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Review

Mesenchymal Stromal Cell Homing: Mechanisms and Strategies for Improvement

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Mesenchymal stromal cells (MSCs) have been widely investigated for their therapeutic potential in regenerative medicine, owing to their ability to home damaged tissue and serve as a reservoir of growth factors and regenerative molecules. As such, clinical applications of MSCs are reliant on these cells successfully migrating to the desired tissue following their administration. Unfortunately, MSC homing is inefficient, with only a small percentage of cells reaching the target tissue following systemic administration. This attrition represents a major bottleneck in realizing the full therapeutic potential of MSC-based therapies. Accordingly, a variety of strategies have been employed in the hope of improving this process. Here, we review the molecular mechanisms underlying MSC homing, based on a multistep model involving (1) initial tethering by selectins, (2) activation by cytokines, (3) arrest by integrins, (4) diapedesis or transmigration using matrix remodelers, and (5) extravascular migration toward chemokine gradients. We then review the various strategies that have been investigated for improving MSC homing, including genetic modification, cell surface engineering, *in vitro* priming of MSCs, and in particular, ultrasound techniques, which have recently gained significant interest. Contextualizing these strategies within the multistep homing model emphasizes that our ability to optimize this process hinges on our understanding of its molecular mechanisms. Moving forward, it is only with a combined effort of basic biology and translational work that the potential of MSC-based therapies can be realized.

INTRODUCTION

Mesenchymal stromal cells (MSCs) are multipotent adult progenitor cells capable of differentiating into various mesenchymal tissues, most prominently bone, cartilage, and adipose. They were first isolated in 1974 from the bone marrow by Friedenstein and colleagues (Friedenstein et al., 1968). Since then, MSCs have been isolated from a variety of other tissues, including adipose (Zuk et al., 2002), perivasculature (Crisan et al., 2008), dental pulp (Gronthos et al., 2000), muscle, dermis (Young et al., 2001), and fetal tissue (Campagnoli et al., 2001; in 't Anker et al., 2003), including the Wharton jelly of umbilical cords (Wang et al., 2004).

The International Society for Cellular Therapy (ISCT) has laid down several defining criteria for the identification of MSCs (Dominici et al., 2006): (1) they must be plastic adherent in standard culture conditions, (2) express the surface markers CD105, CD90, and CD73; (3) not express other lineage markers CD45 (panleukocyte), CD34 (hematopoietic and endothelial), CD14/CD11b (monocytic), CD79a/CD19 (B cell), or human leukocyte antigen (HLA) class II; and (4) show the classical trilineage differentiation into osteoblasts, adipocytes, and chondroblasts. Several nonclassical fates have also been demonstrated, including myoblastic (Crisan et al., 2008), hepatocytic (Snykers et al., 2009), and neural (Arthur et al., 2008), although the neural fate remains controversial. Although MSCs derived from any tissue must meet these minimal criteria, those isolated from different tissues often exhibit considerable differences in their transcriptomic profiles (Jaager et al., 2012; Kern et al., 2006; Stockmann et al., 2012). Of note, MSCs are not a pure population of stem cells; the ISCT criteria actually describe MSCs as a heterogeneous, nonclonal mix of multipotent stem cells, committed progenitors, and differentiated cells (Squillaro et al., 2016). This fact prompted a change in nomenclature from "mesenchymal stem cell" to "mesenchymal stromal cell" to better reflect their cellular heterogeneity, although the terms are still used interchangeably.

Despite these complications surrounding their identity and isolation, there has been much interest revolving around MSCs for their therapeutic potential, especially in regenerative medicine. When tissues are damaged, MSCs are naturally released into circulation, migrate to the site of injury, and secrete molecules to create a microenvironment that promotes regeneration (Chapel et al., 2003; Caplan, 2009). Thus the idea behind their therapeutic potential is that allogenically transplanted MSCs can home

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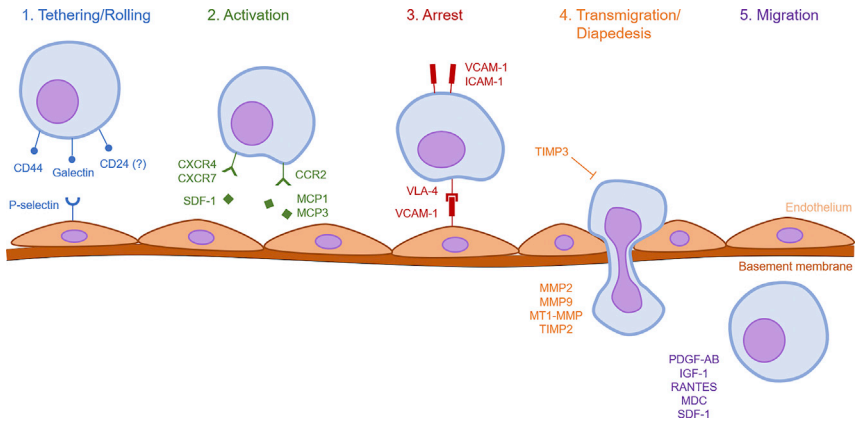

Figure 1. Mesenchymal Stromal Cell Homing Mechanisms

Overview of the molecular mechanisms facilitating each step of mesenchymal stromal cell (MSC) homing.

damaged tissue and act as a "drug store" to aid in recovery or serve as an effector for tissue regeneration (Caplan, 2009). Upon reaching the target tissue, MSCs secrete a variety of factors with powerful immune-modulating, angiogenic, and anti-apoptotic effects (Le Blanc and Mougiakakos, 2012; Singer and Caplan, 2011; Bronckaers et al., 2014). Accordingly, MSCs have been investigated for a wide breadth of clinical applications, such as immune modulation in inflammatory and autoimmune diseases, tissue protection following injury, and regenerative medicine (Frenette et al., 2013). However, a major hurdle still lies in getting MSCs to go where they are needed—that is, optimizing MSC homing efficiency. This review discusses the molecular details of the homing process and the various strategies that have been explored for optimizing it.

