymal stem cells; preconditioning; therapy

Introduction

Although the healthcare sectors have made great advances in medical sciences during recent decades, there are millions of people living with incurable diseases around the world waiting for scientific breakthroughs to improve their health. Stem cell therapy, which may hold promise for patients in their normal life, also became a hope line for the community. As the field of stem cell biology progressed, it was hypothesized that MSCs have the potential to deliver this "promise". Some criteria were proposed to define MSCs; first, MSCs must be plastic-adherent when maintained in standard culture conditions using tissue culture flasks; second, $\geq$ 95% of the MSC population must express CD105, CD73, and CD90; and these cells must lack expression ($\leq$ 2% positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA class II; third, the cells must be able to differentiate into osteoblasts, adipocytes, and chondroblasts under standard in vitro differentiating conditions (Dominici et al., 2006). MSCs have been isolated from bone marrow (Edalatmanesh et al., 2011) and many other tissues, e.g. adipose tissue (Poloni et al., 2013), umbilical cord matrix (Simoes et al., 2013), synovium (Futami et al., 2012), hair follicle (Zhang et al., 2013) and olfactory bulbs (Huang et al.,

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Abbreviations: MSCs, mesenchymal stem cells; GCSF, granulocyte colony-stimulating factor; GPCRs, G protein-coupled receptors; VPA, valproate; Li, lithium; HDAC, histone deaceteylase; SDF, stromal cell derived factor; DFO, deferoxamine; HIF-1α, hypoxia-inducible factor 1α; hAd, human adipose tissue derived; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; IL, Interleukin; MLC, myosin light chain; BMMSC, bone-marrow-derived multipotent stromal cells; PPG, palmitated protein G; IBD, Inflammatory bowel disease; HCELL, hematopoietic cell E-selectin/L-selectin ligand; GPS, glycosyltransferase-programmed stereosubstitution; SLeX, sialyl Lewis X; UTMD, ultrasound-targeted microbubble destruction; CH-GP-HEC, chitosan-beta glycerophosphate-hydroxyethyl cellulose; PLGA, poly (lactic-co-glycolic acid); HDFs, hypo-dermal fibroblasts; ATCs, Achilles tendon cells; HA, hydroxyapatite; LhCG, living hyaline cartilage graft; ECM, extracellular matrix; MCP3, monocyte chemotactic protein-3; EF, electric fields; hiPSCs, human induced pluripotent stem cells; hESCs, human embryonic stem cells; PDGF-BB-R, platelet-derived growth factor BB receptor; TGFβR1, transforming growth factor-β1 receptor; IGF-1, insulin-like growth factor-1; MMP-2, matrix metalloproteinase-2; MT1-MMP, membrane type-1 matrix metalloproteinase

2013). MSCs might be beneficial tools for tissue repair, since they produce a variety of cytokines and paracrine factors, such as anti-inflammatory, neurotrophic, angiogenic, immunomodulatory, antifibrotic, antiapoptotic, and survival factors (Caplan and Correa 2011; Larsen and Lewis, 2011; Mundra et al., 2013).

Endogenous MSCs as well as exogenously transplanted MSCs can migrate and participate in tissue repair. Based on this hypothesis, several clinical trials have assessed the safety and efficacy of MSCs for treatment of several diseases (Ohnishi and Nagaya 2007). GCSF and AMD3100 (a CXCR4-antagonist) can mobilize endogenous MSCs from bone marrow into the peripheral blood followed by integration into injured tissues (Deng et al., 2011; Karimabad et al., 2011). However, efficacy of the cell recruitment by the mobilizing factors in patients has had no therapeutic success in related clinical trials (Karimabad et al., 2011). As a consequence of the failure to reach a practical and therapeutic method, scientists have considered using exogenously expanded MSCs. This approach, however, seems to suffer from a major obstacle, as the transplanted cells fail to find their way to damaged tissue. They either die in circulation without leaving vessels after their intravenous injection into the body (Karp and Leng Teo, 2009), or are trapped in unwanted organs, e.g. liver, lungs, and spleen (Barbash et al., 2003; Makinen et al., 2006; Haddad-Mashadrizeh et al., 2013). About 1% of the delivered cells can find their way to the target tissues (LaBarge and Blau, 2002; Barbash et al., 2003; Zhang et al., 2007). It might be hypothesized that increasing the number of injected cells could compensate for the low density of the migrated stem cells, but injection of too many cells may be risky for disturbance in blood flow causing worse problems (Walczak et al., 2008). To acquire a huge number of cells, they should be cultured for a long period of time, which may change their properties and make them unsuitable for clinical applications. The alternative approach to avoid cell loss would be direct injection of the cells into the damaged tissue. However, the invasive procedures for cell delivery downgrade its validity in clinical level (Charwat et al., 2008; Wagner et al., 2009). Furthermore, most of the locally injected cells escape from the injury site (Dell'Accio et al., 2001; Huang et al., 2008). Thus, the focus should be given on the development of appropriate strategies with standards of safety and efficacy acceptable for clinical practices.

Based on the experimental observations that the effective homing of the exogenously transplanted cells greatly improve the efficacy of cells to integrate and function in the target tissues, this review discusses the two main aspects of subject: (1) factors that increase the ability of stem cells to respond to the migratory stimuli; and (2) methods for modulating the target sites to be more attractive for stem cell recruitment (Figure 1).

Some prefer to use the terminology of mesenchymal stromal cells or mesenchymal stem/stromal cells instead of MSCs because the cells used for research and therapy are often heterogeneously cultured cells that are not strictly all stem cells. This may affect their homing and retention in tissues. In this review, we have tried to keep terms used in the cited articles.

Strategies for improvement of stem cell homing

Increasing the ability of stem cells to respond to migratory stimuli (stem cell-based strategies)

MSCs express a group of receptors (Sordi et al., 2005; Ahmadian Kia et al., 2011) that play a crucial role in cell chemotaxis and migration by interaction with appropriate ligands (Wu and Zaho, 2012). Chemokines and their receptors have been identified as mediators of cell trafficking. Chemokines or chemoattractant cytokines are a large family of small secreted proteins that bind to GPCRs, and which can be categorized into four classes based on the basis of variations in a conserved cysteine motif of the mature proteins. The first group of chemokines is the CC family, composed of 28 members, and the second group is CXC family, possessing a single variable amino acid between the first two cysteines, and having 17 members. The CXC chemokines can be further classified into two subfamilies based on the presence or absence of specific motif, namely glu-leu-arg (ELR). Other families are CX3C and XC, with only one member in each (Lazennec and Richmond, 2010). There are 47 chemokines that bind to four classes of chemokine receptors. Many of these chemokines bind to multiple receptors and most of them, except for CX3CR1 and CXCR4, also bind to multiple chemokines. This suggests the possibility of functional redundancy, and their spatial and temporal control of expression. CXCR4/SDF-1 constitutes one of the most efficient chemokine/chemokine receptor pairs regarding cell homing (Lazennec and Richmond 2010). Inadequate amounts of the crucial receptors on the cell surface may be responsible for inefficient homing of the cells to their target tissues (Wynn et al., 2004; Komarova et al., 2010). Here, we discuss some strategies to overcome this pitfall.

