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Molecular mechanisms of migration and homing of intravenously transplanted mesenchymal stem cells

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Abstract

Mesenchymal stem cells (MSCs) isolated from various tissues are currently regarded as one of the most convenient starting materials for preparation of cell therapy and tissue engineering products. Numerous research groups conducted detailed studies of their therapeutic effects and mechanisms of action in animal models. Some of those effects have been already confirmed in clinical trials. One of the most important properties of mesenchymal stem cells crucial for their medical use is the ability for targeted migration to the sites of ischemic, inflammatory or mechanical injury or site of tumor growth and homing within and around the damaged area. The aim of this review is to delineate the available data concerning the organ and tissue distribution of intravenously transplanted MSCs and the molecular mechanisms underlying their transfer within the bloodstream, penetration through the vascular wall and tissue invasion. The review reveals involvement of chemokines and their receptors, adhesion molecules and matrix metalloproteinases in those processes. Some of the data related to other roots of MSC transplantation, but critical for understanding the essential features of their migration and homing were also included.

Keywords: Mesenchymal stem cells, migration, homing, transplantation, distribution

Introduction

At present stem cell-based technologies comprise the main trend in the emerging field of regenerative medicine, while mesenchymal stem cells (MSCs) isolated from different tissues are regarded as one of the most handy and versatile raw materials for preparation of cell therapy and tissue engineering products. Bone marrow-derived mesenchymal stem cells (BM-MSCs) are definitely the best characterized type of mesenchymal cells, although attention is gradually switching to alternative sources of MSCs, such as adipose tissue, placenta, umbilical cord/Wharton's jelly, umbilical cord blood, and others.

Regardless of the source, cultured MSCs have common characteristics and behavioral traits. The ability to plastic adherence is widely used for their isolation from different tissues [1]. All MSCs have similar fibroblast-like morphology *in vitro* and are able to differentiate into cells of mesodermal lineage, namely, osteocytes, chondrocytes and adipocytes. MSCs from diverse sources may show certain differences in the expression of surface markers. However, in general, the phenotypes of these cells are very similar, and the typical mesenchymal stem cell surface markers are CD44 (receptor for hyaluronic acid), CD54 (ICAM-1; Intercellular Adhesion Molecule 1), CD90 (Thy-1), CD105 (endoglin), CD106 (VCAM-1; vascular cell adhesion molecule 1), HLA-I (MHC class I). Also MSCs do not express hematopoietic and endothelial cell markers, such as CD31, CD34, CD38, CD45, CD133, MHC class II [2,3].

Furthermore, MSCs have unique immunomodulatory properties [4]. *In vitro* co-cultured MSCs modulate differentiation of certain immune precursor cells and/or maturation of differentiated immune cells [5]. The *in vitro* results are in accordance with immunomodulatory action seen both in animal experiments [6] and in clinical studies. Therefore, MSCs are being tested in clinical trials to reduce graft-versus-host disease, and for the treatment of autoimmune disorders such as multiple sclerosis [7,8].

An important property of MSCs is their capacity for migration and homing in or around the zones damaged by ischemia, inflammation, and trauma or tumor sites. Understandably, the efficacy and time course of cell invasion into the damaged tissues depends upon the route of transplantation. Many ways of MSCs administration have been tested in cell therapy experiments and clinical trials. Among those, local (*eg*., directly into ischemic myocardium or brain), intra-arterial or epidural routes of cell administration usually demand at least minor surgery and are often associated with major risks. Iv infusion is probably the most convenient way of MSCs delivery both in experiments and clinical trials. This method is minimally invasive and allows repeated injections of multiple doses of cells at certain time intervals. Moreover, it possibly imitates the likely physiological mechanism of bone marrow-derived stem cell participation in regeneration

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of different tissues [9].

It is now well documented that iv transplanted cells migrate in substantial quantities into the injured tissue [10]. It is noteworthy, though, that transplanted MSCs move not only to the areas of tissue damage, but to at least some stem cell niches including the subventricular zone and the hippocampal subgranular zone in the brain [11]. Here this very important migration route is just mentioned, but not systematically considered.

It is important to understand the mechanisms underlying the migration and homing of MSCs. This review presents recent data concerning the distribution of MSCs in the body after iv administration, as well as possible mechanisms of their migration and homing. It also includes some data related to other routes of MSCs transplantation, but critical for understanding the essential features of their relocation within intact and damaged tissues.

MSC distribution after transplantation

One of the main issues relating to the clinical use of stem cells is the way to deliver them to the target tissue. As mentioned above, there are several routes of cell transplantation including the site-specific, directly into the site of injury or near it, and the systemic, into the bloodstream. Both of these methods have been tested in pre-clinical studies in animal models and in clinical practice.

A number of publications demonstrated that the site-specific, or site-directed, delivery of MSCs resulted in effective engraftment of target tissues by transplanted cells, especially in the damage/inflammation conditions. Thus, in several studies effective functional recovery was observed after BM-MSCs injection directly into the ischemic myocardium [12] . Gojo S. et al., [13] inoculated mouse MSCs into the myocardium of healthy adult animals and found signs of neoangiogenesis near the injection site 7 days after transplantation. In this case, the donor cells were found in the walls of the newly formed blood vessels. They also differentiated into cardiomyocytes, endothelial cells and pericytes, indicating ability to engraft not only in damaged, but in healthy tissue, too.

Hofstetter et al., [14] injected rat MSCs into the spinal cord of rats suffering from paraplegia 1 week after injury, and found that the transplanted cells were concentrated at the core of injury site and stimulated the recovery of transected spinal cord. In our work [15], we injected human placental MSCs labeled with fluorescent microparticles into the mouse spinal cord immediately after injury. We observed that transplanted human cells at 30 days migrated into the mouse spinal cord, and these cells mostly accumulated at the injection site and on the dorsal side of the spinal cord. In addition, the labeled human cells migrated to the rostral and caudal directions from the injury site. A small part of the transplanted cells migrated deeper into the spinal cord tissue and spread within a few millimeters from the injury. Thus, at least a fraction of the injected human placental MSCs survived 1 month in the mouse body and migrated within the host spinal cord, promoting functional recovery of animals after spinal cord injury. Andrews et al., [16] injected human bone marrow MSCs in the ipsilateral hemisphere after one-sided middle cerebral artery occlusion in rats and discovered that at 30 days after transplantation viable human BM-MSCs spread out in the cortex of ipsilateral and contralateral hemispheres.

As follows from the above examples, the site-directed delivery of MSCs provides effective engraftment of area close to the injection site and allows transplanted cell migration to relatively distant locations. Apparently, it creates maximal accumulation of cells in the site of injury, probably contributing to the effectiveness of transplantation. However, it has significant drawbacks and, hence, is not always applicable in clinical practice. Firstly, the injection of MSCs directly into tissues other than skin and mucosal linings requires surgery, which is bothersome, associated with risks, and restricts the possibility of using multiple doses of cells at certain intervals of time. Secondly, local MSCs transplantation causes additional, albeit minor, tissue damage. Finally, most of the cells form dense clusters at the injection site producing undesirable consequences, such as calcification spots in myocardium after intramyocardial injection of MSCs isolated from bone marrow [17].

Cell administration into the bloodstream is more suitable for clinical use. Intra-arterial infusion may be quite effective with respect to attaining maximum cell concentration in the area supplied by a particular artery [18,19]. However, it also requires at least minor surgery and may end up with plugging of local capillaries with transplanted cells.

Iv administration is safer than the above mentioned transplantation routes and at the same time allows cell delivery to the majority of tissues. The main advantages of this method of MSC transplantation are the following: 1) availability and the absence of any contraindications, as opposed to site-directed transplantation; 2) the possibility to inject high doses of cells for a long time, for example, using a dropper, and the ability to infuse multiple doses at certain intervals; and 3) absence of the necessity of surgical intervention. However, this method of stem cell administration has one major drawback, which lies in the fact that not all the injected cells, but rather their smaller number, reach the site of injury.