MSC HOMING MECHANISMS

One of the key benefits of MSC-based therapies is their ability to preferentially home damaged tissues. It is worth elaborating on what exactly we mean by homing, as the term is often used vaguely in the literature. Following the recommendations of previous reviews, we take homing to encompass both non-systemic and systemic homing (Nitzsche et al., 2017). In non-systemic homing, MSCs are transplanted locally at the target tissue and are then guided to the site of injury via a chemokine gradient. In systemic homing, MSCs are administered or endogenously recruited into the bloodstream and then must undergo a multi-step process to exit circulation and migrate to the injury site. The process of systemic homing can be split into five steps: (1) tethering and rolling, (2) activation, (3) arrest, (4) transmigration or diapedesis, and (5) migration (Sackstein, 2005) (Figure 1).

The initial *tethering* is facilitated by selectins expressed by endothelial cells. MSCs express CD44, which catches onto the selectins and causes the cell to begin rolling along the vasculature wall (Sackstein et al., 2008). The exact selectin used by MSCs is still an active area of investigation, especially because they express neither the hematopoietic cell E- and L-selectin ligand (HCELL) nor the P-selectin glycoprotein ligand-1 (PSGL-1) (Sackstein et al., 2008). To model the tethering process, Rüster et al. constructed a parallel plate flow chamber seeded with endothelial cells (Ruster et al., 2006). They demonstrated that anti-P-selectin antibodies suppress MSC binding to endothelial cells, whereas immobilized P-selectin is sufficient to induce MSC *rolling*. However, as MSCs do not express PSGL-1, they must use a different ligand to interact with P-selectin. One study has identified galectin-1 as one such candidate (Suila et al., 2014). Another study has identified CD24 as a potential P-selectin ligand in adipose tissue-derived stromal cells, which resemble MSCs (Bailey et al., 2009).

The second step, *activation*, is facilitated by G protein-coupled chemokine receptors, generally in response to inflammatory signals. Indeed, mice subjected to total body or local irradiation have higher levels of MSC engraftment owing to the resulting inflammation response (Francois et al., 2006). The expression of stromal cell-derived factor (SDF)-1 on endothelial cells is considered critical for this step (Lau and Wang, 2011). SDF-1 is the ligand to the chemokine receptor CXCR4, which is thought to be expressed by MSCs (Wynn et al., 2004; Gao et al., 2009; Honczarenko et al., 2006). Indeed, overexpression of CXCR4 on

MSCs increases homing to the bone marrow (Bobis-Wozowicz et al., 2011). However, some groups report that MSCs do not express CXCR4 (Von Luttichau et al., 2005), suggesting that other receptors are also involved. Indeed, it has been shown that MSCs also express CXCR7, which similarly binds SDF-1 to facilitate homing to various tissues (Li et al., 2013; Wang et al., 2014; Shao et al., 2019). Other chemokines and receptors are known to play a role as well. For example, transgenic mice expressing the inflammation marker MCP-1 on the myocardium were able to recruit MSCs expressing the corresponding receptor CCR2, due to the direct interaction between the ligand and receptor (Belema-Bedada et al., 2008). In a similar study, MCP-3 expression in the myocardium greatly increased MSC engraftment as well (Schenk et al., 2007). MSCs express a variety of other receptors, including CCR1, CCR4, CCR7, CCR9, CCR10, CXCR5, and CXCR6 (Honczarenko et al., 2006; Von Luttichau et al., 2005), although their roles remain to be elucidated in detail. Regardless of the specific receptor-ligand interaction, the role of the activation step is to increase the affinity of integrins by inducing conformational changes in their extracellular domains; these integrins are essential for cell arrest (Lin et al., 2013; Constantin et al., 2000). For example, SDF-1 stimulation recruits the signaling molecules talin and kindlin to the cytoplasmic domain of VLA-4, causing the latter to shift to a high-affinity conformation (Tadokoro et al., 2003). The expression profile of these receptors likely plays a large role in determining the tissues to which MSCs will migrate.

The third step, *arrest*, is facilitated by integrins. MSCs express VLA-4 (integrin $\alpha4\beta1$), which become activated in response to chemokines like SDF-1. Following activation, the VLA-4 integrin binds to VCAM-1 on endothelial cells (Segers et al., 2006; Ruster et al., 2006; Steingen et al., 2008). Indeed, neutralizing antibodies against β1-integrin inhibit MSC homing to ischemic myocardium, although the same was not true for antibodies blocking α4-integrin (Ip et al., 2007). Overexpression of α4-integrin increases MSC homing to the bone marrow (Kumar and Ponnazhagan, 2007). Interestingly, the MSCs themselves also express integrin ligands including vascular cell adhesion molecule (VCAM)-1 and intercellular cell adhesion molecule (ICAM)-1 (Krampera et al., 2005, 2006), although their importance has not been fully evaluated.

In the next step, *transmigration* or *diapedesis*, MSCs must transcellularly travel through the endothelial cell layer and basement membrane. To accomplish this, MSCs secrete matrix metalloproteinases (MMPs) to break down the endothelial basement membrane (Steingen et al., 2008). MMP maturation and activity are regulated by various other proteins, most prominently the tissue inhibitors of metalloproteinases (TIMPs). The expression of these remodeling enzymes is induced by inflammatory cytokines, which serve as a signal for migration into damaged tissue (Ries et al., 2007). Becker et al. showed that knockdown of MMP2 resulted in significantly decreased migration *in vitro*, as did the exogenous addition of TIMP3 to the culture media (De Becker et al., 2007). Ries et al. similarly demonstrated that knockdown of MMP2, MT1-MMP, or TIMP2 in MSCs reduces invasion, whereas knockdown of TIMP1 increases it (Ries et al., 2007). Although it may seem strange that TIMP2 facilitates transmigration, it actually plays a role in the maturation of MMP2 from its proenzyme form to its active form (Will et al., 1996). There are likely more molecular interactions involved in MSC transmigration, although they are as of yet poorly understood. Leukocyte transmigration, for example, requires homophilic interactions between platelet endothelial cell adhesion molecule expressed on both the leukocyte and endothelium as well as between CD99 (Muller, 2011). An equivalent process in MSCs, however, has not yet been described.

