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ScienceDirect
Journal of Molecular and Cellular Cardiology 45 (2008) 514–522
Journal of Molecular and Cellular Cardiology
www.elsevier.com/locate/yjmcc

Review article

Homing and engraftment of progenitor cells: A prerequisite for cell therapy

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Received 12 October 2007; received in revised form 17 December 2007; accepted 1 January 2008
Available online 18 January 2008

Abstract

Cell therapy is a promising therapeutic option for treating patients with ischemic diseases. The efficiency of cell therapy to augment recovery after ischemia depends on the sufficient recruitment of applied cells to the target tissue. Using *in vivo* imaging techniques the extent of homing was shown to be rather low in most experimental and clinical studies. The elucidation of the molecular mechanisms of homing of different progenitor cell subpopulation to sites of injury is essential for the development of new specific therapeutic strategies, in order to improve the efficacy of cell-based therapies. Homing to sites of active neovascularization is a complex process depending on a timely and spatially orchestrated interplay between chemokines (e.g. SDF-1), chemokine receptors, intracellular signaling, adhesion molecules (selectins and integrins) and proteases. The review will focus on the mechanisms underlying homing of adult bone marrow-derived hematopoietic cells, mesenchymal stem cells, and vasculogenic circulating cells and discuss strategies how to optimize cell engraftment.

Keywords: Progenitor cells; Cell therapy; Homing; Chemokines; Integrins; Proteases; Neovascularization

Contents

Cell therapy is a promising option to improve neovascularization and to enhance recovery of left ventricular function after acute myocardial infarction. Various different types of stem or progenitor cells have been successfully used in experimental models including various subsets of adult bone marrow-derived cells, tissue-resident stem cells (cardiac stem cells) and embryonic stem cells (for review see [1]). Some of these experimental studies have been moved to the clinic where bone marrow-derived cells and endothelial progenitor cells (EPC) have been tested in patients with acute and chronic ischemic disease. So far, most studies used bone marrow mononuclear cells (BMC) preparation for the treatment of acute myocardial infarction overall demonstrating that intracoronary infusion of BMC is safe and feasible and improves ejection fraction [2]. The results of the

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doi:10.1016/j.yjmcc.2008.01.004

REPAIR-AMI trial, the largest phase II/III trial, even suggested that BMC might improve event free survival [3]. However, when studies investigated the homing and the long term engraftment of cells, only a low percentage of cells were detectable in animal models as well as in clinical trials. Therefore, the understanding of homing mechanisms might be crucial for enhancing cell engraftment particularly when cells are infused via the vascular route. This review will focus on the mechanisms underlying homing of adult bone marrow-derived and vasculogenic cells (including pro-angiogenic cells and EPC).

1. Extent of cell homing in experimental and clinical studies

In order to determine progenitor cell trafficking and *in vivo* distribution, life imaging is essential. Several non-invasive imaging modalities can be used to assess the biodistribution of the applied cells over time to track homing of the cells to the target tissue but also to visualize the up-take to other organs and tissues where cells potentially may exhibit unwanted side-effects. Non-invasive imaging has been performed by direct labeling of cells with radionucleotides for single-photon emission computed tomography (SPECT) imaging, by using positron emission tomography (PET) tracers such as F18-FDG or by labeling of cells with iron particles for magnetic resonance imaging (MRI) (for review see [4,5]). After intravenous infusion of radioactively labeled circulating blood-derived *ex vivo* cultured endothelial progenitor cells in rats after myocardial infarction, some radioactivity was detected in the heart [6]. However, the amount of radioactivity detected in the ischemic heart was about 2% after 24 to 96h of infusion indicating that only a minor percentage of cells homed to the heart [6]. Similar findings were reported after infusion of uncultured Indium-labeled peripheral blood mononuclear cells [7] or purified $CD34^+$ cells [8]. The majority of the radioactivity after intravenously infusion of labeled bone marrow- or peripheral blood-derived cells was detected in the spleen and the liver [6,7]. Although infusion of the cells in the left ventricular cavity or direct intramuscular application increased the extent of homing, a maximal value of around 10% was achieved [6,7]. The extent of homing was similar in clinical studies where several groups labeled BMC, $CD34^+$ or $CD133^+$ cells and infused the cells in the coronary artery of patients with acute or chronic myocardial infarction [9–11]. In the first hours after infusion 2.6 to 11% of radioactivity was detected in the heart thereafter declining to 1 to 7%. Hofmann et al infused labeled BMC or $CD34^+$ cell with the PET-tracer F18-FDG in three patients with acute myocardial infarction [12]. Purified $CD34^+$ cells were shown to more efficiently home to the heart (14–39%) [12].