Treatment with chemical compounds

MSC treatment with certain chemicals can trigger signaling pathways leading to expression of key mediators involved in cell trafficking. Tsai et al. (2011) showed that treatment of rat MSCs with VPA and/or Li and then their transplantion into a stroke model of rat resulted in robust migration and proper homing of the MSCs towards the ischemic site followed by functional recovery, increased angiogenesis, and a reduced infracted zone in the brain. They proved that enhancement

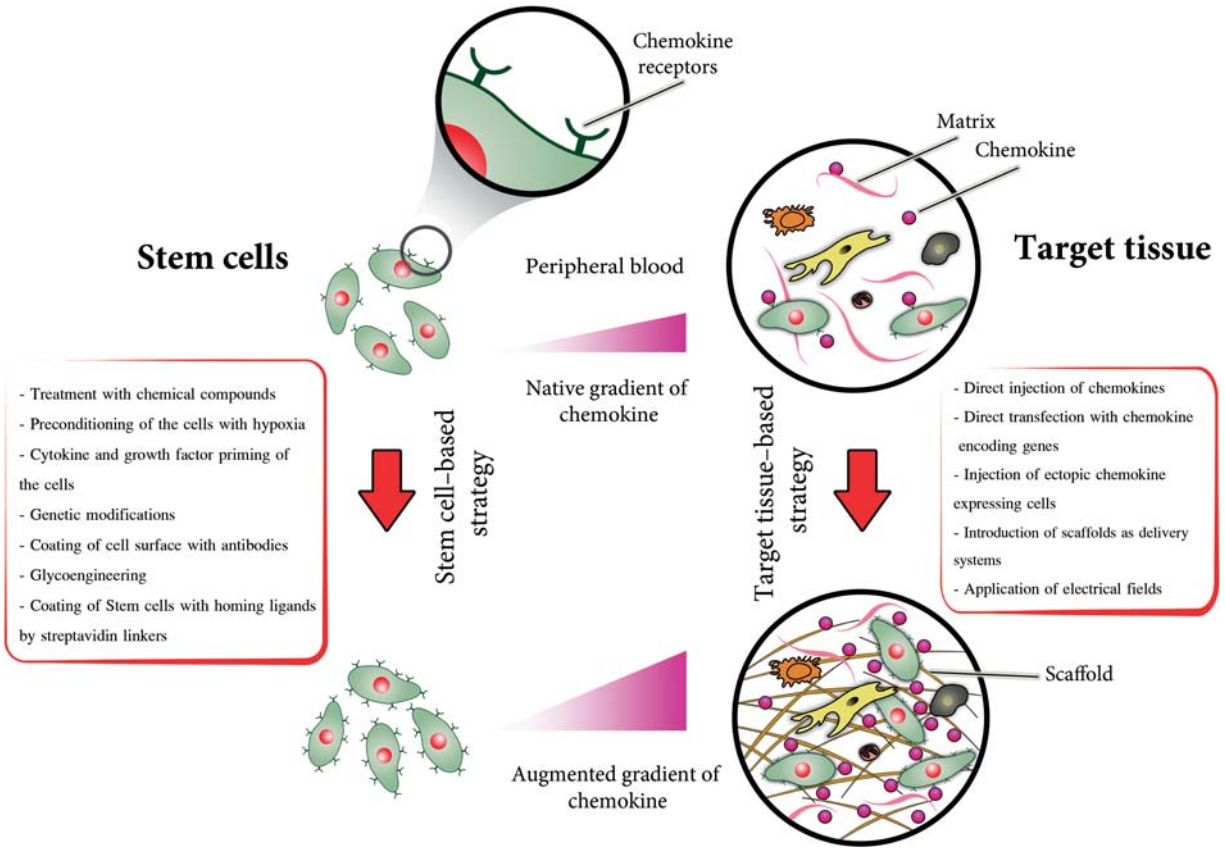

Figure 1 Schematic overview of the experimental strategies to improve homing of MSCs. Strategies can fall into two main categories, i.e. methods that increase the ability of MSCs to better respond to chemotaxis, migratory and homing stimuli, and methods that modulate the target sites to be more attractive for MSCs' recruitment.

of MSC migration is mediated by increasing CXCR4 expression by inhibiting HDAC, including the HDAC1 isoform, or by elevating MMP-9 level through glycogen synthase kinase-3β inhibition. Chemokine SDF-1α and its receptor, CXCR4, are involved in stem cell homing to remote injury sites (Kucia et al., 2004; Pasha et al., 2008; Sharma et al., 2011). Treatment of MSCs with DFO, an iron chelator, leads to increased surface expression of the CXCR4, CCR7, and HIF-1α proteins, and also MMP-2 and MMP-9 activity is significantly increased compared to control groups. The in vitro migration, as well as in vivo homing of DFO-treated MSCs is significantly higher than control groups. It is claimed that this effect is mediated by the availability of HIF-1α (Najafi and Sharifi, 2013). HIFs are transcription factors that respond to changes in available oxygen in the cellular environment. There are different members of the human HIF family, including HIF-1, HIF-2, and HIF-3. The potential roles of HIF-2 and HIF-3 in cell migration have not yet been confirmed. HIF-1 consists of two subunits: HIF-1α and HIF-1β. At the normal oxygen level, HIF-1α protein, is rapidly degraded by prolyl-hydroxylase, whereas HIF-1β is expressed constitutively in all cells and does not respond to oxygen tension. DFO can stabilize HIF-1α under normoxic conditions by inhibiting prolyl-hydroxylase (Sharp and Bernaudin 2004; Chu et al., 2008), and its stabilization increases HIF-1 activity, resulting in transcription of many genes involved in cell migration (Tsai et al., 2012). Cobalt chloride and hydralazine also have similar effects on HIF-1 stabilization and cell migration (Knowles et al., 2004; Hoenig et al., 2008; Yu et al., 2013), which is tempting to consider them as cell migration promoting components.

Preconditioning of the cells with hypoxia

Short term exposure of MSCs to hypoxia might induce the expression of some genes involved in cell migration, e.g. CXCR4, CXCR7, CX3CR1, and SDF-1α (Hung et al., 2007; Liu et al., 2012). HIF-1 was introduced as a master regulator of this effect (Mamalis and Cochran, 2011; Mimeault and Batra, 2013). Hypoxic preconditioning of mice bone marrow derived MSCs could improve cell migration, adhesion and survival. These processes are mediated by activation of PI3K/

AKT-HIF-1α-CXCR4/CXCR7 pathway (Liu et al., 2010). Hu et al. (2011) demonstrated that hypoxic preconditioning increased MSCs migration into the infarcted myocardium of mice, and provided evidence that this effect was mediated by increased expression of the Kv2.1 channel protein, leading to FAK phosphorylation/activation. Activated FAK binds to several proteins involved in regulation of cell adhesion and migration.

Hypoxic preconditioning of MSCs has been introduced as a positive therapeutic approach for ischemic diseases (Wei et al., 2013; Yue et al., 2013). The oxygen tensions depend on the type of cells, as these rates for the typical cell culture conditions, normal bone marrow, and ischemic tissues are 21, 5, and 1% or lower, respectively. In cell transplantation programs, it is believed that the injected MSCs must rapidly adapt themselves to the significantly lower oxygen tension in the ischemic tissue. It seems that in vitro preconditioning of the cells with hypoxia would increase their survival rate in vivo. Previous studies have indicated that the hypoxic preconditioned human MSCs have shown much better performance than unconditioned control cells in motility status and therapeutic potential (Rosova et al., 2008). Therefore, based on these data, short-term hypoxic preconditioning has been introduced as another strategy for increasing the injected MSCs population at an injured site because of their enhanced migration and survival rates.

Priming of the cells with cytokines and growth factors

To see whether the migration activity of hAd-MSCs could be influenced by prior stimulation with chemokines or growth factors, Baek et al. (2011) pretreated hAd-MSCs with RANTES, SDF-1α, HGF, TNF-α, PDGF-AB, or TGF-b1. Among these, TNF-α induced the highest level of chemotaxis. Shi et al. (2007) showed that a cocktail of five cytokine containing Flt-3 ligand, SCF, IL-6, HGF, and IL-3 increased the homing ability of FLK^{+} MSCs derived from human fetal bone marrow to SDF-1. They also proved that this effect is mediated by upregulation of CXCR4 protein in hAd-MSCs, and that the CXCR4/SDF1 axis is important in the homing process.

The effect of CCL25 stimulation on chemotaxis of human MSCs has also been investigated, indicating that the genes coding for proteins, known to be involved in cellular movement, are highly regulated, and in accordance with it, the secretion of proteins and chemotaxis are also increased (Binger et al., 2009).