A number of studies have described the iv route of MSCs administration. Barbash et al., [20] iv injected rat MSCs to animals with myocardial infarction, and found that most of the cells penetrated into the lungs, and a small cell number engrafted into the heart, liver, and spleen. Only some of the MSCs retain their ability to homing into the site of damaged myocardium, however, much less than after intracardiac injection. Many studies after iv injection of cultured MSCs observed accumulation of donor cells in the lungs. At present, there is evidence that the MSCs iv injected into a healthy animals, mostly arrested in

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the vascular system of the lungs [21]. It is likely that this phenomenon can be explained by the fact that MSCs expanded in culture are activated and express a great variety of adhesion molecules; moreover these cells have a relatively large size. However, Gao et al., [22] found that treatment of animals with vasodilating sodium nitroprusside reduced the number of cells penetrated into the lungs.

Despite the fact that MSCs can be arrested in the lungs, there is lot of evidence that showed that MSCs are able to home to the injured tissues after iv administration. Cultured rat and human MSCs migrate to sites of brain damage after cerebral ischemia, when iv transplanted into rats [23,24]. Wu et al., [25] transplanted rat MSCs iv for the treatment of cardiac allograft rejection in rats and found that they vigorously migrated into the site of allograft rejection, mainly differentiated into fibroblasts and a small number of transplanted cells differentiated into myocytes. MSCs have also been used for the treatment of lung injury in mice when administered iv. Ortiz et al., [26] found that mouse MSCs after transplantation into the mice exposed to bleomycin (model of pulmonary fibrosis) are homing to the lungs in response to injury, where they acquired epithelium-like phenotype, and reduced inflammation and collagen deposition. They also found a 23-fold increase in the engraftment level of donor cells compared to mice that were not exposed to bleomycin.

Analysis of distribution after iv MSCs administration was performed by different methods: 1) by fluorescently labeled proteins [27,28,29]; 2) by detection of human genes into animal recipients [30,31]; 3) by histological methods [32]; and 4) by immunohistochemistry [33,34]; 5) by fluorescence in situ hybridization [35]; and 6) by real-time PCR [26,27]. For example, Devine et al., [27] iv injected MSCs transduced with a green fluorescent protein (GFP) retroviral construct into the lethally irradiated baboons. At 9-21 months after MSCs infusion they evaluated for the presence of the GFP transgene in purified genomic DNA by sensitive real-time polymerase chain reaction (PCR). Moreover, two baboons were treated with autologous cells, and one animal was treated with allogeneic MSCs. In both cases, the distribution of transplanted cells was similar. Since it has been shown that most of the transplanted cells found in the gastrointestinal tract and the relatively high number of cells was also observed in the kidney, lung, liver, thymus and skin. The level of engraftment in these tissues was approximately 0.1% to 2.7% of injected cells. In the intact model (health animals) due to detection of GFP-transfected murine MSCs Deak et al., [29] demonstrated that most GFP-positive organs are the lungs, liver, kidneys, skin, and intestines as examined at 24 hours after MSCs transplantation.

However, the aforementioned methods are invasive and static. The development of non-invasive techniques such as magnetic resonance imaging (MRI) of MSCs labeled with superparamagnetic iron oxide nanoparticles (SPIO) [36], the combined single-photon emission CT (SPECT)/CT scanning [37] and tracking quantum dots [38], have improved our ability to investigate homing of MSCs and their fate and organ-specific accumulation. Cell tracking by MRI using SPIO is a method with the least risk to monitoring for the activity of stem cells in humans. Hsiao et al., [39] showed that MSCs successfully labeled Ferucarbotran (ionic SPIO, which is used in the clinic) without the aid of transfection agents, which does not affect cell viability, proliferation, changes in mitochondrial membrane potential, production of reactive oxygen species, or the ability to differentiate. Approximately 45.2% of the labeled MSCs can be detected with a single-level 3D gradient echo sequence and four repetitions using 1.5T MRI. Using SPECT/CT imaging in a model of acute myocardial infarction, Kraitchman et al., [37] demonstrated that the initial localization of BM-MSCs was observed in the lungs and the cells migrated to the organs that are not targets, such as the liver, kidney and spleen at 24 and 48 h after administration. Increase of the number of MSCs in the heart tissue that is affected by a heart attack, occurred simultaneously with a gradual decrease of the initial MSCs concentration in the lungs 24 hours after infusion, and MSCs persisted up to 7 days after injection. In addition, the labeling of BM-MSCs with bioconjugated quantum dots does not alter their self-renewing and differentiation potential toward chondrogenic, osteogenic and adipogenic lineages [40]. Moreover, it is very useful not only for tracking MSCs, but also in the study of behavioral changes in cells when MSCs are injected in combination chemicals, such as heparin [38]. When imaging the mice with acute liver failure Yukawa et al., [38] showed that almost all of the transplanted adipose-derived MSCs (AdMSCs) during 10 minutes accumulate in the lungs in the absence of heparin treatment. However, when heparin is used in combination with AdMSCs, accumulation of transplanted cells is found not only in the lungs, but also in the liver, and the number of accumulated cells increased up to 30% in the injured liver. Thus, studies that use different methods of tracking MSCs showed initial concentration of MSCs in the lungs after iv administration [22,29,37,38,41], then the majority of MSCs gradually migrated to sites of injury [29,37,38,41] or in liver, spleen, kidneys and bone marrow [22].

Mechanisms of migration and homing

Homing is the ability of cells to migrate into the "right" place, "home" organ and/or tissue (stem cell niche), or in the damaged area. Homing to specific organs is a multi-step process that includes cell attachment and rolling in the vessel lumen, adhesion and extravasation across the vascular endothelium and migration through the tissue stroma. Migratory ability of the cells is due to biochemical signals from the "right" area, reception system and the ability of cells to chemotaxis. Based on the foregoing, it can be concluded that the mesenchymal stem cells, regardless of the mode of administration, have a high

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Table 1. The main molecules involved in the process of MSC migration/homing.

Migration stage	Molecules	References
Chemotaxis/traffic	**Chemokines/receptors:** CXCL3, 5, 6, 10-12, 14, 16, CXCR1-6; XCL1, 2; CX3CL1, CX3CR1; CCL1-5, 7, 8, 18, 19, 21, 24-26, CCR1-4, CCR6-9	[47], [52], [58], [59]
	Cytokines/growth factors: PDGF-BB, PDGF-AB, TGF-β1, TNF-α, VEGF	[73], [74], [76]
	Toll-like receptors: TLR3, TLR4, TLR9	[80], [81]
Rolling/transendothelial migration	**Integrins:** VLA-4 (α4β1 integrin), α6β1, α8β1, α9β1	[84], [86],
	Adhesion molecules: VCAM-1, ICAM-1, ICAM-3, ALCAM, endoglin/ CD105, CD166, CD44, PECAM	[47], [84], [88], [89]
	Selectin ligand: P-selectin unidentified carbohydrate ligand (BM-MSCs); P-selectin ligand (placental MSCs)	[47], [84]
Invasion	**Matrix metalloproteinases:** MMP-1, MMP-2	[95]

potential for migration and homing to sites of injury [15,19,20]. However, in order to improve this ability and, as a consequence, increase the therapeutic efficacy of these cells it is necessary to study in detail the mechanisms of migration and homing, and possibility to regulate these processes.

There is much evidence to support the theory that MSCs are homing to different tissues, especially to injured or inflamed tissues. This process involves the migration of cells in the blood stream (probably by rolling), transendothelial migration through the vascular walls and the invasion into the target tissue. The mechanism by which MSCs directed to the tissues and migrate across the endothelium, is not yet fully understood, but it is likely that the damaged tissue expresses specific receptors or ligands to facilitate traffic, adhesion and infiltration of MSCs to the site of injury, as well as with the involvement of leukocytes to sites of inflammation. Chemokine receptors and their ligands are essential components involved in the migration of leukocytes to sites of inflammation, and it was recently shown that MSCs also express some of these molecules. In addition, it is known that some adhesion molecules and integrins involved in leukocyte rolling and transendothelial migration, are also expressed by MSCs. Moreover, for invasion into the targeted tissues MSCs use certain extracellular proteases similar to immune cells, as well as metastatic cancer cells, which use different proteases to penetrate the tissue extracellular matrix, such as matrix metalloproteinases (MMPs), serine, cysteine and aspartate proteases [42-44]. Data about the involvement of certain molecules in the MSC migration/homing summarized in **Table 1**.

