Understanding the molecular and cellular basis of therapeutic stem and progenitor cell transplantation for tissue revascularization

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See also article by Li et al. [6] (pages 64–72) in this issue.

The primary goal of therapy for patients with acute myocardial infarction is rapid revascularization of ischemic tissue. Since thrombolytic therapy or catheter-based intervention can only accomplish so much initially, new strategies are desirable to salvage already injured tissue and restore organ function. A decade ago, several researchers developed and refined the concept of therapeutic angiogenesis by gene therapy, either through the application of cDNA-encoding plasmids or by local injection of the desired protein [1]. Shortcomings of this approach included the lack of precise targeting, fading activity over time, or even clinical complications such as enhancement of rhythm disorders by injuring the electrical conduction system, i.e., when using intramyocardial transfer of DNA plasmids.

Over the past years, it has become clear that bone marrow contains vascular progenitor cells that can mobilize to ischemic sites and facilitate neoangiogenesis from preexisting endothelium. Adult bone marrow is a reservoir of tissue-specific stem and progenitor cells. Angiocompetent hematopoietic cells (hemangioblasts) consist of endothelial progenitor cells (EPCs) and hematopoietic stem cells (HSCs) that develop into hematopoietic progenitor cells (HPCs) [2]. Hence, the application of autologous bone marrow cells as a new approach for tissue revascularization appears to be an intriguing alternative to gene therapy. A variety of clinical and animal pilot studies have demonstrated the efficacy and feasibility of such an approach (see review in Ref. [3]), pending results from ongoing randomized and blinded trials. Although tremendous progress has been made in this emerging research area, there is still uncertainty about the cellular and molecular mechanisms leading to either spontaneous or therapeutic organ revascularization. Chemokines/cytokines such as vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and stromal cell-derived factor-1 (SDF-1) are essential in regulating the mobilization of bone marrow-derived cells, including hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs) into peripheral blood.

An important issue in cell-based therapy is the choice of cells. While angiocompetent hematopoietic cells are particularly useful, only 2% of mononuclear stem cells from the bone marrow is capable of inducing angiogenesis. Therefore, one goal could be to eliminate unnecessary cell populations in order to avoid potential side effects. Very little data exist on the potential properties of cellular subtypes. Endothelial progenitors can be phenotyped by the expression of PECAM-1 (CD31), Flt-1 (VEGF-receptor 1), CD133, CD34, and c-Kit (CD117). Most of these markers are coexpressed on hematopoietic cells, while surface expression of CD133 has been lost in myelomonocytic cells. However, due to the limited number of EPCs in the circulating blood (0.05% of leukocytes), ex vivo expansion of EPCs appears to be necessary. Proliferation of primary human cells is limited by the capacity to divide and the onset of senescence [4].

Adhesion molecules and SDF-1/CXCR4 signaling play a key role in homing and mobilization of hematopoietic progenitor cells [5]. Integrins are essential in this process to
mediate the adhesion of hematopoietic stem cells, progenitor cells, and leukocytes to endothelial cells located in ischemic tissue. While $\beta_2$-integrins are found mainly on hematopoietic cells, $\beta_1$-integrins are expressed by various cell types, including endothelial cells and hematopoietic cells.

In this issue of *Cardiovascular Research*, Li et al. provide new insights into the molecular mechanism of therapeutic angiogenesis by cell implantation [6]. For their purpose, the authors use a mouse ischemic hind limb model and demonstrate that loss of integrin $\beta_1$-expression during ex vivo culture of CD117$^+$-stem cells (stem cells expressing the marker c-Kit) correlates well with diminished angiogenic potency of these cells. Antibody perturbation of $\beta_1$-integrin significantly inhibited neoangiogenesis in this model. While the intriguing results from this study point towards a crucial role of specific integrins in the induction of therapeutic angiogenesis through cell-based therapy, caution is necessary. One may wish to have additional data from a $\beta_1$-integrin knockout model to confirm the results. Unfortunately, deletion of $\beta_1$-integrins in mice results in inner cell mass failure and peri-implantation lethality, requiring the usage of a conditional knockout model [7].

Integrins are heterodimeric, cell-surface receptors (see review in Ref. [8]). Their function depends mainly on their expression on the cell surface, although protein expression itself is not necessarily a measure of their activity. In addition, different integrins may have different functions in various cell types. A recently published article by T. Kong et al. demonstrated that hypoxia can induce leukocyte $\beta_2$-integrin expression and function by transcriptional mechanisms dependent upon the hypoxia-inducible factor 1 (HIF-1) [9]. Our group has just found in a murine model of hind limb ischemia that Sca-1$^+$/Lin$^-$ hematopoietic progenitor cells from $\beta_2$-integrin-deficient mice are less capable of homing to sites of ischemia and of improving neovascularization [10]. Preactivation of the $\beta_2$-integrins expressed on EPCs by activating antibodies augmented the EPC-induced neovascularization in vivo. These results provide evidence for a novel function of $\beta_2$-integrins in postnatal vasculogenesis. In conclusion, it is important to keep in mind that the functional relevance of each integrin can vary with different cell types as well as the specific injury model.

Therefore, future success of therapeutic stem and progenitor cell transplantation for tissue regeneration will largely depend on the exploration and definition of the mechanisms by which these cells direct their incorporation into adult tissues.

References