Finally, the MSC must *migrate* through the interstitium to the site of injury. This step is guided by chemotactic signals released in response to tissue damage. MSCs migrate toward various signals, including the growth factors platelet-derived growth factor-AB and insulin-like growth factor (IGF)-1, and to a lesser extent, the chemokines RANTES, MDC, and SDF-1 (Ponte et al., 2009). Preincubating the MSCs with tumor necrosis factor (TNF)-α increases their migration toward chemokines by upregulating their receptors CCR2, CCR3, and CCR4. The inflammatory chemokine interleukin (IL)-8 may promote migration of MSCs to injured sites (Bi et al., 2014; Bayo et al., 2017) and also stimulates them to secrete regenerative factors like vascular endothelial growth factor (VEGF) (Hou et al., 2014). Detailed knowledge of the molecular events facilitating MSC homing immediately presents a variety of strategies for optimizing the process for therapeutic purposes.

IMPROVING MSC HOMING

One of the biggest challenges facing MSC therapies is improving their homing efficiency. The percentage of intravenously (i.v.) administered MSCs that reach the target tissue is in the low single digits, as demonstrated by various imaging studies (Devine et al., 2003; Barbash et al., 2003; Kraitchman et al., 2005). What

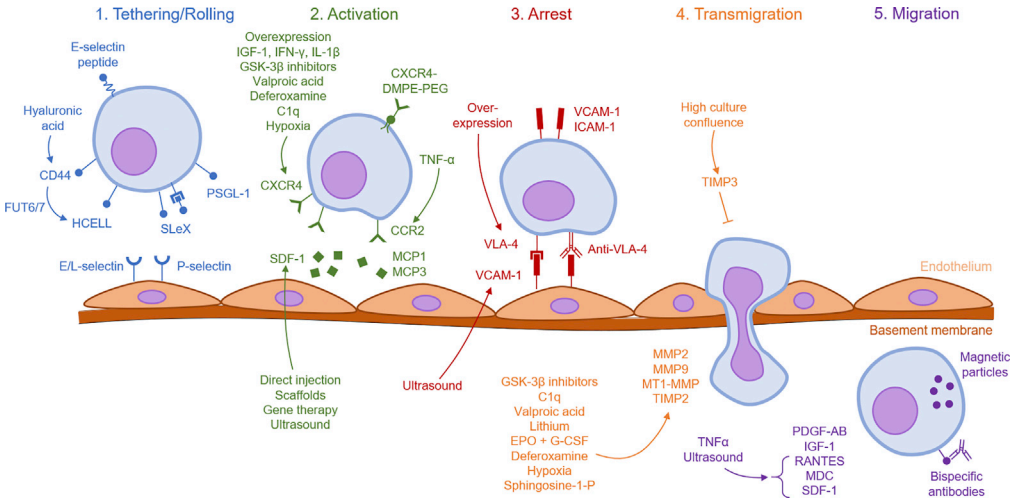

Figure 2. Strategies for improving Mesenchymal Stromal Cell Homing

Overview of the various strategies that have been employed to improve mesenchymal stromal cell (MSC) homing, organized by which step it targets. Arrows indicate upregulation.

causes this low homing efficiency? At least part of the reason is physiological: i.v.-administered MSCs get trapped in the lung capillaries (Scarfe et al., 2018). Indeed, vasodilators and anticoagulants like heparin reduce lung trapping and increase MSC homing to other sites like the liver and bone marrow (Gao et al., 2001; Yukawa et al., 2012). The process of homing, however, is fundamentally based on specific molecular interactions, not passive dissemination. It may be the case that the expression of homing molecules, like CXCR4, is just too low on MSCs (Wynn et al., 2004; Von Luttichau et al., 2005). It has also been observed that the *in vitro* expansion of MSCs gradually leads to the loss in expression of homing molecules (Honczarenko et al., 2006; Rombouts and Ploemacher, 2003). To remedy these problems, a variety of approaches have been taken to improve MSC homing (Figure 2). These strategies can be broadly categorized into seven approaches: (1) targeted administration, (2) magnetic guidance, (3) genetic modification, (4) cell surface engineering, (5) *in vitro* priming, and (6) modification of the target tissue, and (7) radiotherapeutic techniques (Table 1).

TARGETED ADMINISTRATION

Perhaps the most conceptually simple method to improve MSC homing is a physiological one: administer the cells at or near the target tissue, instead of infusing them through standard i.v. routes—that is, utilizing non-systemic rather than systemic homing. It may seem intuitive that direct delivery of MSCs to a tissue may result in greater retention, for example, intramyocardial for heart disease, intratracheal (IT) for lung disease, or intracerebral for neurological diseases.

Considerable work has gone into developing the medical technology needed for targeted administration. Indeed, several clinical trials investigating MSC therapies for ischemic cardiomyopathy use transcatheter injections directly to the myocardium (Williams et al., 2011; Heldman et al., 2014), although none have directly compared the efficacy of different routes of administration. Dick et al. took targeted delivery to the extreme by using magnetic resonance fluoroscopy to identify infarct borders real time in a porcine model (Dick et al., 2003). Here, the authors safely navigated catheters to the infarcted region to deliver MSCs at this site. The injected MSCs were then visible upon delivery and still detectable postmortem using magnetic resonance imaging. Although this study confirmed the successful physical delivery of cells, no attempt was made to quantify the engraftment efficiency, the percentage of MSCs retained in the tissue.

Nevertheless, there is decent evidence that the route of administration has a significant effect on treatment efficacy, presumably due to increased homing. Unfortunately, although many studies administer MSCs directly to the tissue of interest, very few internally compare the targeted administration against standard i.v. administration, so the evidence for the optimal route of administration largely comes from meta-analyses. In ischemic stroke, intracerebral administration of MSCs seems to result in the best improvements in the neurological severity score, followed by intra-arterial, and then i.v. routes (Vu et al., 2014). For