Chemokines and their receptors

As discussed earlier, MSCs have the ability to migrate into the tissue from the circulation, possibly in response to signals that are induced by injury. Although the mechanisms by which MSCs attracted in tissue and transmigrate through vascular endothelial cell layer are not yet fully understood, it is possible that this process involved chemokines and their receptors, similar to hematopoietic stem cells and immune cells [45].

Chemokines is a large family of proteins that regulate many functions, such as chemotaxis. While the majority of chemokines are presented at secreted form and consist of 67-127 amino acid residues, some chemokines are membrane-bound (*eg.,* CXCL16 and CX3CL1). Chemokines are classified into four groups according to the spatial location of the first two cysteine residues near the NH2-end: CXC chemokines, CC chemokines, C chemokines and CX3C chemokines. Chemokine receptors are classified as receptors associated with G-proteins for CXC, CC, C or CX3C chemokines [46].

Over the last decade many works have been aimed at the study of the chemokine profile of mesenchymal stem cells derived from different sources. So, Abumaree et al., [47] conducted a large scale study of chemokine expression profiles and their receptors by placental mesenchymal stem cells (pMSCs). Using RT-PCR the authors found that human pMSCs (first passage) express a wide range of chemokines/receptors, including chemokine/receptor CXC family (CXCL3, CXCL5, CXCL6, CXCL10, CXCL11, CXCL12, CXCL14, CXCL16, CXCR1, CXCR3, CXCR4, CXCR5, and CXCR6), C family (XCL1 and XCL2), CX3C family (CX3CL1 and CX3CR1), and CC family (CCL1, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL18, CCL19, CCL21, CCL24, CCL25, CCL26, CCR1, CCR3, CCR4, CCR6 and CCR7). At the same time low percentage of pMSCs express chemokine receptors at the protein level (≥20% of the cells express CXCR1 and CXCR3; ≤10% of the cells express CXCR2, CXCR4, CXCR7, CX3CR1, XCR1 и CXCL4). In addition, the authors showed that the pMSCs do not

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express CCR1-CCR10, CXCL1, CXCL5, CXCL9, CXCL10 (IP-10), CXCL12, CX3CL1, CCL2 (monocyte chemotactic protein-1: MCP-1) and CCL5 (RANTES) [47]. Thus, the expression of such a wide variety of chemokines and their receptors by pMSCs can determine their high migration capacity, which has repeatedly been shown *in vitro* [48] and *in vivo* [11].

Pattern of chemokine receptors expressed by MSCs isolated from different sources has been studied by many researchers. Ahmadian et al., [49] evaluated the expression levels of chemokine receptors such as CCR1, CXCR4, CCR7, CXCR6 and CXCR3, in human MSCs derived from bone marrow and adipose tissue. The results showed that the expression of CCR1, CXCR4, CCR7, CXCR6 and CXCR3 at mRNA level was relatively low in the MSCs derived from adipose tissue, and very low or no detectable in most of the samples obtained from the bone marrow. It was previously shown that the chemokine receptors are important in the regulation of migration different types of stem/progenitor cells and their engraftment into various tissues [50-52]. A number of studies have also shown that these chemokine receptors are important for transendothelial migration of cancer cells [53-55].

Previously, several groups have studied the expression of chemokine receptors on human MSCs derived from bone marrow. Wynn et al., [56] evaluated the expression of CXCR4 on hMSCs isolated from bone marrow (hBM-MSCs), and showed that the receptor is present on the cell surface membrane of less than 1% of the cells; although they found, that 83% -98% of the hBM-MSCs expressed intracellular CXCR4 at high level. Other studies have shown functional expression of CXCR4 at the surface of BM-MSCs [57]; expression of CCR1, CCR7, CXCR4, CXCR6, and CX3CR1 was shown on individual cells (2-25%) [52]. Honczarenko M. et al., [58] performed flow cytometric analysis of the expression of CC chemokine receptors (except for CCR10), CXC receptors and CX3CR1. They found, that 43%–70% of the hBM-MSCs expressed functional (as determined by chemotaxis assay) CCR1, CCR7, CCR9, CXCR4, CXCR5 and CXCR6. Another group showed expression of CCR2, CCR8, CXCR1, CXCR2, and CXCR3 in BM-MSCs by RT-PCR and immunohistochemistry [59]. Ponte et al., [60] demonstrated that hBM-MSCs expressed CCR2, CCR3, CCR4, and CXCR4, and found that TNF increased the expression of CCR2, CCR3 and CCR4, but not CXCR4.

Despite contradictory data obtained in different studies concerning expression of several chemokine receptors, it is obvious that MSCs express a great variety of these receptors. Such contradictions may be due to several factors: the heterogeneity of ex vivo expanded MSCs, which is a feature of these cells, the differences in the methods of MSCs isolation and cultivation and the number of passages that have undergone cells before analysis. In this context, the number of passages is particularly important in the analysis of chemokine receptor expression. Thus, ex vivo cultured MSCs, which were initially positive for CCR1, CCR7, CCR9, CXCR4, CXCR5, and CXCR6, at passage 12-16 loss of their surface chemokine receptor expression, which was accompanied by a lack of chemotactic response to chemokines, and by further decline in the expression of adhesion molecules, including ICAM-1, ICAM-2 and VCAM-1 [58]. In addition to the long-term cultivation of MSCs and to cultural conditions, changes in the expression pattern of surface receptors dependent on confluency of cells, site of isolation and the environment in the process of incubation (normoxic or hypoxic conditions) [61].

Furthermore, the fact that MSCs derived from different sources, express distinct set of chemokine receptors may indicate that they have a different ability to migrate into various tissues. For example, similar to the white blood cells, MSCs expressing CCR9 can use this receptor for homing to the intestine, and CCR1-expressing MSCs can use the receptor for homing into inflamed tissue of the joints in rheumatoid arthritis, or in the brain in multiple sclerosis.

The most studied of chemokine/receptor pair in cell migration and homing are CXCL12, or SDF-1 (stromal cell-derived factor-1) and its receptor CXCR4. It is known that CXCL12 is a major chemotactic factor that promotes hematopoietic cell homing into the bone marrow at the development process, maintenance them in the adult bone marrow, as well as migration of mature lymphocytes towards sites of inflammation and injury [62]. In addition, CXCL12 and its receptor CXCR4 are involved in the migration of primordial germ cells [63], as well as in the attracting endothelial progenitor cells into ischemic tissue [64].

However, in the MSCs migration and homing this chemokine and its receptor play a less significant role, except when the expression of CXCR4 was stimulated by various factors. For example, it was found that IGF-1 is not only itself induced migration of MSCs, but also initiated the migratory activity of MSCs in response to SDF-1α through upregulation of CXCR4 [65]. Interestingly, the BM-MSCs after stimulation with TNF-α also showed increased susceptibility to SDF-1α, despite on the invariably of SDF-1α surface binding and CXCR4 expression. Moreover, short-term treatment of BM-MSCs with cytokine cocktail, which includes Flt-3 ligand, stem cell factor (SCF), IL-6, hepatocyte growth factor (HGF) and IL-3, induced a significant up-regulation of surface and intracellular CXCR4 [66].