Genetic modifications

Overexpression of α4 subunit of the VLA-4 integrin in MSCs, using adenoviral vector, results in increased MSCs homing to bone marrow in a mouse model (Kumar and Ponnazhagan 2007). VLA-4 integrin is composed of CD49d (α4) and CD29 (β1), whose heterodimerization and interaction with VCAM1 results in firm adherence of circulating cells to the endothelium, followed by endothelial transmigration (Springer 1994; Jacobsen et al., 1996; Schweitzer and Drager, 1996).

Bobis-Wozowicz et al. (2011) found that hAd-MSCs, with an overexpressed level of CXCR4, showed increased motility, invasiveness and homing to bone marrow of NOD/SCID mice. Ryser et al. (2008) also showed that overexpression of the CXCR4 receptor at mRNA level allows the transient initiation of chemotaxis in MSCs. Transient over-expression of CXCR4 could lead to an increased in vivo mobilization, and engraftment of the MSCs into the ischemic areas promoted neomyoangiogenesis and alleviated early signs of the left ventricular remodeling (Zhang et al., 2008).

CXCR4 and CXCR7 genes have been ectopically overexpressed in mouse bone marrow derived MSCs (BM-MSCs). However, the results indicated that the migration of both native and genetically manipulated MSCs to the injured kidney were the same at very low level, and that the transplantation of the manipulated cells gave no signs of tissue recovery (Gheisari et al., 2012).

CXCR4 mRNA transcripts have been transfected into the human MSCs, without any significant improvement in their cell migration; and therefore, it was concluded that there might be other factors responsible for MSC chemokinesis, independent from CXCR4/SDF-1α axis (Wiehe et al., 2012). Although, CXCR4/SDF-1α axis has emerged as an important regulator of cell mobilization and trafficking during tissue regeneration, it seems that this might not be the precise axis to enhance the MSCs homing. Hence, the challenge remains to introduce the responsible players beside the previously reported CXCR4/SDF-1α axis in the process of cell homing.

Coating of cell surface with antibodies

Making an antibody with double affinity has been another innovative idea introduced for targeting and retaining stem cells in the damaged tissues. Gundlach et al. (2011) synthesized a bispecific antibody, including an anti-CD90 recognizing MSCs and an anti-MLC. MLC increases after cardiac infarction in ischemic myocardium (Lyn et al., 2000). This construct induced murine BMMSC adhesion to the immobilized MLC1 substrate (Gundlach et al., 2011), while the efficiency of this construct in clinical application has been remained to be examined.

MSCs have been coated with antibodies that react against VCAM-1 and MAdCAM-1; these endothelial addressins direct leukocyte migration to inflamed tissues by their cognate receptors, such as α4β1 integrin (VLA-4), that binds VCAM-1 or fibronectin (Alon et al., 1995), and α4β7 that binds MAdCAM-1 (Takada et al., 2007). Conjugation of the antibodies to the surface of MSCs was done with

intervention of PPG. This coating increased cell homing to the inflamed colon after systemic delivery and elevated the efficacy of the MSCs to improve treatment of IBD. This effect was mediated by MSCs immunosuppressive capabilities (Ko et al., 2010).

MSCs coated with PPG followed by antibodies against ICAM-1 promoted MSCs attachment to the endothelial cells, which resulted in resistance to high flow conditions (Ko et al., 2009). However, whether rolling and transmigration of the MSCs from endothelium is possible after this thigh attachment, remains questionable.

Glycoengineering

Cell migration involves a cascade of events initiated by shear-resistant adhesive interactions between flowing and endothelial cells at the target tissue. Interaction of E-selectin which is expressed on the endothelial cells, with its ligand on the migrating cells has a key role in this step. E-selectin is a lectin that binds to the specialized carbohydrate determinants, prototypically consisting of sialofucosylations containing an α-2,3-linked sialic acid substitution on galactose and an α-1,3-linked fucose modification on N-acetylglucosamine. Together they are displayed as the terminal tetrasaccharide sialyl Lewis X. This ligand is also named HCELL, because it is expressed in the hematopoietic stem cells. MSCs do not express E-selectin ligands, whereas expression of a CD44 glycoform bearing α-2,3-sialyl modifications by them is obvious. After application of an α-1,3-fucosyltransferase under specific enzymic conditions, the native CD44 glycoform on MSCs is converted to a ligand for E-selectin without effects on cell viability or multipotency. As E-selectin is mostly expressed in bone marrow, dermal microvascular endothelium and post-capillary venules at all sites of the injured tissues, HCELL in its engineered form on the human MSCs therefore can serve as a homing receptor (Sackstein, 2009, 2011a,b). Injection of the HCELL-bearing human MSCs into mice led to significant homing of the cells into bone marrow (Sackstein et al., 2008). A high level of HCELL directly induces VLA-4 activation via a Rac1/Rap1 GTPase signaling pathway, resulting in transendothelial migration of human MSCs to the stimulated human umbilical vein endothelial cells without chemokine input (Thankamony and Sackstein 2011). GPS was named after the technology developed for modifying CD44 glycans to create HCELL on the surface of living cells (Sackstein, 2009, 2012a,b).

Coating of stem cells with homing ligands by streptavidin linkers

Tethering, rolling, adhesion, extravasation, and engraftment are consecutive steps of homing processes. Enhancement of each step could lead to improvement of the cell homing process. Some researchers have focused on improvement of rolling step by introduction of SLeX to the surface of MSCs (Sarkar et al., 2008, 2010, 2011a,b). SLeX with selectins, expressed by endothelial cells of inflamed tissues, is required for promotion of cell rolling (Zhang et al., 2004; Luster et al., 2005; Simon and Green, 2005). To achieve this goal, SLeX was conjugated to the surface of primary human MSCs through a simple procedure (Sarkar et al., 2008, 2010, 2011a,b). They first modified the surface of MSCs by biotinylated lipid vesicles, followed by incubation with streptavidin to provide biotin-streptavidin bridges. Biotinylated SLeX was added to the culture to immobilize the homing ligand of SLeX on the cell surfaces. There was an increased rolling of the SLeX-MSCs on P-selectin coated substrate in vitro, and their migration towards the inflamed tissue was enhanced in vivo when administered systemically. This strategy seems to be applicable for different cell types and also for targeting a number of tissues in cell therapies. For better effect, identification of the receptors, expressed specifically on endothelium of the target tissues, is a very crucial step. This would pave the way for construction of chemically engineered cells with proposed ligands to improve the results.

Although a number of strategies has been introduced to increase the ability of stem cells to respond to migratory stimuli, ex vivo expansion and manipulation may alter some characteristics, such as proliferative capacity, differentiation potential, and genetic stability of cells. This may negatively affect their safety at clinical level. Therefore some prefer to modulate the target sites, an approach for designing more attractive environments to enhance stem/progenitor cells recruitment. These strategies are conceived as being more effective for targeted homing than stem cell-based strategies.

Modulating the target sites for attraction of stem cells

After tissue injury, SDF-1α expression increases in the damaged cells leading to recruitment and retention of progenitor cells at the injury site via chemotactic attraction towards a gradient of SDF-1α (Hu et al., 2007; Saxena et al., 2008). However, since the natural phenomenon of increased SDF-1α does not seem sufficient for complete regeneration and repair of the lesions, more comprehensive approaches are being sought to enhance chemotactic attraction of the stem/progenitor cells to the injured tissue/organs, as discussed below.

Direct injection of chemokines

The direct injection of the chemokines into target sites is under investigation. Sasaki et al. (2007) found that direct injection of SDF-1α into the ischemic myocardium in mouse model decreased infarction by enhancing recruitment of the

bone marrow cells to the location, followed by angiogenesis. Similar results were reported by Yamaguchi et al. (2003) in limb ischemia, from which it was suggested that functional recovery of an injured organ after direct delivery of SDF-1α was probably due to the enhanced recruitment of the circulating cells, which is followed by neovascularization (Saxena et al., 2008). However, due to the short half-life of SDF-1 protein and its degradation by proteolytic enzymes in the injured tissues, a bioengineered protease-resistant SDF-1 that retains its chemotactic potential was used (Segers et al., 2007, 2011).

