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Homing of Mesenchymal Stem Cells



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An Update to: Concise Review: Mesenchymal Stem Cells: Their Phenotype, Differentiation Capacity, Immunological Features, and Potential for Homing
Giselle Chamberlain, James Fox, Brian Ashton, and Jim Middleton
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Mesenchymal stem cells (MSCs) show therapeutic potential in preclinical inflammatory disease models and in some clinical trials in patients with Crohn's disease, diabetes, stroke, cartilage and bone injury, graft-versus-host disease (GVHD), and myocardial infarction [1]. The definition of MSC phenotype has evolved and the International Society for Cellular Therapy recommends a number of assays to standardize MSCs for clinical trials based on their immunomodulatory properties [2].

One problem facing MSC usage for diseased tissue regeneration is the low level of recruitment and retention of cells in affected tissues; typically, less than 1% of systemically injected MSCs reach their target. Deficient MSC homing is usually attributed to an absence of relevant cell-surface homing molecules classically expressed by hematopoietic stem cells and leukocytes [3] and potentially due to MSC heterogeneity [4]. Several recent in vitro studies investigated mechanisms of MSC transendothelial migration and the effects of chemokines and shear stress [5, 6–7]. MSC adhesion and transmigration increased upon activation of endothelium with TNF-α, and chemokines CXCL9, CXCL16, CCL20, and CCL25 enhanced MSC firm adhesion, crawling, and spreading. Shear-resistant arrest of MSCs on endothelial cell surfaces occurred when cells were left under shear-free conditions for several minutes before flow was reinstated; no interactions were observed under conditions of constant shear flow [5]. The results of this study are in line with previously proposed passive and active homing for MSCs

[3]. MSCs may become passively arrested in narrow capillaries leading to chemokine presentation, integrin activation, adhesion, crawling, and spreading before chemoattraction along a chemokine gradient into extravascular tissue. Early MSC transmigration was associated with nonapoptotic membrane blebbing that was previously described for metastatic tumor and embryonic germ cells, whilst some MSCs migrated through discrete endothelial pores and gaps by transcellular and paracellular processes [6]. Aldridge et al. demonstrated that human MSCs were recruited to injured liver in a β1-integrin- and CD44-dependent manner [7].

MSC homing could potentially be improved by several methods; for example, modification of MSC surface with sialyl LewisX (sLeX) [8], a key mediator of leukocyte rolling, or CXCR4 [9] have both been shown to enhance MSC homing to inflamed tissue. Hypoxic preconditioning of MSCs also increases their recruitment in a mouse focal cerebral ischemia model by upregulating CXCR4, MMP-2, and MMP-9 expression [10].

The recent paradigm shift in MSC utilization for therapy based on their immunomodulatory and anti-inflammatory properties arises from observations that MSC therapy lessened inflammation, fibrosis, and apoptosis in disease models without engraftment in the diseased tissue and differentiation [11]. MSCs may function in immunomodulation predominantly using paracrine mechanisms via growth factor, cytokine, and chemokine secretion and through production of extracellular vesicles (EVs) that contain various proteins, lipids, and nucleic acids, as found in MSC-conditioned medium [12]. The primary advantages of EVs over MSCs are in mitigating safety issues related to living or engineered stem cell therapies.

Advances in our understanding of MSC homing have been made and will likely continue to contribute to improve their clinical efficacy; there is also an appreciation that MSC paracrine effects and EVs might hold promise, but several questions remain.

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