Song et al., [67] found that tumor conditioned medium induced up-regulation of CXCR4 on BM-MSCs, so that the cells acquire capacity to increased migration toward tumor cells. However, AMD3100 (a specific inhibitor of CXCR4) is not completely abolished migration of BM-MSCs to tumor cells PC3 (human prostate cancer cell line), MCF-7 (breast cancer cell line) and RIF-1 (fibrosarcoma), which suggests that there must be other factors involved in the specific migration of BM-MSCs to tumors. Interestingly, the CXCR4 inhibitor had no effect on the migration of BM-MSCs toward human prostate cancer cell line DU145, showing that different tumors may use different mechanisms to

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attract BM-MSCs. In addition, tumor conditioned medium induced the production of SDF-1α by human BM-MSCs [68]. Gao et al., [69] show that SDF-1 acts as a signaling molecule and not necessarily as a chemotactic factor to facilitate hMSC migration towards tumor environment. It is possible that SDF-1 acts in conjunction with other factors, including cytokines such as IL-8 and IL-6, to provide hMSC migration in response to different stimuli. It is possible to assume that the expression levels and distribution patterns of CXCR4 may be regulated by various cytokines and growth factors. It is known that at the damage of various tissues, such as myocardial infarction [70], ischemic stroke [71] and others, in the site of injury produced a wide range of cytokines and growth factors that can simultaneously serve as chemoattractants for MSCs, and stimulate these cells to expression of different chemokine receptors, particular CXCR4. The same can be said for solid tumors, which are often seen as unhealed wound [72], which is a continuous producer of inflammatory mediators (cytokines, chemokines and other potential chemoattractant molecules).

Cytokines, growth factors, and receptors

In addition to chemokines and their receptors, different cytokines and growth factors play an important role in the MSC homing. It is known that during the inflammatory process damaged tissues release a large number of cytokines, including IL-6, PDFG-BB and IGF-1 [73]. Thus, a number of studies have shown the active role of these cytokines in the migration of BM-MSCs [74]. Moreover, PDGF-BB shows greater attracting potential, than the other cytokines. Other inflammatory cytokines, such as transforming growth factor (TGF)-β1, interleukin (IL)-1β and tumor necrosis factor (TNF)-α, stimulate the production of matrix metalloproteinases (MMPs) by the MSCs, leading to powerful stimulation of chemotactic migration through the extracellular matrix [75]. Human adipose-derived MSCs (AdMSCs) migrate in response to various growth factors and cytokines, including platelet-derived growth factor (PDGF)-AB, TGF-β1, TNF-α, and SDF-1α [76]. Spaeth et al., [73] demonstrated that the combination of PDGF and VEGF acts as chemoattractants, inducing migration of MSCs *in vitro*; this combination of growth factors is more powerful than each growth factor separately. These results show that increasing of MSC homing can be achieved by modulating their response to different growth factors and cytokines, which may allow improving their therapeutic potential.

Toll-like receptors (TLR) is an essential component of the innate immune response. In humans, there were found 11 TLRs, each of which recognizes a wide range of conservative molecules known as pathogen-associated molecular patterns. Depending on the stimulation TLR signaling may regulate the expression of both CC and CXC chemokines by activation of nuclear factor κB [77]. Dimers of TLR1/2 and 2/6 recognize lipopeptides and peptidoglycans; TLR3 recognizes double-stranded RNA; TLR4 recognizes lipopolysaccharides; TLR5 recognizes the extracellular matrix molecules; TLR7 and 8 recognize pathogen-associated molecular patterns (PAMPs) that are expressed on infectious agents; TLR9 recognizes unmethylated CpG sequences in DNA molecules [78].

TLR1-6 have been identified on primary human MSCs [79]. Waterman et al., [80] shown that stimulation of TLR enhanced MSC migration function; the most powerful induction of migration occurs when stimulated TLR3 and TLR4, and their inhibition reduced the migration ability of MSCs by more than 50%. Nurmenniemi et al., [81] showed constitutive expression of TLR9 in human BM-MSCs, and stimulation of the cells with TLR9 agonist, CpG oligonucleotides, increased the expression of MMP-13 and enhanced the ability of these cells to invasion *in vitro*.

Integrins and adhesion molecules

One of the most important stages of cell homing, including MSCs, is their movement in the bloodstream and transmigration through the vascular endothelium. This multi-step process includes several types of adhesion molecules, cytokines and proteases [82]. It is assumed that MSCs, moving through the blood vessels, use the same mechanism of rolling, as a white blood cells and HSCs. In order to leave the blood stream, mature lymphocytes and hematopoietic progenitor cells undergo a series of coordinated adhesion steps, which are mainly mediated by selectins and their ligands [83]. Then the cells roll along the vascular endothelium and at some point encounter chemokines, which ultimately activate integrins, leading to arrest of the cells in a certain place of vasculature and their subsequent transendothelial migration.

Rüster B. et al., [84] demonstrated that hBM-MSCs interact with endothelial cells, including rolling with rapid extension of podia and activation of selectin-dependent and integrin-dependent binding. The authors contend that although hBM-MSCs do not express P-selectin glycoprotein ligand-1 (PSGL-1) and an alternative ligand CD24, they interact with endothelial cells in the P-selectin-dependent manner. At the same time, in contrast to HSCs, human MSCs do not express or express small amounts of E-and L-selectins, and their contribution to traffic MSC is not significant when compared with the P-selectin. That would suggest that MSCs express a new carbohydrate ligand, which can serve counterligand for P-selectin expressed on endothelium. Also these data suggest that hMSCs, like white blood cells, rolled on endothelial cells at the first stage of their recruitment [84].

The majority of leukocyte adhesion molecules, such as β2 integrin-related molecules, are not expressed on the surface of MSCs [85]. However, MSCs express very late antigen-4 (VLA-4, α4β1 integrin) and vascular cell adhesion molecule-1 (VCAM-1) [84]. It was shown that β1 integrins are important for the intramyocardial traffic of MSCs [86] and, as mentioned above, are crucial in the rolling and

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adhesion of human MSCs [84]. Moreover, an anti-VCAM-1 antibody reduces the adhesion of rat MSCs to endothelial cells of microvessels [87]. In addition, it was found that VCAM-1 and VLA-4 are key receptors for transendothelial migration of human MSCs. Because transmigration of MSCs is not blocked completely by anti-VCAM-1 and anti-VLA-4 antibodies, it is possible that this process may involve other integrin α-chain.

It was confirmed that BM-MSCs also express other, than integrin α4β1, combinations of integrin subunits, such as α6β1, α8β1 and α9β1 [86], as well as integrins α1, α2, α3, α4, α5, αv, β3 and β4 and the number of adhesion molecules, which include ICAM-1, ICAM-3, ALCAM and endoglin/CD105 [88,89]. For human pMSCs, Abumaree et al., [47] first showed that the pMSCs express a wide range of adhesion molecules, including α7, α8, α10, αE, αM, β3, ICAM-2, PECAM, and, in contrast to BM-MSCs, P-selectin ligand. Moreover, it was shown that pMSCs expressed a molecule α1, α2, α2b, α3, α4, α5, α6, α7, α8, α11, αV, β1, β4, β5, ICAM-1, VCAM, CD166 and CD44. However, the importance of these molecules in biology, not only pMSCs, but also MSCs obtained from other sources, yet to be studied, but it is likely that these molecules may mediate their adhesion to endothelial cells and migration into the tissue by homing mechanism, similar to the homing of leukocytes.

Vascular endothelium forms a major barrier to the transmigration of molecules and cells from the blood into the surrounding tissue. It has been shown that endothelial cells actively modulate leukocyte diapedesis [90]. To date, there is very little data concerning the effects of vascular endothelium on MSC transmigration. In various areas of vasculature endothelium is functionally different, and, therefore, varies its barrier function [91]. It is known that various endothelial phenotypes reflect functional differences. For example, variations in the number of intercellular tight junctions exist at various points throughout the vasculature and are the cause of differences in endothelium permeability [91]. Steingen et al., [92] showed that endothelial phenotype strictly influences on transmigration of human bone marrow MSCs *in vitro*. Coronary artery endothelium enables the most rapid integration of MSCs *in vitro*. In contrast, MSC transmigration through the venous endothelium was most effective over time. On the other hand, the adhesion of rat MSCs to endothelial cells of the aorta and cardiac microvascular endothelial cells did not differ significantly [87]. In summary, the above data demonstrate that the rolling, transmigration and invasion efficiency of MSCs into different organs depend on the patterns of adhesion molecules and integrins expressed by MSCs, and may vary depending on the type of surrounding vessels.