Direct transfection of the target tissue with chemokine encoding genes

UTMD may be a non-invasive and selective approach for gene delivery. In this approach, plasmids containing gene of interest are conjugated with lipid microbubbles, which release plasmid DNA when exposed to ultrasound beam (Bekeredjian et al., 2005). In a study, therapeutic genes of SCF and SDF-1α were delivered to infracted myocardium of rat by UTMD method. The results indicated a significant increase in SDF-1α at mRNA and protein levels, followed by an increased homing of CXCR4-positive cells to the myocardium (Fujii et al., 2011). In a clinical trial (phase I), 17 patients were enrolled to receive JVS-100 by endomyocardial injection. JVS-100 is a DNA plasmid encoding SDF-1. After 12 months, improvement in quality of life was reported (Penn et al., 2013).

Injection of cells expressing ectopic chemokine

Considering the increased natural level of SDF-1 after organ injury and its effect in recruitment of the endogenous stem/progenitor cells, it was hypothesized that transplantation of stem cells with elevated level of SDF-1 might be an advantage. Zhao et al. (2009) found that injection of MSCs overexpressing SDF-1α to the ischemic hearts significantly increased migration of bone marrow derived progenitor cells and greatly enhanced the cardiac regeneration. Others have confirmed functional recovery following the increased migration of the endogenous cells in the case of ischemic myocardium and diabetic wounds after applying of same protocol (Di Rocco et al., 2010; Blumenthal et al., 2011).

Application of scaffolds as delivery systems in target tissue

Controlled release of a chemokine from various biomaterials enhances recruitment of MSCs towards them. Recently, it has been proposed that injectable hydrogels, such as CH-GP-HEC, are good candidates for in situ cartilage tissue regeneration by recruitment of MSCs (Naderi-Meshkin et al., 2014). Schantz et al. (2007) achieved site-specific homing of MSCs toward a cellular polycaprolactone scaffold, which was constantly releasing SDF-1 with micro delivery device in vivo. Gelatin hydrogel (Kimura and Tabata 2010), PLGA scaffolds (Thevenot et al., 2010), and poly (lactide ethylene oxide fumarate) hydrogel (He et al., 2010) have also been used to achieve MSCs recruitment. In particular, Shen et al. (2010) developed a bioactive knitted silk-collagen sponge scaffold by incorporation of exogenous SDF-1α. This strategy enabled selective migration and homing of CXCR4-expressing fibroblast cells, HDFs and ATCs, and resulted in in situ tendon regeneration and decreased accumulation of inflammatory cells.

ch/γ-PGA polyelectrolyte multilayer films (PEMS) have been used as scaffold and optimized as SDF-1 delivery system. SDF-1 retained its biological activity after incorporation with proposed scaffold, and also sustained and controlled release of SDF-1 promoted migration of the MSCs in vitro (Goncalves et al., 2012).

Incorporation of some bone matrix molecules, such as collagen I and HA, into scaffold would increase adsorption and release of growth factors, followed by enhanced migration and adhesion of the MSCs to the scaffold (Phipps et al., 2012). In these studies, scaffolds were used as delivery systems for the chemokines. Others have preferred to use the scaffolds as delivery systems for vectors carrying the genes, required for chemokine secretion. Zhang et al. (2013) used a recombinant adenoviral vector, carrying SDF-1 transgene that was constructed and applied to transduce LhCG which is a cartilage graft composed of living chondrocytes and their cartilaginous ECM. After implantation, SDF-1-LhCG released recombinant SDF-1 chemokine in an animal model and increased migration rate of the stem/progenitor cells via systemic circulation towards the implanted graft and also enhanced the cartilage regeneration of the proposed graft.

In some other studies, scaffolds were used as delivery systems for modified cells. Shinohara et al. (2011) showed that transplantation of a collagen scaffold, equipped with MSCs overexpressing SDF-1 or MCP3, adjacent to a fracture site enhanced homing of systemic circulating osteogenic cells. This was support for the hypothesis claiming the positive impact of SDF-1 and MCP3 for induction of homing in stem cells.

Thieme et al. (2009) reported that 3D porous bone substitute scaffolds, equipped with modified BM-MSCs, not only serve as scaffold in large bone defects but also attract MSCs to the location. They showed that transient overexpression of the CXCR4 gene in human BM-MSCs, induced by mRNA transfection, enhances SDF-1α directed chemotactic capacity to internal compartments of the implanted SDF-1α releasing scaffolds in vitro and in vivo. These techniques seem to be more targeted; localized and high efficiency, however, makes it difficult to optimize the release profile of chemokines in vivo.

Application of electrical fields

EF induce rapid and directed migration of the neural precursor cells (Babona-Pilipos et al., 2011; Feng et al., 2012). A clinical trial in spinal cord injury showed considerable recovery of the injured area after exposure to the weak EF (Borgens 1988; Tator 2005). Li et al. (2008) found that physiological EFs enhanced neural stem/progenitor cell migration toward the cathode and suggested that the underlying signal transduction pathway might be NMDAR/Rac1/actin. It has been established that endogenous EF in embryo has a critical role in correct migration of the neural stem cells and development of the nervous system (Nuccitelli 2003; McCaig et al., 2005).

Zhang et al. (2011) investigated the application of EFs to guide migration of hiPSCs, and hESCs in 2D (matrigel-coated electrotactic chamber) and 3D (custom designed 3D electrotactic chambers filled with polymerized matrigel) culture conditions. hiPSCs migrated directionally in the

Table 1 Advantage and disadvantage of suggested strategies to increase homing of stem cells to the target tissues.

Strategy	Advantages	Bottlenecks	References
I) Strategies for improvement of stem cells respond to migratory stimuli (Stem cell-based)			
Treatment with chemical compounds	Simple, Fast	Safety problems, Probable changes in gene expression, Insignificant effect on preventing cell distribution into non-targeted organs	Knowles et al., 2004; Hoenig et al., 2008; Tsai et al., 2011; Tsai et al., 2012; Najafi and Sharifi 2013; Yu et al., 2013
Preconditioning of the cells with hypoxia	Simple, Fast	Optimization problems, Insignificant effect on preventing cell distribution into non-targeted organs	Hung et al., 2007; Rosova et al., 2008; Liu et al., 2010; Hu et al., 2011; Liu et al., 2012; Wei et al., 2013; Yue et al., 2013
Cytokine and growth factor priming of cells	Simple, Fast	Safety problems, Probable changes in expression of unwanted genes, Expensive, Insignificant effect on preventing cell distribution into non-targeted organs	Shi et al., 2007; Binger et al., 2009; Baek et al. 2011
Genetic modifications	More directed	Safety problems, Difficult and expensive, Risk of tumorigenicity, Insignificant effect in preventing cell distribution into non-targeted organs	Kumar and Ponnazhagan, 2007; Ryser et al., 2008; Zhang et al., 2008; Bobis-Wozowicz et al., 2011; Gheisari et al., 2012; Wiehe et al., 2012
Coating of cell surface with antibodies	More directed	Difficult and expensive	Ko et al., 2009, 2010; Gundlach, 2011
Glycoengineering	More directed	Difficult and expensive	Sackstein et al., 2008; Sackstein, 2009, 2011, 2012a,b
Coating of stem cells with homing ligands bystrept-avidin linkers	More directed	Difficult and expensive	Sarkar et al., 2008, 2010, 2011a,b
II) Modulating the target sites for being more attractive for stem cells recruitment (Target tissue/organ-based)			
Direct injection of chemokines	Simple, Fast, Targeted	Short half-life of chemokines, Diffusion to surrounding milieu, Degradation by resident proteases	Yamaguchi et al., 2003; Sasaki et al., 2007; Segers et al., 2007, 2011; Saxena et al., 2008
Direct transfection of target tissue with chemokine encoding genes	Targeted	Immunogenicity, Retroviral-mediated insertional mutagenesis, Expensive, Difficult	Fujii et al., 2011; Penn et al., 2013
Injection of ectopic chemokine expressing cells	High efficiency	Safety problems, Difficult and expensive	Zhao et al., 2009; Di Rocco et al., 2010; Blumenthal et al., 2011
Application of scaffolds as delivery systems into target tissues	More targeted, Localized, Highly efficient	Difficulty of optimization for release profile of chemokines, Expensive	Schantz et al., 2007; Thieme et al., 2009; He et al., 2010; Kimura and Tabata, 2010; Shen et al., 2010; Thevenot et al., 2010; Shinohara et al., 2011; Goncalves et al., 2012; Phipps et al., 2012; Zhang et al., 2013; Naderi Meshkin et al., 2014
Application of electrical fields	Easy to use, Cheap	Hard to optimize	Borgens, 1988; Nuccitelli, 2003; McCaig et al., 2005; Tator, 2005; Li et al., 2008; Babona-Pilipos et al., 2011; Griffin et al., 2011; Zhang et al., 2011; Feng et al., 2012