Technique	Tethering/Rolling	Activation	Arrest	Transmigration	Migration
Magnetic guidance		(Yun et al., 2018)			(Arbab et al., 2004; Kobayashi et al., 2008; Yanai et al., 2012; Yun et al., 2018)
Genetic modification					
Infection	(Lo et al., 2016)	(Cheng et al., 2008; Zhang et al., 2008; Bobis-Wozowicz et al., 2011; Chen et al., 2018b; Gheisari et al., 2012; Shao et al., 2019)	(Kumar and Ponnazhagan, 2007; Cui et al., 2017)		
Transfection	(Levy et al., 2013; Liao et al., 2016; Dykstra et al., 2016; Chou et al., 2017)	(Ryser et al., 2008; Wiehe et al., 2013)			
Cell surface engineering					
Enzymatic modification	(Sackstein et al., 2008; Abdi et al., 2015; Lo et al., 2016; Dykstra et al., 2016; Chou et al., 2017)				
Ligand conjugation	(Sarkar et al., 2008; Cheng et al., 2012; Lo et al., 2013)	(Won et al., 2014)	(Ko et al., 2009, 2010)		(Lee et al., 2007; Gundlach et al., 2011)
Priming					
Culture media additives	(Corradetti et al., 2017)	(Shi et al., 2007; Li et al., 2007; Duijvestein et al., 2011; Fan et al., 2012b; Kim et al., 2013; Tsai et al., 2010, 2011; Najafi and Sharifi, 2013; Annabi et al., 2003; Hung et al., 2007; Liu et al., 2010; Meng et al., 2018; Chu et al., 2008; Qiu et al., 2012; Ponte et al., 2009)		(Kim et al., 2013; Qiu et al., 2012; Tsai et al., 2010; Yu et al., 2011; Najafi and Sharifi, 2013; Annabi et al., 2003; Kang et al., 2015; Chen et al., 2018a)	
Culture confluence			(Kim et al., 2014)	(De Becker et al., 2007)	
Coculture		(Zhang et al., 2012; Ran et al., 2018)		(Luo et al., 2018)	(Zhidkova et al., 2018)
Modification of target tissue					
Direct injection		(Yamaguchi et al., 2003; Sasaki et al., 2007; Saxena et al., 2008; Segers et al., 2007, 2011)			

Table 1. Overview of Strategies Targeting Each Step of Mesenchymal Stromal Cell Homing

(Continued on next page)

Technique	Tethering/Rolling	Activation	Arrest	Transmigration	Migration
Genetic modification		(Fujii et al., 2011; Sundararaman et al., 2011; Penn et al., 2013; Chung et al., 2015)			
Scaffolds		(Kimura and Tabata, 2010; He et al., 2010; Goncalves et al., 2012; Shen et al., 2010; Schantz et al., 2007; Thevenot et al., 2010)			
Radiotherapy		(Ponomaryov et al., 2000)			
Ultrasound	(Wang et al., 2015)	(Li et al., 2015; Burks et al., 2011, 2013, 2017, 2018; Tebebi et al., 2015, 2017; Ziadloo et al., 2012; Jang et al., 2017; Kovacs et al., 2017; Wang et al., 2015)	(Burks et al., 2011, 2013, 2017; Tebebi et al., 2015, 2017; Ziadloo et al., 2012; Wang et al., 2015)	(Kovacs et al., 2017)	(Tebebi et al., 2015; Burks et al., 2017)

Table 1. Continued

myocardial infarction in swine models, transendocardial administration of MSCs seems to reduce infarct size, whereas intramyocardial, intracoronary, and i.v. administration showed no significant improvement (Kanelidis et al., 2017). However, in a different meta-analysis of human trials, MSCs were found to improve left ventricular ejection fraction via intracoronary, i.v., and intramyocardial routes, in descending order of effect size (Jeong et al., 2018). For bronchopulmonary dysplasia, the most effective routes of administration are, from best to worst, i.v., IT, intraperitoneal, and intranasal, with the last showing no significant improvement (Augustine et al., 2017). In acute lung injury, IT and i.v. administration both seem effective, whereas intraperitoneal is not (McIntyre et al., 2016). However, the route of administration does not appear to affect MSC therapy outcomes for traumatic brain injury (Peng et al., 2015). Evidently, it should not always be presumed that direct administration of MSCs to the target organ will yield the best outcomes. In one of the few studies that internally compared different administration routes, Antunes et al. administered MSCs into a porcine model of emphysema via either the i.v. or IT route (Antunes et al., 2014). Both routes led to decreased lung inflammation and cell damage and restored elastic fiber content. However, only the i.v. route improved cardiovascular function and shifted lung macrophage phenotypes from M1 to M2. This may be a special case for the lung, given that i.v.-administered MSCs will naturally get trapped in the lung capillaries.

Several groups have explored transplantation of MSC sheets rather than suspensions. MSC sheets are monolayers of cells that are grown in culture that then spontaneously detach with a decrease in temperature. Using a rat model of chronic myocardial infarction, Ishikane et al. transplanted MSC sheets directly onto scarred myocardium (Ishikane et al., 2013). Compared with untreated controls, the treated mice showed significantly improved cardiac function, reduced myocardial fibrosis, and greater capillary density in the infarcted region. The transplantation also elicited an M2 macrophage response. Kawamura et al. showed a similar result using a xenotransplantation model of human MSC sheets into a porcine model of ischemic cardiomyopathy (Kawamura et al., 2015), demonstrating improved cardiac performance, attenuated ventricular remodeling, and increased vascularization in pigs transplanted with MSC sheets, compared with controls. Unlike these previous two studies, which did not compare MSC sheet transplant against intraorgan injection, Tano et al. directly assessed the efficacy of epicardial MSC sheet placement versus intramyocardial injection in a rat model of ischemic cardiomyopathy (Tano et al., 2014), showing that the MSC sheets improved myocardial repair more so than MSC suspensions injected intramyocardially. Using a rat model of colitis, Pak et al. endoscopically transplanted MSC sheets into the colon (Pak et al., 2018). The MSC sheets successfully attached to the inflamed mucosa and led to significantly reduced ulcer size

and inflammation compared with sham-treated controls, although no comparisons were made to other routes of administration. Kaibuchi et al. tested MSC sheet transplantation as a treatment for osteonecrosis of the jaw (Kaibuchi et al., 2016). The MSC sheet group showed significantly improved wound healing (12.5% occurrence of bone exposure) compared with both the control and the i.v. injection groups (80% and 100% occurrence of bone exposure, respectively). The directly transplanted sheets also resulted in greater vascularization (106 vessels/mm^2) compared with both the control and i.v. injection groups (40 and 62 vessels/mm^2, respectively). MSC sheet transplantation may be superior to injection of MSC suspensions because of (1) a better safety profile (no risk of embolism), (2) improved donor cell survival, and (3) improved secretion of regenerative factors. Although such studies strongly indicate the importance of targeted administration, the results are of course highly dependent on the tissue and disease model.