Proteases

MSC invasion into the targeted tissue requires not only their transmigration through the endothelial barrier, but also through the basement membrane and extracellular matrix. It is known that leukocyte transmigration is due to the binding of α4β1 integrin on the surface of white blood cells with VCAM-1 on the surface of vascular endothelium in the site of inflammation, which then induces the expression of matrix metalloproteinase MMP-2, which facilitates invasion of the subendothelial matrix [93]. Matrix metalloproteinases (MMPs) are a family of endoproteinases that can cleave all of the extracellular matrix components and, thus, contribute to cell migration through the matrix. This system is regulated by the interaction of MMP with four tissue-specific inhibitors of MMPs (tissue inhibitor of metalloproteinase, TIMP). The balance of MMP/TIMP plays an important role in angiogenesis, proliferation, apoptosis and invasion. High expression of MMP associated with low levels of TIMP secretion promotes a higher rate of metastasis or tumor growth [75,94].

Son B.R. et al., [95] demonstrated that BM-MSCs and umbilical cord blood MSCs (UCB-MSCs) express membrane type of MMP-1 and MMP-2, which cleaves the main component of basement membrane collagen IV. In addition, De Becker et al., [82] showed that MMP-2, but not MMP-9, which is not expressed by these cells, plays a role in the MSC migration through the bone marrow endothelium. Steingen et al., [92] confirmed that MSCs do not express MMP-9 at the protein level and showed that in the myocardium active MMP localized precisely in areas of MSC transmigration and invasion, showing that during homing in cardiac tissue MSCs secrete MMP-2 to transmigrate through the basement membrane and penetrate the surrounding extracellular matrix.

Tondreau et al., [74] using qRT-PCR and protein analysis demonstrated constitutive expression of MMP-2, TIMP-1 and TIMP-2, but not MMP-9, and a very low level of TIMP-4 by BM-MSCs. The authors also found that the mRNA levels of MMP/TIMP in response to PDGF-BB, IL-6, IGF-I and SDF-1α significantly varied. Although MMP-2 and MMP-13 production is not always increased significantly in response to these chemokines/cytokines, variable levels of TIMP-1 and TIMP-2 were observed, confirming their participation in the migration process. Thus, the migration of BM-MSCs in the presence of PDGF-BB was the result of decreasing production of TIMP balanced by increasing levels of MMP-2. High migration of MSCs observed in the presence of IL-6 is due to the increasing level of MMP-13 without modulating of TIMP. At the same time adding SDF-1α did not affect the production of MMP/TIMP and correlated with the absence of migration. On the other hand, Song and Li [67] showed that normally BM-MSCs did not express MMP-2. However, MMP-2 expression is induced by treatment of BM-MSCs with tumor conditioned medium as early as 2 h, and after 24 hours its amount decreases, which indicates that the expression of MMP-2 is strictly regulated, possibly through tissue inhibitor of matrix metalloproteinase (TIMP)-1 and TIMP-2 at various stages of homing/engraftment BM-MSC

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into the tumor.

The results presented in this chapter clearly indicate that MSCs similar to HSCs use matrix metalloproteinases, such as MMP-2, for transendothelial migration and invasion in the targeted tissue.

Conclusions

Despite the fact that the process of cell homing, particularly white blood cells and hematopoietic progenitor cells has been studied in detail, it is not possible to extrapolate the available knowledge on the migration and homing of mesenchymal stem cells. As can be seen from the presented review, the milestone events in homing of different cell types are the same, but the molecular mechanisms of these stages are different. Moreover, MSCs derived from different sources express different pattern of chemokines and their receptors, which may indicate the possibility of a preferred migration of different MSCs into various tissues. In addition, ex vivo culturing conditions of MSCs and number of passages can have a significant effect on the expression of chemokines/receptors as well as matrix metalloproteinases, which in turn affects the ability of the cells to migration and homing.

Thus, in order to create the most complete picture of the mechanisms of MSC migration and homing require more detailed studies aimed at investigating the various molecular signaling pathways involved in these processes. A more complete understanding of the mechanisms of MSC homing and migration will help effectively apply these cells in clinical practice and regenerative medicine when administered systemically. The possibility to modulate the migration ability of these cells, for example, by inflammatory cytokines, opens broad prospects for the development of directed migration of greater number of iv injected cells to the injury site.

List of abbreviations

MSCs: mesenchymal stem cells
BM-MSCs: bone marrow-derived mesenchymal stem cells
AdMSCs: adipose-derived MSCs
MMPs: metalloproteinases
pMSCs: placental mesenchymal stem cells
ICAM-1: Intercellular Adhesion Molecule 1
PCR: polymerase chain reaction
GFP: green fluorescent protein
MRI: magnetic resonance imaging
SPIO: superparamagnetic iron oxide nanoparticles
TNF: tumor necrosis factor
VCAM-1: Vascular cell adhesion molecule 1
SDF-1: stromal cell-derived factor-1
IGF-1: Insulin-like growth factor 1
SCF: stem cell factor
HGF: hepatocyte growth factor
PDFG: platelet-derived growth factor
TGF-β1: tumor growth factor β1
VEGF: vascular endothelial growth factor
TLR: Toll-like receptor
VLA-4: very late antigen-4
ALCAM: Activated leukocyte cell adhesion molecule
PECAM: platelet/endothelial cell adhesion molecule 1
TIMP: tissue inhibitor of metalloproteinase
UCB-MSCs: umbilical cord blood MSCs

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Irina V. Kholodenko participated in the design of this paper and drafted the manuscript; Irina V. Kholodenko is a specialist in the field of the cell biology and immunofluorescence methods (immunohistochemistry and immunocytochemistry). Alina A. Konieva conducted the analysis of the literature on the topic of the manuscript; Alina A. Konieva is a specialist in the creation of animal models of stroke and spinal cord injury. Roman V. Kholodenko helped to draft the manuscript; he is a specialist for flow cytometry. Konstantin N. Yarygin led the writing of the manuscript and participated in its design, drafted critical revision, carried out the design of the previous experimental work. Final version of the manuscript was read and approved by all the authors.

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References

1. Beyer Nardi N and da Silva Meirelles L. **Mesenchymal stem cells: isolation, *in vitro* expansion and characterization**. *Handb Exp Pharmacol.* 2006; **174**:249-82. | Article | PubMed
2. Sivasubramaniyan K, Lehnen D, Ghazanfari R, Sobiesiak M, Harichandan A, Mortha E, Petkova N, Grimm S, Cerabona F, de Zwart P, Abele H, Aicher WK, Faul C, Kanz L and Buhring HJ. **Phenotypic and functional heterogeneity of human bone marrow- and amnion-derived MSC subsets**. *Ann N Y Acad Sci.* 2012; **1266**:94-106. | Article | PubMed
3. Suzdal'tseva YG, Burunova VV, Petrakova NV, Vakhrushev IV, Yarygin KN and Yarygin VN. **Comparatine analysis of cytophenotypes of cells of mesenchymal lineage isolated from human tissues**. *Bull Exp Biol Med.* 2007; **143**:147-54. | Article | PubMed
4. Kholodenko IV, Konieva AA, Kholodenko RV, Burunova VV, Plotnikov EYu, Lupatov AYu, Yarygin KN. **Immunosuppressive properties of mesenchymal stem cells isolated from human placenta.** *Modern Problems of Dermatovenerology, Immunology and Medical Cosmetology (Russia).* 2010; **6**:8-12.
5. Lupatov AYu, Karalkin PA, Moldaver MV, Burunova VV, Poltavtseva RA, Pavlovich SV, Yarygin KN, Suhih GT. **Bone marrow mesenchymal stem cells suppress differentiation of allogeneic dendritic cells in vitro and do not affect their maturation.** *Immunologiya (Russia).* 2011*;* **32**:122-127.
6. Karalkin PA, Lupatov AY, Burunova VV, Holodenko IV, Yarygin KN, Moldaver MV, Poltavtseva RA, Pavlovich SV and Sukhikh GT. **Immunoregulatory properties of human stem cells of mesenchymal and ectodermal origin after their transplantation to BALB/c mice**. *Bull Exp Biol Med.* 2012; **153**:118-23. | Article | PubMed
7. Kim N, Im KI, Lim JY, Jeon EJ, Nam YS, Kim EJ and Cho SG. **Mesenchymal stem cells for the treatment and prevention of graft-versus-host disease: experiments and practice**. *Ann Hematol.* 2013; 1-14. | Article | PubMed
8. Mohyeddin Bonab M, Mohajeri M, Sahraian MA, Yazdanifar M, Aghsaie A, Farazmand A and Nikbin B. **Evaluation of Cytokines in Multiple Sclerosis Patients Treated with Mesenchymal Stem Cells**.