presence of EF in a voltage dependent manner and EF exposure did not affect expression of stem cell markers. hiPSCs showed more sensitivity and directedness to the EF in comparison with hESCs. Accordingly, they suggested a critical role for Rho/ROCK signaling in galvanotaxis of hiPSCs. Griffin et al. (2011) found that BM-MSCs treated by EF significantly overexpressed several migratory related genes, including SDF-1/CXCR4, PDGF-BB-R, TGFβR1, IGF-1, and its receptor IGF-1 receptor (IGF-1R). EF treated cells also showed higher cell invasion through the collagen barrier which correlates with the higher expression of MMP-2 and MT1-MMP.

Although optimization is hard in vivo, EFs seem to be safe in human, thus they are used in cell therapy and can bring better clinical results by enhancing directed cell migration to the damaged tissues.

Advantages and drawbacks

In this review, two kinds of strategies regarding chemokine/chemokine receptor interactions, and their potential impacts on cell therapy to improve stem cell homing, have been discussed. Despite the promising literature, the notion still suffers from seveal drawbacks and there may be a gap between these experimental approaches and their application in clinic. Some of the advantages and drawbacks faced by stem/progenitor cells and target tissues/organs regarding application of the above mentioned strategies are summarized in Table 1.

Conclusions and future outlook

A number of stem/progenitor cells respond positively to chemokines with a direct or indirect correlation to the homing of cells. Accordingly, considerable effort has been made to develop engineering techniques, targeting either cells or target tissues/organs utilizing chemokine ligand/receptor axis to enhance stem cell homing to the injury site. In spite of preliminary success in the improvement of cell properties (cell-based strategies) to yield higher homing efficiency, they are either expensive or difficult to accomplish. These strategies also have safety problems from different points of view, including incomplete localization to the injury site. Therefore, to address these concerns, many have focused on developing target tissue/organ-based strategies. Among different strategies involved in modulating target sites, it seems that using equipped scaffolds for the delivery of the chemokines are more attractive. Several SDF1-incorporated scaffolds have been designed to attract endogenous or transplanted stem/progenitor cells with high content of its specific receptor, CXCR4, to regenerate damaged tissues in situ. In an innovative way, it is proposed combining the two kinds of strategies to get greater efficiency of homing and better subsequent outcomes, i.e. using both cell-based and target tissue-based methods together.

These extensive investigations have provided significant potential for enhancing targeted stem/progenitor cell homing. There are some limitations that make it difficult to apply these findings in clinics. To overcome these limitations, we need to understand the molecular and cellular mechanisms underlying endogenous cell trafficking during physiological and pathological events, e.g. embryogenesis, inflammation, wound healing and, cancer metastasis.

Addressing these biological issues would lead to higher efficiency and efficacy of stem cell homing, and hopefully clinical trials will be replaced by routine clinical application of cells in the case of incurable diseases.

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References

Ahmadian Kia N, Bahrami AR, Ebrahimi M, Matin MM, Neshati Z, Almohaddesin MR, Aghdami N, Bidkhori HR (2011) Comparative analysis of chemokine receptor's expression in mesenchymal stem cells derived from human bone marrow and adipose tissue. J Mol Neurosci 44(3): 178–85.

Alon R, Kassner PD, Carr MW, Finger EB, Hemler ME, Springer A (1995) The integrin VLA-4 supports tethering and rolling in flow on VCAM-1. J Cell Biol 128(6): 1243–53.

Babona-Pilipos R, Droujinine IA, Popovic MR, Morshead CM (2011) Adult subependymal neural precursors, but not differentiated cells, undergo rapid cathodal migration in the presence of direct current electric fields. PLoS ONE 6(8): e23808.

Baek SJ, Kang SK, Ra C (2011) In vitro migration capacity of human adipose tissue-derived mesenchymal stem cells reflects their expression of receptors for chemokines and growth factors. Exp Mol Med 43(10): 596–603.

Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes LH, Kloner RA, Leor J (2003) Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. Circulation 108(7): 863–8.

Bekeredjian R, Grayburn PA, Shohet RV (2005) Use of ultrasound contrast agents for gene or drug delivery in cardiovascular medicine. J Am Coll Cardiol 45(3): 329–35.

Binger T, Stich S, Andreas K, Kaps C, Sezer O, Notter M, Sittinger M, Ringe J (2009) Migration potential and gene expression profile of human mesenchymal stem cells induced by CCL25. Exp Cell Res 315(8): 1468–79.

Blumenthal B, Poppe A, Golsong P, Blanke P, Rylski B, Beyersdorf F, Schlensak C, Siepe M (2011) Functional regeneration of ischemic myocardium by transplanted cells overexpressing stromal cell-derived factor-1 (SDF-1): intramyocardial injection versus scaffold-based application. Eur J Cardiothorac Surg 40(4): e135–e141.

Bobis-Wozowicz S, Miekus K, Wybieralska E, Jarocha D, Zawisz A, Madeja Z, M (2011) Genetically modified adipose tissue-derived mesenchymal stem cells overexpressing CXCR4 display increased motility, invasiveness, and homing to bone marrow of NOD/SCID mice. Exp Hematol 39(6): 686–96 e684.

Borgens RB (1988) Stimulation of neuronal regeneration and development by steady electrical fields. Adv Neurol 47: 547–64.

Caplan AI, Correa D (2011) The MSC: an injury drugstore. Cell Stem Cell 9(1): 11–5.

Charwat S, Gyongyosi M, Lang I, Graf S, Beran G, Hemetsberger R, Nyolczas N, Sochor H, Glogar D (2008) Role of adult bone marrow stem cells in the repair of ischemic myocardium: current state of the art. Exp Hematol 36(6): 672–80.

Chu K, Jung KH, Kim SJ, Lee ST, Kim J, Park HK, Song EC, Kim SU, Kim M, Lee SK, Roh K (2008) Transplantation of human neural stem cells protect against ischemia in a preventive mode via hypoxia-inducible factor-1alpha stabilization in the host brain. Brain Res 1207: 182–92.

Dell'Accio F, De Bari C, Luyten P (2001) Molecular markers predictive of the capacity of expanded human articular chondrocytes to form stable cartilage. Arthritis Rheum 44(7): 1608–19.

Deng J, Zou ZM, Zhou TL, Su YP, Ai GP, Wang JP, Xu H, Dong W (2011) Bone marrow mesenchymal stem cells can be mobilized into peripheral blood by G-CSF *in vivo* and integrate into traumatically injured cerebral tissue. Neurol Sci 32(4): 641–51.

Di Rocco G, Gentile A, Antonini A, Ceradini F, Wu JC, Capogrossi MC, Toietta G (2010) Enhanced healing of diabetic wounds by topical administration of adipose tissue-derived stromal cells overexpressing stromal-derived factor-1: biodistribution and engraftment analysis by bioluminescent imaging. Stem Cells Int 2011: 304562.

Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4): 315–7.

Edalatmanesh MA, Bahrami AR, Hosseini E, Hosseini M, Khatamsaz S (2011) Bone marrow derived mesenchymal stem cell transplantation in cerebellar degeneration: a behavioral study. Behav Brain Res 225(1): 63–70.

Edalatmanesh MA, Bahrami AR, Hosseini E, Hosseini M, Khatamsaz S (2011) Neuroprotective effects of mesenchymal stem cell transplantation in animal model of cerebellar degeneration. Neurol Res 33(9): 913–20.

