



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 (e.g., 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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