Additional studies addressed the engraftment of mesenchymal stem cells (MSC). In contrast to hematopoietic or endothelial progenitor cell populations, the size of MSC is higher and these cells (at least the ones being *ex vivo* expanded) are not well adapted to circulate in the blood, and, therefore, MSC have initially been injected intramuscularly in the experimental studies [13,14]. Injected MSC have been detected up to 21days by MRT after labeling with iron particles in large animal models [13,14]. However, the body distribution after intravenous injection of allogeneic MSC surprisingly documented a redistribution of the infused cells from initial lung homing to non target organs (liver, kidney, spleen) but also to the infarcted heart [15]. The targeted cardiac localization, however, was only detectable by SPECT/CT but not by MRI indicating that the concentration of incorporated cells in the heart is below the detection level of MRI [15].

In summary, the up-take of cells appears rather low independent on the used cell type or the route of delivery. Although one study by Hoffmann reports a significantly higher incorporation when using $CD34^+$ cells, different studies with $CD133^+$ cells did not confirm such a high up-take of purified hematopoietic stem cells. Since an overlapping set of cells (approximately 30%) express CD34 and CD133 further studies have to address putative differences between homing of purified cell populations. Clearly, the clinical trials assessing the biodistribution of the cells by non-invasive imaging cannot give insights into the morphological integration and the cell fate after prolonged time and may be confounded by either false positive (e.g. labeled cells are dying and are taken up by macrophages) or false negative effects (e.g. labeling is released by the cells or is diluted by proliferation). To get more detailed insights in the cell fate, immunohistochemistry would be required, which is unfortunately not useful in patients treated with autologous cells.

2. Mechanism of homing

Homing and engraftment is a prerequisite for all cell types to exhibit any type of activity in the target tissue particularly when cells are infused via the vascular route. While the homing of leukocytes to sites of inflammation is well studied [16–18], the mechanisms of progenitor cell homing to sites of ischemia or injury are poorly understood. During inflammation, the recruitment of inflammatory cells requires a coordinated sequence of multistep adhesive and signaling events including selectin-mediated rolling, leukocyte activation by chemokines leading to activation of integrins, integrin-mediated firm adhesion on endothelial cell monolayers, diapedesis through the endothelial cell monolayers and finally the migration/invasion in the extracellular matrix involving integrin-dependent processes and matrix degrading proteases [16–18].

Homing mechanisms of endothelial progenitor cells to sites of tumor neovascularization and to sites of ischemia appears to share at least some common features with the homing of leukocytes to sites of inflammation (Fig. 1). Embryonic EPC arrested within tumor microvessels, extravasated into the interstitium and incorporated into neovessels suggesting that adhesion and transendothelial migration are involved in the recruitment of endothelial progenitor cells to sites of tumor angiogenesis [19]. Furthermore, recent studies support the idea that EPC and progenitor cells utilize adhesion molecules for homing to sites of neovascularization similar to the adhesion molecules engaged by leukocytes for recruitment to sites of inflammation. In the following chapters we will focus on the role of chemokines, adhesion molecules and proteases for the homing of bone marrow-derived progenitor cells to ischemic tissues.