Feng JF, Zhang XZ, Zhang L, Jiang JY, Nolta J, Zhao M (2012) Guided migration of neural stem cells derived from human embryonic stem cells by an electric field. Stem Cells 30(2): 349–55.

Fujii H, Li SH, Wu J, Miyagi Y, Yau TM, Rakowski H, Egashira K, Guo J, Weisel RD, Li K (2011) Repeated and targeted transfer of angiogenic plasmids into the infarcted rat heart via ultrasound targeted microbubble destruction enhances cardiac repair. Eur Heart J 32(16): 2075–84. doi: 10.1093/eurheartj/ehq475. Epub2010 Dec 31.

Futami I, Ishijima M, Kaneko H, Tsuji K, Ichikawa-Tomikawa N, Sadatsuki R, Muneta T, Arikawa-Hirasawa E, Sekiya I, Kaneko K (2012) Isolation and characterization of multipotential mesenchymal cells from the mouse synovium. PLoS ONE 7(9): e45517.

Gheisari Y, Azadmanesh K, Ahmadbeigi N, Nassiri SM, Golestaneh AF, Naderi M, Vasei M, Arefian E, Mirab-Samiee S, Shafiee A, Soleimani M, Zeinali S (2012) Genetic modification of mesenchymal stem cells to overexpress CXCR4 and CXCR7 does not improve the homing and therapeutic potentials of these cells in experimental acute kidney injury. Stem Cells Dev 21(16): 2969–80.

Goncalves RM (2012) Mesenchymal stem cell recruitment by stromal derived factor-1-delivery systems based on chitosan/poly(gamma-glutamic acid) polyelectrolyte complexes. Eur Cell Mater 23: 249–60; discussion 241–260.

Griffin M, Iqbal SA, Sebastian A (2011) Degenerate wave and capacitive coupling increase human MSC invasion and proliferation while reducing cytotoxicity in an in vitro wound healing model. J Colthurst and A Bayat 6(8): e23404.

Gundlach C,W, Caivano T,A, Cabreira-Hansen Mda G, Gahremanpour A, Brown WS, Zheng Y, McIntyre BW, Willerson JT, Dixon RA, Perin EC, Woodside DG (2011) Synthesis and evaluation of an anti-MLC1 x anti-CD90 bispecific antibody for targeting and retaining bone-marrow-derived multipotent stromal cells in infarcted myocardium. Bioconjug Chem 22 (8): 1706–14.

Haddad-Mashadrizeh A, Bahrami AR, Matin MM, Edalatmanesh MA, Zomorodipour A, Fallah A, Gardaneh M, Ahmadian N, Sanjarmoosavi N (2013) Evidence for crossing the blood barrier of adult rat brain by human adipose-derived mesenchymal stromal cells during a 6-month period of post-transplantation. Cytotherapy 15(8): 951–60.

He X, Ma J, Jabbari E (2010) Migration of marrow stromal cells in response to sustained release of stromal-derived factor-1alpha from poly(lactide ethylene oxide fumarate) hydrogels. Int J Pharm 390(2): 107–16.

Hoenig MR, Bianchi C, Sellke W (2008) Hypoxia inducible factor-1 alpha, endothelial progenitor cells, monocytes, cardiovascular risk, wound healing, cobalt and hydralazine: a unifying hypothesis. Curr Drug Targets 9(5): 422–35.

Hu X, Dai S, Wu WJ, Tan W, Zhu X, Mu J, Guo Y, Bolli R, Rokosh G (2007) Stromal cell derived factor-1 alpha confers protection against myocardial ischemia/reperfusion injury: role of the cardiac stromal cell derived factor-1 alpha CXCR4 axis. Circulation 116(6): 654–63.

Hu X, Wei L, Taylor TM, Wei J, Zhou X, Wang JA, Yu SP (2011) Hypoxic preconditioning enhances bone marrow mesenchymal stem cell migration via Kv2. 1 channel and FAK activation. Am J Physiol Cell Physiol 301(2): C362–C372.

Huang AH, Yeger-McKeever M, Stein A, Mauck L (2008) Tensile properties of engineered cartilage formed from chondrocyte- and MSC-laden hydrogels. Osteoarthritis Cartilage 16(9): 1074–82.

Huang YS, Li IH, Chueh SH, Hueng DY, Tai MC, Liang CM, Lien SB, Sytwu HK, Ma H (2013) Mesenchymal stem cells from rat olfactory bulbs can differentiate into cells with cardiomyocyte characteristics. J Tissue Eng Regen Med doi: 10.1002/term.1684.

Hung SC, Pochampally RR, Hsu SC, Sanchez C, Chen SC (2007) Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment *in vivo*. J Spees and D J Prockop 2(5): e416.

Jacobsen K, Kravitz J, Kincade PW, Osmond G (1996) Adhesion receptors on bone marrow stromal cells: *in vivo* expression of vascular cell adhesion molecule-1 by reticular cells and sinusoidal endothelium in normal and gamma-irradiated mice. Blood 87(1): 73–82.

Karimabad HM, Shabestari M, Baharvand H, Vosough A, Gourabi H, Shahverdi A, Shamsian A, Abdolhoseini S, Moazzami K, Marjanimehr MM, Emami F, Bidkhori HR, Hamedanchi A, Talebi S, Farrokhi F, Jabbari-Azad F, Fadavi M, Garivani U, Mahmoodi M, Aghdami N (2011) Lack of beneficial effects of granulocyte colony-stimulating factor in patients with subacute myocardial infarction undergoing late revascularization: a double-blind, randomized, placebo-controlled clinical trial. Acta Cardiol 66(2): 219–24.

Karp JM, Leng Teo S (2009) Mesenchymal stem cell homing: the devil is in the details. Cell Stem Cell 4(3): 206–16.

Kimura Y, Tabata Y (2010) Controlled release of stromal-cell-derived factor-1 from gelatin hydrogels enhances angiogenesis. J Biomater Sci Polym Ed 21(1): 37–51.

Knowles HJ, Tian YM, Mole DR, Harris L (2004) Novel mechanism of action for hydralazine: induction of hypoxia-inducible factor-1alpha, vascular endothelial growth factor, and angiogenesis by inhibition of prolyl hydroxylases. Circ Res 95(2): 162–9.

Ko IK, Kean TJ, Dennis E (2009) Targeting mesenchymal stem cells to activated endothelial cells. Biomaterials 30(22): 3702–10.

Ko IK, Kim BG, Awadallah A, Mikulan J, Lin P, Letterio JJ, Dennis JE (2010) Targeting improves MSC treatment of inflammatory bowel disease. Mol Ther 18(7): 1365–72.

Komarova S, Roth J, Alvarez R, Curiel DT, Pereboeva L (2010) Targeting of mesenchymal stem cells to ovarian tumors via an artificial receptor. J Ovarian Res 3: 12. doi: 10.1186/1757-2215-3-12.

Kucia M, Jankowski K, Reca R, Wysoczynski M, Bandura L, Allendorf DJ, Zhang J, Ratajczak J, Ratajczak MZ (2004) CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion. J Mol Histol 35(3): 233–45.

Kumar S, Ponnazhagan S (2007) Bone homing of mesenchymal stem cells by ectopic alpha 4 integrin expression. Faseb J 21(14): 3917–27.

LaBarge MA, Blau M (2002) Biological progression from adult bone marrow to mononucleate muscle stem cell to multinucleate muscle fiber in response to injury. Cell 111(4): 589–601.

Larsen S, Lewis D (2011) Potential therapeutic applications of mesenchymal stromal cells. Pathology 43(6): 592–604.

Lazennec G, Richmond A (2010) Chemokines and chemokine receptors: new insights into cancer-related inflammation. Trends Mol Med 16(3): 133–44.

Li L, El-Hayek YH, Liu B, Chen Y, Gomez E, Wu X, Ning K, Chang N, Zhang L, Wang Z, Hu X, Wan Q (2008) Direct-current electrical field guides neuronal stem/progenitor cell migration. Stem Cells 26(8): 2193–200.