Arch Med Res. 2013; **44**:266-72. | Article | PubMed

9. Rennert RC, Sorkin M, Garg RK and Gurtner GC. **Stem cell recruitment after injury: lessons for regenerative medicine**. *Regen Med.* 2012; **7**:833-50. | Article | PubMed
10. Kim JW, Ha KY, Molon JN and Kim YH. **Bone marrow-derived mesenchymal stem cell transplantation for chronic spinal cord injury in rats: comparative study between intralesional and intravenous transplantation**. *Spine (Phila Pa 1976).* 2013; **38**:E1065-74. | Article | PubMed
11. Kholodenko IV, Yarygin KN, Gubsky LV, Konieva AA, Tairova RT, Povarova OV, Kholodenko RV, Burunova VV, Yarygin VN and Skvortsova VI. **Intravenous xenotransplantation of human placental mesenchymal stem cells to rats: comparative analysis of homing in rat brain in two models of experimental ischemic stroke**. *Bull Exp Biol Med.* 2012; **154**:118-23. | Article | PubMed
12. Charwat S, Gyongyosi M, Lang I, Graf S, Beran G, Hemetsberger R, Nyolczas N, Sochor H and Glogar D. **Role of adult bone marrow stem cells in the repair of ischemic myocardium: current state of the art**. *Exp Hematol.* 2008; **36**:672-80. | Article | PubMed
13. Gojo S, Gojo N, Takeda Y, Mori T, Abe H, Kyo S, Hata J and Umezawa A. **In vivo cardiovasculogenesis by direct injection of isolated adult mesenchymal stem cells**. *Exp Cell Res.* 2003; **288**:51-9. | Article | PubMed
14. Hofstetter CP, Schwarz EJ, Hess D, Widenfalk J, El Manira A, Prockop DJ and Olson L. **Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery**. *Proc Natl Acad Sci U S A.* 2002; **99**:2199-204. | Article | PubMed Abstract | PubMed Full Text
15. Kholodenko IV, Konieva AA, Lupatov AY, Yegorov YE, Yarygin KN. **Transplantation of human mesenchymal stem cells and syngeneic macrophages into mice with contusive spinal cord injury.** *J. Tissue Eng. Regen. Med.* 2012; **6 (Suppl. 1)**:86-87.
16. Andrews EM, Tsai SY, Johnson SC, Farrer JR, Wagner JP, Kopen GC and Kartje GL. **Human adult bone marrow-derived somatic cell therapy results in functional recovery and axonal plasticity following stroke in the rat**. *Exp Neurol.* 2008; **211**:588-92. | Article | PubMed
17. Breitbach M, Bostani T, Roell W, Xia Y, Dewald O, Nygren JM, Fries JW, Tiemann K, Bohlen H, Hescheler J, Welz A, Bloch W, Jacobsen SE and Fleischmann BK. **Potential risks of bone marrow cell transplantation into infarcted hearts**. *Blood.* 2007; **110**:1362-9. | Article | PubMed
18. Zhuo W, Liao L, Fu Y, Xu T, Wu W, Yang S and Tan J. **Efficiency of endovenous versus arterial administration of mesenchymal stem cells for ischemia-reperfusion-induced renal dysfunction in rats**. *Transplant Proc.* 2013; **45**:503-10. | Article | PubMed
19. Zonta S, De Martino M, Bedino G, Piotti G, Rampino T, Gregorini M, Frassoni F, Dal Canton A, Dionigi P and Alessiani M. **Which is the most suitable and effective route of administration for mesenchymal stem cell-based immunomodulation therapy in experimental kidney transplantation: endovenous or arterial?** *Transplant Proc.* 2010; **42**:1336-40. | Article | PubMed
20. Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes LH, Kloner RA and Leor J. **Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution**. *Circulation.* 2003; **108**:863-8. | Article | PubMed
21. Kyriakou C, Rabin N, Pizzey A, Nathwani A and Yong K. **Factors that influence short-term homing of human bone marrow-derived mesenchymal stem cells in a xenogeneic animal model**. *Haematologica.* 2008; **93**:1457-65. | Article | PubMed
22. Gao J, Dennis JE, Muzic RF, Lundberg M and Caplan AI. **The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion**. *Cells Tissues Organs.* 2001; **169**:12-20. | Article | PubMed
23. Goldmacher GV, Nasser R, Lee DY, Yigit S, Rosenwasser R and Iacovitti L. **Tracking transplanted bone marrow stem cells and their effects in the rat MCAO stroke model**. *PLoS One.* 2013; **8**:e60049. | Article | PubMed Abstract | PubMed Full Text
24. Yarygin KN, Kholodenko IV, Konieva AA, Burunova VV, Tairova RT, Gubsky LV, Cheglakov IB, Pirogov YA, Yarygin VN and Skvortsova VI. **Mechanisms of positive effects of transplantation of human placental mesenchymal stem cells on recovery of rats after experimental ischemic stroke**. *Bull Exp Biol Med.* 2009; **148**:862-8. | Article | PubMed
25. Wu GD, Nolta JA, Jin YS, Barr ML, Yu H, Starnes VA and Cramer DV. **Migration of mesenchymal stem cells to heart allografts during chronic rejection**. *Transplantation.* 2003; **75**:679-85. | Article | PubMed
26. Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N and Phinney DG. **Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects**. *Proc Natl Acad Sci U S A.* 2003; **100**:8407-11. | Article | PubMed Abstract | PubMed Full Text
27. Devine SM, Cobbs C, Jennings M, Bartholomew A and Hoffman R. **Mesenchymal stem cells distribute to a wide range of tissues following systemic infusion into nonhuman primates**. *Blood.* 2003; **101**:2999-3001. | Article | PubMed
28. Nagaya N, Fujii T, Iwase T, Ohgushi H, Itoh T, Uematsu M, Yamagishi M, Mori H, Kangawa K and Kitamura S. **Intravenous administration of mesenchymal stem cells improves cardiac function in rats with acute myocardial infarction through angiogenesis and myogenesis**. *Am J Physiol Heart Circ Physiol.* 2004; **287**:H2670-6. | Article | PubMed
29. Deak E, Seifried E and Henschler R. **Homing pathways of mesenchymal stromal cells (MSCs) and their role in clinical applications**. *Int Rev Immunol.* 2010; **29**:514-29. | Article | PubMed
30. Mahmood A, Lu D, Qu C, Goussev A and Chopp M. **Human marrow stromal cell treatment provides long-lasting benefit after traumatic brain injury in rats**. *Neurosurgery.* 2005; **57**:1026-31. | Article | PubMed Abstract | PubMed Full Text
31. Fatar M, Stroick M, Griebe M, Marwedel I, Kern S, Bieback K, Giesel FL, Zechmann C, Kreisel S, Vollmar F, Alonso A, Back W, Meairs S and Hennerici MG. **Lipoaspirate-derived adult mesenchymal stem cells improve functional outcome during intracerebral hemorrhage by proliferation of endogenous progenitor cells stem cells in intracerebral hemorrhages**. *Neurosci Lett.* 2008; **443**:174-8. | Article | PubMed
32. Morigi M, Introna M, Imberti B, Corna D, Abbate M, Rota C, Rottoli D, Benigni A, Perico N, Zoja C, Rambaldi A, Remuzzi A and Remuzzi G. **Human bone marrow mesenchymal stem cells accelerate recovery of acute renal injury and prolong survival in mice**. *Stem Cells.* 2008; **26**:2075-82. | Article | PubMed
33. Horita Y, Honmou O, Harada K, Houkin K, Hamada H and Kocsis JD. **Intravenous administration of glial cell line-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in the adult rat**. *J Neurosci Res.* 2006; **84**:1495-504. | Article | PubMed Abstract | PubMed Full Text
34. Omori Y, Honmou O, Harada K, Suzuki J, Houkin K and Kocsis JD. **Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats**. *Brain Res.* 2008; **1236**:30-8. | Article | PubMed Abstract | PubMed Full Text
35. Jiang W, Ma A, Wang T, Han K, Liu Y, Zhang Y, Dong A, Du Y, Huang X, Wang J, Lei X and Zheng X. **Homing and differentiation of mesenchymal stem cells delivered intravenously to ischemic myocardium in vivo: a time-series study**. *Pflugers Arch.* 2006; **453**:43-52. | Article | PubMed
36. Reagan MR and Kaplan DL. **Concise review: Mesenchymal stem cell tumor-homing: detection methods in disease model systems**. *Stem Cells.* 2011; **29**:920-7. | Article | PubMed
37. Kraitchman DL, Tatsumi M, Gilson WD, Ishimori T, Kedziorek D, Walczak P, Segars WP, Chen HH, Fritzges D, Izbudak I, Young RG, Marcelino M, Pittenger MF, Solaiyappan M, Boston RC, Tsui BM, Wahl RL and Bulte JW. **Dynamic imaging of allogeneic mesenchymal stem cells trafficking to myocardial infarction**. *Circulation.* 2005; **112**:1451-