MAGNETIC GUIDANCE

Another physical approach to targeting MSCs comes in the form of magnetic guidance, wherein cells labeled with magnetic particles are directed to the organ of interest using an external magnetic field. Arbab et al. labeled MSCs with iron oxide (ferumoxide) particles, which were injected i.v. into rats with or without an external magnet positioned over the liver (Arbab et al., 2004). Rats that wore the external magnet had around 2-fold the number of labeled MSCs in the liver 15 days post-administration. In the rats not wearing magnets, the MSCs mostly localized around the portal triad, but in the rats that did wear magnets, the MSCs infiltrated deeper into the liver parenchyma. This study did not explore which particular step of homing was enhanced, but it is presumed that the slowed intravascular movement of the MSCs played an essential role. Using an *ex vivo* system, Kobayashi et al. were able to target magnetically labeled MSCs onto an osteochondral defect in the knee joint, with the use of an external magnetic field (Kobayashi et al., 2008). Using an *in vivo* rat model, Yanai et al. were able to target magnetically labeled MSCs to the retina following both intravitreal or i.v. administration, with the assistance of an external magnet placed in the orbit of the rat (Yanai et al., 2012). The rats with the external magnet had significantly higher retinal levels of anti-inflammatory molecules (IL-10) and growth factors (hepatocyte growth factor [HGF]) compared with those without the magnet, suggesting a therapeutic benefit as well. Yun et al. successfully targeted magnetically labeled MSCs to damaged olfactory bulbs using a magnet implanted in the scalp (Yun et al., 2018). Interestingly, they noted an upregulation of CXCR4 resulting from internalization of the magnetic particles, which would facilitate MSC activation. Much work has been done exploring different types of magnetic particles, which have varying effects on MSC viability, proliferation, differentiation, and gene expression (Wang et al., 2017). In most studies, however, there has been no observed effect of magnetic labeling on MSC function (Hsiao et al., 2007; Song and Ku, 2007). Of course, in a real clinical setting, the placement of a permanent magnet must also be practical and not excessively invasive, limiting the target sites for which this technique might be useful.

GENETIC MODIFICATION

Permanent Overexpression

Many early studies exploring genetic modification of MSCs utilized the permanent overexpression of homing factors via viral transduction. The overexpression of CXCR4 in MSCs increases their activation and engraftment to ischemic myocardium in rats, which expresses the CXCR4 ligand SDF-1. This enhanced homing has been shown to improve post-myocardial infarction recovery (Cheng et al., 2008; Zhang et al., 2008). CXCR4-overexpressing MSCs also show increased homing to the bone marrow in mice (Bobis-Wozowicz et al., 2011; Chen et al., 2013), as well as to damaged intestinal mucosa in a mouse model of colitis (Chen et al., 2018b). CXCR7 overexpression has been demonstrated to promote MSC homing to injured lung tissue (Shao et al., 2019). However, it seems that neither CXCR4 nor CXCR7 overexpression improves homing to the kidney in mouse models of acute kidney injury (AKI) (Gheisari et al., 2012).

At the step of cell arrest, overexpression of the α4-integrin, a component of the VLA-4 integrin, increases MSC homing to the bone marrow (Kumar and Ponnazhagan, 2007). However, α4-integrin overexpression did not increase homing to the heart in a rat model of stroke, although it did decrease the formation of potentially harmful cell aggregates (Cui et al., 2017). As with any type of gene therapy, such approaches come with inherent safety concerns; the integration of viral DNA within a tumor suppressor gene, for example, can result in insertional oncogenesis. Viral transduction is also a lengthy and relatively costly process.

Transient Overexpression

Owing to the potential safety concerns of viral transduction, several groups have instead opted for mRNA transfection because of its simplicity, rapid protein expression, and transience. Levy et al. sought to improve MSC tethering by transfecting mRNA for PSGL-1 and SLeX, the ligands for P- and E-/L-selectin, respectively (Levy et al., 2013). Transfected cells successfully rolled on inflamed endothelium *in vitro* and *in vivo* and showed enhanced homing to the bone marrow and the inflamed ear in a mouse model. Liao et al. used a similar transfection strategy, showing that the modified MSCs significantly increased rolling and adherence on inflamed brain microvascular endothelial cells and enhanced homing to inflamed spinal cord in a mouse model of encephalomyelitis, where they were better able to increase myelination and decrease inflammation (Liao et al., 2016). Ryser et al. transfected CXCR4 mRNA into MSCs, which increased migration in transwell migration experiments toward an SDF-1 gradient (Ryser et al., 2008). However, Wiehe et al. were unable to replicate such results; although they successfully overexpressed CXCR4 following mRNA nucleofection, the modified MSCs showed no improvement in cell migration (Wiehe et al., 2013). The authors use their results to emphasize the importance of other factors responsible for MSC activation, outside of the SDF-1/CXCR4 axis.

CELL SURFACE ENGINEERING

Enzymatic Modification

Given the potential safety concerns of genetic modification, many groups have attempted to directly chemically engineer the cell surface of MSCs. Unlike viral transduction, these modifications are temporary. However, as transmigration occurs just a few hours post-administration (Teo et al., 2012), even a transient modification should be sufficient to improve homing. MSCs naturally express the selectin ligand CD44, but not HCELL, the ligand for E- and L-selectin that hematopoietic stem cells use to home to the bone marrow. In a seminal study, Sackstein et al. were able to enzymatically convert CD44 into HCELL via sugar modifications (specifically, an α(1,3)-exofucosylation), allowing MSCs to utilize E- and L-selectin to tether and home to the bone marrow (Teo et al., 2012). In a mouse model of diabetes, this modification increased infiltration of MSCs to pancreatic islets by 3-fold following i.v. administration and durably reversed hyperglycemia (Abdi et al., 2015). These sugar modifications can also be exploited via genetic modification: expression of the α(1,3)-fucosyltransferase FUT6 or FUT7 in MSCs converts CD44 to HCELL, allowing for E-selectin binding (Lo et al., 2016; Dykstra et al., 2016; Chou et al., 2017).

Ligand Conjugation

Instead of modifying existing surface glycoproteins, cell surface engineering methods can be used to directly conjugate desired ligands. Sarkar et al. developed a platform that can theoretically attach any ligand to the MSC surface. They used biotinylated lipid vesicles to coat MSCs in biotin. They then attached a streptavidin adaptor, followed by biotinylated SLeX, the active site of the P-selectin ligand PSGL-1 (although any biotinylated ligand could theoretically be attached). The modification was able to improve adhesion to a P-selectin-coated surface (Sarkar et al., 2008).