Liu H, Liu S, Li Y, Wang X, Xue W, Ge G, Luo X (2012) The role of SDF-1-CXCR4/CXCR7 axis in the therapeutic effects of hypoxia-preconditioned mesenchymal stem cells for renal ischemia/reperfusion injury. PLoS One 7(4): e34608.

Liu H, Xue W, Ge G, Luo X, Li Y, Xiang H, Ding X, Tian P, Tian X (2010) Hypoxic preconditioning advances CXCR4 and CXCR7 expression by activating HIF-1alpha in MSCs. Biochem Biophys Res Commun 401(4): 509–15.

Luster AD, Alon R, von Andrian UH (2005) Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol 6(12): 1182–90.

Lyn D, Liu X, Bennett NA, Emmett L (2000) Gene expression profile in mouse myocardium after ischemia. Physiol Genomics 2(3): 93–100.

Makinen S, Kekarainen T, Nystedt J, Liimatainen T, Huhtala T, Narvanen A, Laine J, Jolkkonen J (2006) Human umbilical cord blood cells do not improve sensorimotor or cognitive outcome following transient middle cerebral artery occlusion in rats. Brain Res 1123(1): 207–15.

Mamalis AA, Cochran L (2011) The therapeutic potential of oxygen tension manipulation via hypoxia inducible factors and mimicking agents in guided bone regeneration. A review Arch Oral Biol 56(12): 1466–75.

McCaig CD, Rajnicek AM, Song B, Zhao M (2005) Controlling cell behavior electrically: current views and future potential. Physiol Rev 85(3): 943–78.

Mimeault M, Batra K (2013) Hypoxia-inducing factors as master regulators of stemness properties and altered metabolism of cancer- and metastasis-initiating cells. J Cell Mol Med 17(1): 30–54.

Mundra V, Gerling IC, Mahato I (2013) Me senchymal stem cell-based therapy. Mol Pharm 10(1): 77–89.

Naderi-Meshkin H, Andreas K, Matin MM, Sittinger M, Bidkhori HR, Ahmadiankia N, Bahrami AR, Ringe J (2014) Chitosan-based injectable hydrogel as a promising in situ forming scaffold for cartilage tissue engineering. Cell Biol Int 38(1): 72–84.

Najafi R, Sharifi M (2013) Deferoxamine preconditioning potentiates mesenchymal stem cell homing in vitro and in streptozotocin-diabetic rats. Expert Opin Biol Ther 13(7): 959–72.

Nuccitelli R (2003) Endogenous electric fields in embryos during development, regeneration and wound healing. Radiat Prot Dosimetry 106(4): 375–83.

Ohnishi S, Nagaya N (2007) Prepare cells to repair the heart: mesenchymal stem cells for the treatment of heart failure. Am J Nephrol 27(3): 301–7.

Pasha Z, Wang Y, Sheikh R, Zhang D, Zhao T, Ashraf M (2008) Preconditioning enhances cell survival and differentiation of stem cells during transplantation in infarcted myocardium. Cardiovasc Res 77(1): 134–42.

Penn MS, Mendelsohn FO, Schaer GL, Sherman W, Farr M, Pastore J, Rouy D, Clemens R, Aras R, Losordo W (2013) An open-label dose escalation study to evaluate the safety of administration of nonviral stromal cell-derived factor-1 plasmid to treat symptomatic ischemic heart failure. Circ Res 112(5): 816–25.

Phipps MC, Xu Y, Bellis L (2012) Delivery of platelet-derived growth factor as a chemotactic factor for mesenchymal stem cells by bone-mimetic electrospun scaffolds. PLoS One 7(7): e40831.

Poloni A, Maurizi G, Serrani F, Mancini S, Zingaretti MC, Frontini A, Cinti S, Olivieri A, Leoni P (2013) Molecular and functional characterization of human bone marrow adipocytes. Exp Hematol 41(6): 558–66.

Rosova I, Dao M, Capoccia B, Link D, Nolta A (2008) Hypoxic preconditioning results in increased motility and improved therapeutic potential of human mesenchymal stem cells. Stem Cells 26(8): 2173–82.

Ryser MF, Ugarte F, Thieme S, Bornhauser M, Roesen-Wolff A, Brenner S (2008) MRNA transfection of CXCR4-GFP fusion–simply generated by PCR-results in efficient migration of primary human mesenchymal stem cells. Tissue Eng Part C Methods 14(3): 179–84.

Sackstein R (2009) Glycosyltransferase-programmed stereosubstitution (GPS) to create HCELL: engineering a roadmap for cell migration. Immunol Rev 230(1): 51–74.

Sackstein R (2011) The biology of CD44 and HCELL in hematopoiesis: the 'step 2-bypass pathway' and other emerging perspectives. Curr Opin Hematol 18(4): 239–48.

Sackstein R (2012) Engineering cellular trafficking via glycosyltransferase-programmed stereosubstitution. Ann N Y Acad Sci 1253: 193–200.

Sackstein R (2012) Glycoengineering of HCELL, the human bone marrow homing receptor: sweetly programming cell migration. Ann Biomed Eng 40(4): 766–76.

Sackstein R, Merzaban JS, Cain DW, Dagia NM, Spencer JA, Lin CP, Wohlgemuth R (2008) Ex vivo glycan engineering of CD44 programs human multipotent mesenchymal stromal cell trafficking to bone. Nat Med 14(2): 181–7.

Sarkar D, Vemula PK, Teo GS, Spelke D, Karnik R, Wee Y, Karp M (2008) Chemical engineering of mesenchymal stem cells to induce a cell rolling response. Bioconjug Chem 19(11): 2105–9.

Sarkar D, Vemula PK, Zhao W, Gupta A, Karnik R, Karp M (2010) Engineered mesenchymal stem cells with self-assembled vesicles for systemic cell targeting. Biomaterials 31(19): 5266–74.

Sarkar D, Zhao W, Gupta A, Loh WL, Karnik R, Karp M (2011a) Cell surface engineering of mesenchymal stem cells. Methods Mol Biol 698: 505–23.

Sarkar D, Spencer JA, Phillips JA, Zhao W, Schafer S, Spelke DP, Mortensen LJ, Ruiz JP, Vemula PK, Sridharan R, Kumar S, Karnik R, Lin CP, Karp M (2011b) Engineered cell homing. Blood; 15;118(25):e 184–91.

Sasaki T, Fukazawa R, Ogawa S, Kanno S, Nitta T, Ochi M, Shimizu K (2007) Stromal cell-derived factor-1alpha improves infarcted heart function through angiogenesis in mice. Pediatr Int 49(6): 966–71.

Saxena A, Fish JE, White MD, Yu S, Smyth JW, Shaw RM, DiMaio JM, Srivastava D (2008) Stromal cell-derived factor-1alpha is cardioprotective after myocardial infarction. Circulation 117 (17): 2224–31.

Schantz JT, Chim H, Whiteman M (2007) Cell guidance in tissue engineering: SDF-1 mediates site-directed homing of mesenchymal stem cells within three-dimensional polycaprolactone scaffolds. Tissue Eng 13(11): 2615–24.

Schweitzer KM, Drager AM, P. van der Valk, Thijsen SF, Zevenbergen A, Theijsmeijer AP, van der Schoot CE, Langenhuijsen MM (1996) Constitutive expression of E-selectin and vascular cell adhesion molecule-1 on endothelial cells of hematopoietic tissues. Am J Pathol 148(1): 165–75.

Segers VF, Revin V, Wu W, Qiu H, Yan Z, Lee RT, Sandrasagra A (2011) Protease-resistant stromal cell-derived factor-1 for the treatment of experimental peripheral artery disease. Circulation 123(12): 1306–15.

Segers VF, Tokunou T, Higgins LJ, MacGillivray C, Gannon J, Lee RT (2007) Local delivery of protease-resistant stromal cell derived factor-1 for stem cell recruitment after myocardial infarction. Circulation 116(15): 1683–92.