61. | Article | PubMed Abstract | PubMed Full Text

38. Yukawa H, Watanabe M, Kaji N, Okamoto Y, Tokeshi M, Miyamoto Y, Noguchi H, Baba Y and Hayashi S. **Monitoring transplanted adipose tissue-derived stem cells combined with heparin in the liver by fluorescence imaging using quantum dots**. *Biomaterials.* 2012; **33**:2177-86. | Article | PubMed

39. Hsiao JK, Tai MF, Chu HH, Chen ST, Li H, Lai DM, Hsieh ST, Wang JL and Liu HM. **Magnetic nanoparticle labeling of mesenchymal stem cells without transfection agent: cellular behavior and capability of detection with clinical 1.5 T magnetic resonance at the single cell level**. *Magn Reson Med.* 2007; **58**:717-24. | Article | PubMed

40. Shah BS, Clark PA, Moioli EK, Stroscio MA and Mao JJ. **Labeling of mesenchymal stem cells by bioconjugated quantum dots**. *Nano Lett.* 2007; **7**:3071-9. | Article | PubMed

41. Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, Semprun-Prieto L, Delafontaine P and Prockop DJ. **Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6**. *Cell Stem Cell.* 2009; **5**:54-63. | Article | PubMed

42. Del Rosso M, Fibbi G, Pucci M, D'Alessio S, Del Rosso A, Magnelli L and Chiarugi V. **Multiple pathways of cell invasion are regulated by multiple families of serine proteases**. *Clin Exp Metastasis.* 2002; **19**:193-207. | PubMed

43. Egeblad M and Werb Z. **New functions for the matrix metalloproteinases in cancer progression**. *Nat Rev Cancer.* 2002; **2**:161-74. | Article | PubMed

44. Turk V, Kos J and Turk B. **Cysteine cathepsins (proteases)--on the main stage of cancer?** *Cancer Cell.* 2004; **5**:409-10. | Article | PubMed

45. Ji JF, He BP, Dheen ST and Tay SS. **Interactions of chemokines and chemokine receptors mediate the migration of mesenchymal stem cells to the impaired site in the brain after hypoglossal nerve injury**. *Stem Cells.* 2004; **22**:415-27. | Article | PubMed

46. Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ and Power CA. **International union of pharmacology. XXII. Nomenclature for chemokine receptors**. *Pharmacol Rev.* 2000; **52**:145-76. | Article | PubMed

47. Abumaree MH, Al Jumah MA, Kalionis B, Jawdat D, Al Khaldi A, AlTalabani AA and Knawy BA. **Phenotypic and functional characterization of mesenchymal stem cells from chorionic villi of human term placenta**. *Stem Cell Rev.* 2013; **9**:16-31. | Article | PubMed

48. Li G, Zhang XA, Wang H, Wang X, Meng CL, Chan CY, Yew DT, Tsang KS, Li K, Tsai SN, Ngai SM, Han ZC, Lin MC, He ML and Kung HF. **Comparative proteomic analysis of mesenchymal stem cells derived from human bone marrow, umbilical cord, and placenta: implication in the migration**. *Proteomics.* 2009; **9**:20-30. | Article | PubMed

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

50. Perez AL, Bachrach E, Illigens BM, Jun SJ, Bagden E, Steffen L, Flint A, McGowan FX, Del Nido P, Montecino-Rodriguez E, Tidball JG and Kunkel LM. **CXCR4 enhances engraftment of muscle progenitor cells**. *Muscle Nerve.* 2009; **40**:562-72. | Article | PubMed Abstract | PubMed Full Text

51. Croitoru-Lamoury J, Lamoury FM, Zaunders JJ, Veas LA and Brew BJ. **Human mesenchymal stem cells constitutively express chemokines and chemokine receptors that can be upregulated by cytokines, IFN-beta, and Copaxone**. *J Interferon Cytokine Res.* 2007; **27**:53-64. | Article | PubMed

52. 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 and Piemonti L. **Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets**. *Blood.* 2005; **106**:419-27. | Article | PubMed

53. Krohn A, Song YH, Muehlberg F, Droll L, Beckmann C and Alt E. **CXCR4 receptor positive spheroid forming cells are responsible for tumor invasion in vitro**. *Cancer Lett.* 2009; **280**:65-71 1. | Article | PubMed

54. Wang CL, Sun BS, Tang Y, Zhuang HQ and Cao WZ. **CCR1 knockdown suppresses human non-small cell lung cancer cell invasion**. *J Cancer Res Clin Oncol.* 2009; **135**:695-701. | Article | PubMed

55. Varney ML, Johansson SL and Singh RK. **Distinct expression of CXCL8 and its receptors CXCR1 and CXCR2 and their association with vessel density and aggressiveness in malignant melanoma**. *Am J Clin Pathol.* 2006; **125**:209-16. | Article | PubMed

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

57. Kortesidis A, Zannettino A, Isenmann S, Shi S, Lapidot T and Gronthos S. **Stromal-derived factor-1 promotes the growth, survival, and development of human bone marrow stromal stem cells**. *Blood.* 2005; **105**:3793-801. | Article | PubMed

58. Honczarenko M, Le Y, Swierkowski M, Ghiran I, Glodek AM and Silberstein LE. **Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors**. *Stem Cells.* 2006; **24**:1030-41. | Article | PubMed

59. Ringe J, Strassburg S, Neumann K, Endres M, Notter M, Burmester GR, Kaps C and Sittinger M. **Towards in situ tissue repair: human mesenchymal stem cells express chemokine receptors CXCR1, CXCR2 and CCR2, and migrate upon stimulation with CXCL8 but not CCL2**. *J Cell Biochem.* 2007; **101**:135-46. | Article | PubMed

60. Ponte AL, Marais E, Gallay N, Langonne A, Delorme B, Herault O, Charbord P and Domenech J. **The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities**. *Stem Cells.* 2007; **25**:1737-45. | Article | PubMed

61. Karp JM and Leng Teo GS. **Mesenchymal stem cell homing: the devil is in the details**. *Cell Stem Cell.* 2009; **4**:206-16. | Article | PubMed

62. Horuk R and Peiper SC. **Chemokines: molecular double agents**. *Curr Biol.* 1996; **6**:1581-2. | Article | PubMed

63. Doitsidou M, Reichman-Fried M, Stebler J, Koprunner M, Dorries J, Meyer D, Esguerra CV, Leung T and Raz E. **Guidance of primordial germ cell migration by the chemokine SDF-1**. *Cell.* 2002; **111**:647-59. | Article | PubMed

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

65. Li Y, Yu X, Lin S, Li X, Zhang S and Song YH. **Insulin-like growth factor 1 enhances the migratory capacity of mesenchymal stem cells**. *Biochem Biophys Res Commun.* 2007; **356**:780-4. | Article | PubMed