Cheng et al. conjugated an E-selectin-binding peptide to MSCs via an NHS-PEG_2-maleimide linker molecule (Cheng et al., 2012). The preparation time was quick (30 min), and the modified MSCs adhered better than controls to an *in vitro* model of inflamed endothelium.

The attachment of antibodies to the MSC cell surface is another popular strategy. One such technique uses palmitated protein G: the palmityl group serves as an anchor to the cell membrane, whereas protein G serves as a dock for binding antibodies. Lo et al. used this method to attach a fragment of PSGL-1 bound to an IgG tail, which successfully facilitated tethering and rolling at high shear stresses (Lo et al., 2013). Ko et al. used the same system to attach anti-ICAM-1 antibodies, which facilitated cell arrest in a flow chamber (Ko et al., 2009). The same group also attached anti-VCAM-1 antibodies to MSCs, which they tested in a mouse model of inflammatory bowel disease. Compared with untreated MSCs, the anti-VCAM-1-coated MSCs showed improved homing to the inflamed lymph nodes (1.3-fold) and colon (1.8-fold), as well as dramatically improved survival rates and clinical endpoints (Ko et al., 2010).

Bispecific antibodies have also been investigated, with one end recognizing a native MSC marker and the other end recognizing a target. Lee et al. generated bispecific antibodies, one end of which attached to CD44 on the MSC surface and the other end of which recognized myosin light chain expressed by infarcted

myocardium. The armed MSCs were able to localize to the infarcted region of the heart (Lee et al., 2007). Gundlach et al. synthesized a bispecific antibody that recognized CD90 expressed by MSCs on one end and MLC expressed by ischemic myocardium on the other end (Gundlach et al., 2011). The construct improved MSC adhesion to immobilized MLC *in vitro*, although it still has not been tested *in vivo*. Both these studies seeked to enhance the migration of MSCs to the damaged tissue following extravasation by targeting injury markers at the final destination.

Unlike the previous studies that focused on the initial tethering, Won et al. sought to optimize the activation step. They conjugated recombinant CXCR4 to DMPE-PEG, a phospholipid that provides cell membrane anchoring. These modified MSCs were better able to migrate toward an SDF-1 gradient, in a CXCR4-dose-dependent manner (Won et al., 2014).

In nearly all these studies, cell viability, proliferation, adhesion, and differentiation were not affected. However, these cell surface engineering methods tend to be complex, requiring complicated reactions and optimization for each specific ligand or receptor.

IN VITRO PRIMING

Priming methods avoid genetic and chemical modifications entirely by simply altering culture conditions to affect gene expression. These methods have been used to improve the tethering, activation, and transmigration steps of systemic homing.

Culture Media Supplementation

At the tethering step, coating MSCs with hyaluronic acid leads to the upregulation of CD44, the selectin ligand. This treatment doubled *in vitro* invasion and increased targeting to an LPS-induced inflamed ear murine model, subsequently reducing inflammation (Corradetti et al., 2017).

The greatest amount of attention has been focused at the activation step by increasing CXCR4 expression. Several combinations of soluble factors have been found to increase its expression, including (1) a combination of FLT3LG, stem cell factor (SCF), IL-3, IL-6, and HGF (Shi et al., 2007); (2) IGF-1 (Li et al., 2007); (3) interferon (IFN)-γ (Duijvestein et al., 2011); (4) IL-1β (Fan et al., 2012b); (5) glycogen synthase kinase (GSK)-3β inhibitors (Kim et al., 2013); (6) the mood stabilizer drug valproic acid (Tsai et al., 2010, 2011); and (7) the iron chelator deferoxamine (Najafi and Sharifi, 2013). Hypoxic cell culture conditions induce hypoxia-inducible factor (HIF)-1α, which increases the expression of CXCR4 (Annabi et al., 2003) as well as CX3CR1 (Hung et al., 2007) and CXCR7 (Liu et al., 2010; Meng et al., 2018). Deferoxamine seems to stabilize HIF-1α even under normal oxygen levels (Chu et al., 2008), increasing the expression of various homing genes (Najafi and Sharifi, 2013). Exposure to complement 1q (C1q) enhances MSC migration toward SDF-1, partly by increasing surface expression of CXCR4 (Qiu et al., 2012). Other homing receptors can be upregulated by culture conditions as well. Treatment with TNF-α was found to increase MSC migration toward chemokines by upregulating expression of several chemokine receptors including CCR2, CCR3, and CCR4, but not CXCR4 (Ponte et al., 2009).

Several of these treatments also facilitate transmigration by increasing the expression of MMPs. GSK-3β inhibitors increase MMP2 and MT1-MMP expression (Kim et al., 2013). C1q treatment increases secretion of MMP2 (Qiu et al., 2012). Two mood stabilizer drugs, valproic acid and lithium, increase MMP2 and MMP9 activity, respectively (Tsai et al., 2010). The combination of erythropoietin and granulocyte colony-stimulating factor also increases MMP2 expression, improving MSC migration (Yu et al., 2011). The iron chelator deferoxamine increases expression of MMP2 and MMP9 through HIF-1α signaling (Najafi and Sharifi, 2013). Hypoxic conditions seem to have a mixed effect on MMP expression: MMP2 is downregulated, whereas MT1-MMP is upregulated, although the overall effect is still significantly increased transmigration (Annabi et al., 2003). Treatment with sphingosine-1-phosphate has been found to enhance MSC migration in *in vitro* transwell assays (Kang et al., 2015) and increase homing to infarcted myocardium, possibly by upregulating MMP9 (Chen et al., 2018a).

Culture Confluence

Interestingly, the cell culture confluence also seems to affect MSC migratory ability, although there are conflicting results in the literature. De Becker et al. found that MSCs cultured to high confluence secrete more

TIMP3, an inhibitor of MMPs, resulting in decreased migration compared with MSCs cultured at low confluence (De Becker et al., 2007). Kim et al. conducted thorough gene expression profiling of MSCs grown at low or high density. Low-confluence MSCs expressed more proliferation-related genes, whereas high-confluence MSCs expressed more genes linked to activation (CXCL1, CXCL2, CXCL5, CXCL6, CXCL8, CXCL16), immune modulation (IL-1B, IL-6), migration, and regeneration (VEGFA, FGF9, PDFGD, A2M, MDK, WISP2, GDF15) (Kim et al., 2014). Thus it is unclear whether low- or high-density MSC cultures are preferable for therapeutic applications.