Sharma M, Afrin F, Satija N, Tripathi RP, Gangenahalli U (2011) Stromal-derived factor-1/CXCR4 signaling: indispensable role in homing and engraftment of hematopoietic stem cells in bone marrow. Stem Cells Dev 20(6): 933–46.

Sharp FR, Bernaudin M (2004) HIF1 and oxygen sensing in the brain. Nat Rev Neurosci 5(6): 437–48.

Shen W, Chen X, Chen J, Yin Z, Heng BC, Chen W, Ouyang W (2010) The effect of incorporation of exogenous stromal cell-derived factor-1 alpha within a knitted silk-collagen sponge scaffold on tendon regeneration. Biomaterials 31(28): 7239–49.

Shi M, Li J, Liao L, Chen B, Li B, Chen L, Jia H, Zhao C (2007) Regulation of CXCR4 expression in human mesenchymal stem cells by cytokine treatment: role in homing efficiency in NOD/SCID mice. Haematologica 92(7): 897–904.

Shinohara K, Greenfield S, Pan H, Vasanji A, Kumagai K, Midura RJ, Kiedrowski M, Penn MS, Muschler F (2011) Stromal cell-derived factor-1 and monocyte chemotactic protein-3 improve recruitment of osteogenic cells into sites of musculoskeletal repair. J Orthop Res 29(7): 1064–9.

Simoes IN, Boura JS, Dos Santos F, Andrade PZ, Cardoso CM, Gimble JM, da Silva CL, Cabral M (2013) Human mesenchymal stem cells from the umbilical cord matrix: successful isolation and ex-vivo expansion using serum-/xeno-free culture media. Biotechnol J 8(4): 448–58.

Simon SI, Green E (2005) Molecular mechanics and dynamics of leukocyte recruitment during inflammation. Annu Rev Biomed Eng 7: 151–85.

Sordi V, Malosio ML, Marchesi F, Mercalli A, Melzi R, Giordano T, Belmonte N, Ferrari G, Leone BE, Bertuzzi F, Zerbini G, Allavena P, Bonifacio E, Piemonti L (2005) Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. Blood 106(2): 419–27.

Springer TA (1994) Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 76(2): 301–14.

Takada Y, Ye X, Simon S (2007) The integrins. Genome Biol 8(5): 215.

Tator CH (2005) Phase 1 trial of oscillating field stimulation for complete spinal cord injury in humans. J Neurosurg Spine 2(1): 1; discussion 1–2.

Thankamony SP, Sackstein R (2011) Enforced hematopoietic cell E- and L-selectin ligand (HCELL) expression primes transendothelial migration of human mesenchymal stem cells. Proc Natl Acad Sci U S A 108(6): 2258–63.

Thevenot PT, Nair AM, Shen J, Lotfi P, Ko CY, Tang L (2010) The effect of incorporation of SDF-1alpha into PLGA scaffolds on stem cell recruitment and the inflammatory response. Biomaterials 31(14): 3997–4008.

Thieme S, Ryser M, Gentsch M, Navratiel K, Brenner S, Stiehler M, Rolfing J, Gelinsky M, Rosen-Wolff A (2009) Stromal cell-derived factor-1alpha-directed chemoattraction of transiently CXCR4-overexpressing bone marrow stromal cells into functionalized three-dimensional biomimetic scaffolds. Tissue Eng Part C Methods 15(4): 687–96.

Tsai CC, Yew TL, Yang DC, Huang WH, Hung C (2012) Benefits of hypoxic culture on bone marrow multipotent stromal cells. Am J Blood Res 2(3): 148–59.

Tsai LK, Wang Z, Munasinghe J, Leng Y, Leeds P, Chuang DM (2011) Mesenchymal stem cells primed with valproate and lithium robustly migrate to infarcted regions and facilitate recovery in a stroke model. Stroke 42(10): 2932–9.

Wagner J, Kean T, Young R, Dennis JE, Caplan AI (2009) Optimizing mesenchymal stem cell-based therapeutics. Curr Opin Biotechnol 20(5): 531–6.

Walczak P, Zhang J, Gilad AA, Kedziorek DA, Ruiz-Cabello J, Young RG, Pittenger MF, van Zijl PC, Huang J, Bulte JW (2008) Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. Stroke 39(5): 1569–74.

Wei N, Yu SP, Gu X, Taylor TM, Song D, Liu XF, Wei L (2013) Delayed intranasal delivery of hypoxic-preconditioned bone marrow mesenchymal stem cells enhanced cell homing and therapeutic benefits after ischemic stroke in mice. Cell Transplant 22(6): 977–91.

Wiehe JM, Kaya Z, Homann JM, Wohrle J, Vogt K, Nguyen T, Rottbauer W, Torzewski J, Fekete N, Rojewski M, Schrezenmeier H, Moepps B, Zimmermann O (2012) GMP-adapted overexpression of CXCR4 in human mesenchymal stem cells for cardiac repair. Int J Cardiol 167(5): 2073–81.

Wu Y, Zaho C (2012) The role of chemokines in mesenchymal stem cell homing to myocardium. Stem Cell Rev 8(1): 243–50.

Wynn RF, Hart CA, Corradi-Perini C, O'Neill L, Evans CA, Wraith JE, Fairbairn LJ, Bellantuono I (2004) A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 104(9): 2643–5.

Yamaguchi J, Kusano KF, Masuo O, Kawamoto A, Silver M, Murasawa S, Bosch-Marce M, Masuda H, Losordo DW, Isner JM, Asahara T (2003) Stromal cell-derived factor-1 effects on ex vivo expanded endothelial progenitor cell recruitment for ischemic neovascularization. Circulation 107 (9): 1322–8.

Yu X, Lu C, Liu H, Rao S, Cai J, Liu S, Kriegel AJ, Greene AS, Liang M, Ding X (2013) Hypoxic preconditioning with cobalt of bone marrow mesenchymal stem cells improves cell migration and enhances therapy for treatment of ischemic acute kidney injury. PLoS One 8(5): e62703.

Yue Y, Zhang P, Liu D, Yang JF, Nie C, Yang D (2013) Hypoxia preconditioning enhances the viability of ADSCs to increase the survival rate of ischemic skin flaps in rats. Aesthetic Plast Surg 37(1): 159–70.

Zhang D, Fan GC, Zhou X, Zhao T, Pasha Z, Xu M, Zhu Y, Ashraf M, Wang Y (2008) Over-expression of CXCR4 on mesenchymal stem cells augments myoangiogenesis in the infarcted myocardium. J Mol Cell Cardiol 44(2): 281–92.

Zhang F, Leong W, Su K, Fang Y, Wang A (2013) A Transduced Living Hyaline Cartilage Graft Releasing Transgenic Stromal Cell-Derived Factor-1 Inducing Endogenous Stem Cell Homing In Vivo. Tissue Eng Part A 19(9–10): 1091–9.

Zhang J, Calafiore M, Zeng Q, Zhang X, Huang Y, Li RA, Deng W, Zhao M (2011) Electrically guiding migration of human induced pluripotent stem cells. Stem Cell Rev 7(4): 987–96.

Zhang M, Mal N, Kiedrowski M, Chacko M, Askari AT, Popovic ZB, Koc ON, Penn S (2007) SDF-1 expression by mesenchymal stem cells results in trophic support of cardiac myocytes after myocardial infarction. FASEB J 21(12): 3197–207.

Zhang X, Bogorin DF, Moy T (2004) Molecular basis of the dynamic strength of the sialyl Lewis X–selectin interaction. Chemphyschem 5(2): 175–82.

Zhang X, Wang Y, Gao Y, Liu X, Bai T, Li M, Li L, Chi G, Xu H, Liu F, Liu JY, Li Y (2013) Maintenance of high proliferation and multipotent potential of human hair follicle-derived mesenchymal stem cells by growth factors. Int J Mol Med 31(4): 913–21.

Zhao T, Zhang D, Millard RW, Ashraf M, Wang Y (2009) Stem cell homing and angiomyogenesis in transplanted hearts are enhanced by combined intramyocardial SDF-1alpha delivery and endogenous cytokine signaling. Am J Physiol Heart Circ Physiol 296(4): H976–986.

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