66. Shi M, Li J, Liao L, Chen B, Li B, Chen L, Jia H and Zhao RC. **Regulation of CXCR4 expression in human mesenchymal stem cells by cytokine treatment: role in homing efficiency in NOD/SCID mice**. *Haematologica.* 2007; **92**:897-904. | Article | PubMed

67. Song C and Li G. **CXCR4 and matrix metalloproteinase-2 are involved in mesenchymal stromal cell homing and engraftment to tumors**. *Cytotherapy.* 2011; **13**:549-61. | Article | PubMed

68. Menon LG, Picinich S, Koneru R, Gao H, Lin SY, Koneru M, Mayer-Kuckuk P, Glod J and Banerjee D. **Differential gene expression associated with migration of mesenchymal stem cells to conditioned medium from tumor cells or bone marrow cells**. *Stem Cells.* 2007; **25**:520-8. | Article | PubMed

69. Gao H, Priebe W, Glod J and Banerjee D. **Activation of signal transducers and activators of transcription 3 and focal adhesion kinase by stromal cell-derived factor 1 is required for migration of human mesenchymal stem cells in response to tumor cell-conditioned medium**. *Stem Cells.* 2009; **27**:857-6565. | Article | PubMed

70. Wu Y and Zhao RC. **The role of chemokines in mesenchymal stem cell homing to myocardium**. *Stem Cell Rev.* 2012; **8**:243-50. | Article

| PubMed

71. Hill WD, Hess DC, Martin-Studdard A, Carothers JJ, Zheng J, Hale D, Maeda M, Fagan SC, Carroll JE and Conway SJ. **SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: association with bone marrow cell homing to injury**. *J Neuropathol Exp Neurol.* 2004; **63**:84-96. | Article | PubMed
72. Dvorak HF. **Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing**. *N Engl J Med.* 1986; **315**:1650-9. | Article | PubMed
73. Spaeth E, Klopp A, Dembinski J, Andreeff M and Marini F. **Inflammation and tumor microenvironments: defining the migratory itinerary of mesenchymal stem cells**. *Gene Ther.* 2008; **15**:730-8. | Article | PubMed
74. Tondreau T, Meuleman N, Stamatopoulos B, De Bruyn C, Delforge A, Dejeneffe M, Martiat P, Bron D and Lagneaux L. **In vitro study of matrix metalloproteinase/tissue inhibitor of metalloproteinase production by mesenchymal stromal cells in response to inflammatory cytokines: the role of their migration in injured tissues**. *Cytotherapy.* 2009; **11**:559-69. | Article | PubMed
75. Ries C, Egea V, Karow M, Kolb H, Jochum M and Neth P. **MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines**. *Blood.* 2007; **109**:4055-63. | Article | PubMed
76. Baek SJ, Kang SK and Ra JC. **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.* 2011; **43**:596-603. | Article | PubMed Abstract | PubMed Full Text
77. Boyd JH, Divangahi M, Yahiaoui L, Gvozdic D, Qureshi S and Petrof BJ. **Toll-like receptors differentially regulate CC and CXC chemokines in skeletal muscle via NF-kappaB and calcineurin**. *Infect Immun.* 2006; **74**:6829-38. | Article | PubMed Abstract | PubMed Full Text
78. West AP, Koblansky AA and Ghosh S. **Recognition and signaling by toll-like receptors**. *Annu Rev Cell Dev Biol.* 2006; **22**:409-37. | Article | PubMed
79. Tomchuck SL, Zwezdaryk KJ, Coffelt SB, Waterman RS, Danka ES and Scandurro AB. **Toll-like receptors on human mesenchymal stem cells drive their migration and immunomodulating responses**. *Stem Cells.* 2008; **26**:99-107. | Article | PubMed Abstract | PubMed Full Text
80. Waterman RS, Tomchuck SL, Henkle SL and Betancourt AM. **A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an Immunosuppressive MSC2 phenotype**. *PLoS One.* 2010; **5**:e10088. | Article | PubMed Abstract | PubMed Full Text
81. Nurmenniemi S, Kuvaja P, Lehtonen S, Tiuraniemi S, Alahuhta I, Mattila RK, Risteli J, Salo T, Selander KS, Nyberg P and Lehenkari P. **Toll-like receptor 9 ligands enhance mesenchymal stem cell invasion and expression of matrix metalloprotease-13**. *Exp Cell Res.* 2010; **316**:2676-82. | Article | PubMed
82. De Becker A, Van Hummelen P, Bakkus M, Vande Broek I, De Wever J, De Waele M and Van Riet I. **Migration of culture-expanded human mesenchymal stem cells through bone marrow endothelium is regulated by matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-3**. *Haematologica.* 2007; **92**:440-9. | Article | PubMed
83. Springer TA. **Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm**. *Cell.* 1994; **76**:301-14. | Article | PubMed
84. Ruster B, Gottig S, Ludwig RJ, Bistrian R, Muller S, Seifried E, Gille J and Henschler R. **Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells**. *Blood.* 2006; **108**:3938-44. | Article | PubMed
85. Pittenger MF and Martin BJ. **Mesenchymal stem cells and their potential as cardiac therapeutics**. *Circ Res.* 2004; **95**:9-20. | Article | PubMed
86. Ip JE, Wu Y, Huang J, Zhang L, Pratt RE and Dzau VJ. **Mesenchymal stem cells use integrin beta1 not CXC chemokine receptor 4 for myocardial migration and engraftment**. *Mol Biol Cell.* 2007; **18**:2873-82. | Article | PubMed Abstract | PubMed Full Text
87. Segers VF, Van Riet I, Andries LJ, Lemmens K, Demolder MJ, De Becker AJ, Kockx MM and De Keulenaer GW. **Mesenchymal stem cell adhesion to cardiac microvascular endothelium: activators and mechanisms**. *Am J Physiol Heart Circ Physiol.* 2006; **290**:H1370-7. | Article | PubMed
88. Minguell JJ, Erices A, Conget P. **Mesenchymal stem cells.** *Exp. Biol. Med. (Maywood).* 2001; **226**:507–520.
89. Krampera M, Pizzolo G, Aprili G and Franchini M. **Mesenchymal stem cells for bone, cartilage, tendon and skeletal muscle repair**. *Bone.* 2006; **39**:678-83. | Article | PubMed
90. Dejana E, Zanetti A and Del Maschio A. **Adhesive proteins at endothelial cell-to-cell junctions and leukocyte extravasation**. *Haemostasis.* 1996; **26 Suppl 4**:210-9. | Article | PubMed
91. Dejana E, Corada M and Lampugnani MG. **Endothelial cell-to-cell junctions**. *FASEB J.* 1995; **9**:910-8. | Article | PubMed
92. Steingen C, Brenig F, Baumgartner L, Schmidt J, Schmidt A and Bloch W. **Characterization of key mechanisms in transmigration and invasion of mesenchymal stem cells**. *J Mol Cell Cardiol.* 2008; **44**:1072-84. | Article | PubMed
93. Graesser D, Mahooti S and Madri JA. **Distinct roles for matrix metalloproteinase-2 and alpha4 integrin in autoimmune T cell extravasation and residency in brain parenchyma during experimental autoimmune encephalomyelitis**. *J Neuroimmunol.* 2000; **109**:121-31. | Article | PubMed
94. Sakata K, Shigemasa K, Nagai N and Ohama K. **Expression of matrix metalloproteinases (MMP-2, MMP-9, MT1-MMP) and their inhibitors (TIMP-1, TIMP-2) in common epithelial tumors of the ovary**. *Int J Oncol.* 2000; **17**:673-81. | Article | PubMed
95. Son BR, Marquez-Curtis LA, Kucia M, Wysoczynski M, Turner AR, Ratajczak J, Ratajczak MZ and Janowska-Wieczorek A. **Migration of bone marrow and cord blood mesenchymal stem cells in vitro is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases**. *Stem Cells.* 2006; **24**:1254-64. | Article | PubMed

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