Coculture

Coculture with other cell populations also influences MSC migration. Sertoli cells are found in the testes and are generally thought of as "nurse cells" to developing germ cells. Coculturing MSCs with Sertoli cells upregulates proliferation genes as well as homing genes in the former, including CXCR4 (Zhang et al., 2012) and MMP-2 (Luo et al., 2018). Coculture of amniotic MSCs with amniotic epithelial cells enhances proliferation and upregulates CXCR4 (Ran et al., 2018). Treating MSCs with conditioned media from endothelial cells increases their migration *in vitro*, possibly due to the presence of cytokines like IL-6 and IL-8 (Zhidkova et al., 2018).

MODIFICATION OF TARGET TISSUE

All previous methods have sought to modify the MSCs to potentiate their homing ability. Instead of modifying the MSCs, however, perhaps the target tissue can be modified to make them a more attractive destination.

Direct Injection of Homing Factors

The direct injection of SDF-1 into ischemic tissue has been demonstrated to enhance neovascularization in both skeletal muscle (Yamaguchi et al., 2003) and myocardium (Sasaki et al., 2007; Saxena et al., 2008). Although the study did not use MSCs, Yamaguchi et al. found that SDF-1 injection into ischemic hindlimb muscle improved the homing of i.v.-infused endothelial progenitor cells 1.8-fold in mice (Yamaguchi et al., 2003). Sasaki et al. directly injected SDF-1 into ischemic myocardium and observed increased endogenous homing of bone marrow cells, although these were not confirmed to be MSCs (Sasaki et al., 2007). One critical drawback to this technique is the short half-life of SDF-1 because of its quick degradation by proteolytic enzymes. To overcome this, Segers et al. bioengineered a protease-resistant version of SDF-1 that was still capable of binding CXCR4, improve cardiac function following myocardial infarction, and improve blood flow following peripheral artery disease (Segers et al., 2007, 2011). To our knowledge, no study has combined direct SDF-1 injection with MSC administration.

Genetic Modification of Target Tissue

Other groups have attempted to actually transfect the target tissue with constructs encoding for chemokines (Penn et al., 2012). Fujii et al. used a method known as ultrasound-mediated microbubble destruction (UMMD) to deliver an SDF-1- or SCF-containing plasmid into the myocardium. The plasmids are injected alongside microbubbles, which cavitate in response to ultrasound and create shear stress that facilitates uptake of the plasmid. This technique successfully increased SDF-1 expression in the myocardium and increased homing of endogenous CXCR4-expressing progenitor cells (Fujii et al., 2011). Sundararaman et al. achieved similar results without the use of UMMD, instead injecting the SDF-1 plasmid directly into the heart (Sundararaman et al., 2011). Treated mice showed improved angiogenesis and cardiac function. This therapy was taken into a phase I clinical trial, where 17 patients with ischemic cardiomyopathy were administered the SDF-1 plasmid directly do the infarcted region (Penn et al., 2013). After 12 months, the patients demonstrated improvements in walk distance and quality of life, in a dose-dependent manner. This initial human study did not include a control group. In the follow-up phase II placebo-controlled study, there was no significant difference between placebo and treatment groups based on the primary endpoints of 6-min walk distance or the Minnesota Living with Heart Failure Questionnaire score (Chung et al., 2015). However, by limiting the analysis to the sickest one-third of patients, there was significant improvement in ejection fraction, attenuation of left ventricle size, and stroke volume. As is the case with the genetic modification of MSCs, though, transfection of the target tissue comes with concerns regarding immunogenicity and insertional mutagenesis, as well as cost.

Scaffold Implantation

A final method of cytokine delivery comes in the form of scaffolds. Many of the scaffolds being studied release SDF-1 after they are implanted at the target site. Kimura and Tabata developed a gelatin hydrogel that slowly releases SDF-1. Subcutaneous implantation of the hydrogel was superior to injection of SDF-1, as measured by angiogenesis and CXCR4 expression at the implantation site (Kimura and Tabata, 2010). Similarly, He et al. synthesized a poly(lactide ethylene oxide fumarate) hydrogel loaded with SDF-1, which was able to increase bone marrow stromal cell migration *in vitro* in a dose-dependent manner (He et al., 2010). Goncalves et al. developed a chitosan/poly(γ-glutamic acid) complex incorporated with SDF-1, which increased MSC migration *in vitro* (Goncalves et al., 2012). Shen et al. engineered a bioactive knitted silk-collagen sponge scaffold that could be incorporated with SDF-1. In a rat Achilles tendon injury model, the scaffold successfully enhanced migration of endogenous progenitor cells and enhanced tendon regeneration (Shen et al., 2010). In a slightly more involved system, Schantz et al. developed a cellular polycaprolactone scaffold, from which SDF-1 could be constantly delivered using a microneedle apparatus (Schantz et al., 2007). Similarly, Thevenot et al. designed a poly(lactic-co-glycolic acid) scaffold that releases SDF-1 via a miniosmotic pump. After subcutaneous implant in mice, these scaffolds resulted in a 3-fold increase in homing (Thevenot et al., 2010). Although such scaffolds may serve as a "homing beacon" for MSCs, they may be difficult to optimize, and come with safety and cost concerns.

Radiotherapeutic Techniques

When target tissues are irradiated, they show a higher rate of MSC engraftment (Chapel et al., 2003; Mouiseddine et al., 2007). This increase is due to upregulated expression of SDF-1, thus promoting the activation step of homing (Ponomaryov et al., 2000). Of course, radiation therapy comes with inherent safety concerns in human patients, and so although these results are conceptually interesting, it may not be an option that can be implemented clinically. This is especially true with safer alternative techniques that achieve similar improvements in MSC homing—namely, the use of sound waves.

Ultrasound Techniques

In addition to its diagnostic applications, ultrasound has been adopted for a variety of therapeutic applications (Miller et al., 2012). Unlike diagnostic ultrasound, therapeutic ultrasound is selectively focused on the tissue of interest. Sophisticated image guidance technology allows for the targeting of deep structures without affecting intervening tissue. At the target site, the mechanical pressure exerted by sound waves induces various biological effects that aid in regeneration.

Many studies have investigated UMMD for improving MSC homing. In this technique, microbubbles are administered systemically alongside the MSCs. Ultrasound is focused on the target tissue, which cavitates the microbubbles, causing shock waves and shear stress that exert various biological effects. These effects include changes in gene expression, and the disruption of endothelial linings, which increases vascular permeability. Several studies have utilized UMMD in combination with MSCs to increase cardiac recovery following myocardial infarction (Zen et al., 2006; Ghanem et al., 2009; Xu et al., 2010). This effect likely arises from both the increased vascular permeability, as well as changes in gene expression. Li et al. found that UMMD both elevates secretion of SDF-1 on the target tissue and increases the proportion of MSCs that express CXCR4 (Li et al., 2015). In the kidney, UMMD has been shown to promote MSC homing by the upregulation of cytokines, integrins, selectins, and other trophic factors (Wang et al., 2015). UMMD to the brain has been shown to induce a sterile inflammatory response that upregulates a variety of inflammatory and trophic factors, including MMPs (Kovacs et al., 2017), although MSC homing has not yet been assessed in this system. However, as microbubble cavitation is known to be damaging to the host tissue (Burgess et al., 2011; Chonpathompikunlert et al., 2012; Fan et al., 2012a), some investigators have begun looking into focused ultrasound without microbubbles.

Pulsed focused ultrasound (pFUS), as its name implies, administers focused pulses of high-intensity sound waves. The non-continuous administration of the waves prevents extreme temperatures and tissue damage (Burks et al., 2013). Instead, pFUS exerts its effects solely by mechanical pressure, activating mechanotransduction pathways that upregulate inflammatory and chemoattractive molecules (Ziadloo et al., 2012). There has been a quickly growing body of literature studying the molecular changes induced by pFUS. In the muscle, Burks et al. demonstrated that pFUS creates a transient local chemical gradient. Upregulated molecules include cytokines, growth factors, and cell adhesion molecules, like ICAM-1 and

VCAM-1 (Burks et al., 2011). This chemical gradient enhances homing of MSCs to the muscle and induces an anti-inflammatory M2 macrophage response (Burks et al., 2013). To establish this local gradient, pFUS seems to induce an initial activation of TNF-α, which drives cyclooxygenase-2 (COX2) signaling that upregulates various cytokines and homing factors (Tebebi et al., 2015). In a mouse model of limb ischemia, pFUS + MSCs increased MSC homing 4-fold compared with MSCs alone, resulting in improved clinical outcomes (Tebebi et al., 2017). Parallel results have been achieved in the kidney, where pFUS created a similar chemical gradient without any physiological damage to the host tissue, and dramatically increased MSC homing (Ziadloo et al., 2012). Similar to muscle, pFUS causes initial activation of TNFα and IL-1α in the kidney, which drive signaling through the nuclear factor-κB and COX2 pathways (Burks et al., 2017). In a mouse model of cisplatin-induced AKI, pFUS + MSCs significantly enhanced kidney homing and clinical outcomes compared with MSCs alone (Burks et al., 2015). In the AKI model, pFUS was found to upregulate IFN-γ in the kidney, which signals MSCs to produce the anti-inflammatory IL-10 (Burks et al., 2018). Jang et al. used pFUS on the heart and observed a similar initial increase in TNF-α followed by the upregulation of cytokines and growth factors, although MSC homing was not assessed (Jang et al., 2017). Although further studies are needed on its long-term effects, ultrasound appears to be a promising avenue for enhancing MSC homing.

Conclusions

The effort to improve MSC homing has taken on a wide breadth of strategies. Some of these strategies focus on non-systemic homing, such as the targeted administration and magnetic guidance. Most of the other techniques discussed here focus on systemic homing, a multistep process governed by specific molecular interactions. Unlike our relatively comprehensive knowledge on the homing of blood cells (Muller, 2011), MSC homing mechanisms remain poorly understood at several steps, such as tethering or rolling and transmigration. It is also unclear which of these steps is the major bottleneck for MSC attrition and would thus be the most fruitful for further investigation. Understanding the underlying biology has provided a wealth of optimization strategies at each step of the homing process. Each approach comes with its own drawbacks. Targeted administration may not always be feasible or may be highly invasive, depending on the target tissue. Most modifications to the MSCs do not prevent them from distributing to non-targeted organs. On the other hand, modifying the target tissue via chemical or genetic means raises safety concerns. These limitations present formidable barriers to applying them in the clinic. Although still an active area of study, the use of ultrasound to enhance MSC homing seems a promising avenue, with easy targeting of both deep and superficial organs and, to our current knowledge, a lack of significant safety concerns.

Although homing is perhaps the major impediment to realizing MSC-based therapies, other hurdles lie in the way as well. MSCs used in clinical settings are derived from healthy donors, and although these cells may be homogeneous in their expression of defining surface markers, they are not necessarily homogeneous in their function. Notably, the activity of IFN-γ-induced Indoleamine 2,3-dioxygenase (IDO) has been shown to be critical for MSC-facilitated immunosuppression, but donor variation gives rise to substantial differences in IDO responsiveness (Francois et al., 2012b). Furthermore, large-scale *in vitro* expansion of MSCs, which is necessary for clinical applications, results in senescence that impairs their therapeutic effect (Capasso et al., 2015). Contrary to conventional wisdom, which states that MSCs are immune privileged, studies have shown that MSCs may in fact undergo immune rejection due to HLA mismatches (Nauta et al., 2006; Eliopoulos et al., 2005). Finally, clinical trials almost universally use freshly thawed MSC stocks; however, cryopreservation appears to impair the immunosuppressive properties of MSCs and shorten their persistence *in vivo* (Francois et al., 2012a; Chinnadurai et al., 2016). These difficulties may well be the cause of conflicting results in both basic science and clinical settings (Galipeau, 2013). Moving forward, it will be critical to be cognizant of these sources of variation. Although much work still needs to be done, tackling the basic biological mechanisms underlying MSC biology will reveal new paths for optimization. Such investigations will continue to push forward the field of cell-based therapies, broadly boosting the effectiveness of therapeutics in applications ranging from immune modulation to regeneration.

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