PI3Kγ Helps an SDF Seeking Home . . . for EPCs

Ziad Mallat

It is increasingly recognized that the quality of tissue repair following an ischemic insult is highly influenced by the phenotype and plasticity of newly recruited blood-borne cells. The latter are capable of switching the tissue response to injury toward either a pathological remodeling, leading progressively to organ failure or to a repair process that preserves and restores tissue function. Thus, identification of the critical pathophysiological pathways that govern mobilization, recruitment, and function of these blood-borne elements is of utmost importance to our understanding of the tissue repair process. Since the first isolation of blood-borne endothelial progenitor cells (EPCs), an important body of evidence has been presented indicating that EPCs form a functionally important population endowed with neovascularization promoting capacity. Whatever the mechanisms operated by EPCs to enhance neovascularization, through paracrine effects and/or direct incorporation into vascular beds, their preferential recruitment and homing into the ischemic sites appears to be critical for this function.

Recruitment of EPCs into injured tissues involves an interplay among chemokines/chemokine receptors, integrins, and adhesion molecules, leading to a multistep cascade of events from rolling and adhesion to transendothelial migration and incorporation into sites of neovascularization. The chemokine stromal cell–derived factor (SDF)-1α, also called CXCL12, is a powerful chemoattractant for human and murine primitive hematopoietic cells. SDF-1α signals through its single high-affinity 7-transmembrane pertussis toxin-sensitive G protein–coupled receptor, CXCR4. The signal transduction pathways initiated by the binding to CXCR4 are critical to the ability of bone marrow–derived progenitors and EPCs to migrate along an SDF-1α gradient, adhere to the activated endothelium, and transmigrate into the ischemic tissue. One of the first signaling pathways initiated by SDF-1/CXCR4 leads to activation of the GTPase RAP1 by the cAMP-dependent GTP exchange factor EPAC (Figure). Binding of RAP1 to RAPL contributes in many cellular signaling pathways, including RAP1-, RhoA-, and Dock-dependent pathways (Figure). In an article published in this issue of Circulation Research, Chavakis et al have now further clarified the role of PI3K in the migratory and homing potential of progenitor cells in response to chemokine stimulation. PI3K is present in multiple isoforms. Chavakis et al performed a series of experiments in which both chemical and genetic inhibition of a specific PI3K isoform, the class IB PI3Kγ, were used to assess its role in integrin-dependent adhesion, migration, and diapedesis of human (peripheral blood mononuclear cell–derived EPCs) and murine (bone marrow Lin−) progenitor cells, in vitro and in vivo. Pharmacological inhibition or genetic deletion of PI3Kγ significantly impaired integrin activation and SDF-1–induced migration and adhesion of human EPCs and murine Lin− bone marrow-derived cells to intercellular adhesion molecule-1 and human umbilical vein endothelial cell monolayers. In addition, in a model of hindlimb ischemia, systemic transfer of murine Lin− bone marrow–derived cells from PI3Kγ-deficient mice resulted in reduced accumulation of the progenitor cells into ischemic sites, associated with a marked reduction in tissue neovascularization. The results extend recent data showing that migration of human peripheral blood–derived EPCs in response to SDF-1α could be completely blocked by PI3K inhibitors and endothelial NO synthase inhibitor but was insensitive to inhibition of extracellular signal-regulated kinase 1/2. As acknowledged by Chavakis et al, the inhibition of migration and homing to ischemic tissues was not complete in the absence of PI3Kγ, suggesting alternative parallel and complementary signaling pathways, including RAP1-, RhoA-, and Dock-dependent pathways (Figure). In addition, the authors have not completely eliminated a potential role for PI3Kγ in the proliferation and/or survival of the circulating progenitor cells in vivo, which could have accounted, at least in part, for differences in progenitor cell accumulation within the ischemic tissues. Nevertheless, the results of Chavakis et al clearly indicate that PI3Kγ is required for optimal integrin-dependent homing of progenitor cells to sites of ischemia (Figure) and for promotion of postischemic neovascularization. Downstream of PI3K, a recent study has shown that transient activation of Akt is critical for efficient migration and adhesion of primary CD34+ cord blood cells in response to SDF-1α, highlighting the important role of the

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See related article, pages 942–949
regulation of both the level and duration of intracellular signals at the leading edge of a migrating cell.

A classic way to end an editorial such as this one is to state that a better understanding of the mechanisms involved in progenitor cell homing into ischemic tissues may lead to the development of innovative therapeutic strategies to improve postischemic neovascularization. I am afraid, we are still a long way from that valuable aim, at least if the aim is selective modulation of the homing of specific cell types, here, EPCs. For example, it is amazing to see how similar the mechanisms involved in the recruitment and homing of EPCs and leukocytes are, not the least monocytes. Promotion of presently known molecular mechanisms involved in EPCs homing to ischemic tissues would inevitably lead to promotion of leukocyte recruitment into atherosclerotic arteries,\textsuperscript{19} which, if operated on a long-term basis, as it would be required in a setting of chronic ischemia, could lead to undesirable progression of atherosclerosis. Maybe more specific and selective pathways that could ultimately lead to differential recruitment of EPCs and monocytes are to be found in a better understanding of the mechanisms responsible for medullar production of these different cell types, their mobilization from the bone marrow, and their survival in the circulating blood. Finally, as experienced by many in this field, EPCs themselves are not created equal and molecular requirements for their recruitment may vary according to the type and maturation stage of the EPC, which emphasizes the growing need for a better characterization of the different subtypes of progenitor cells at the functional, cellular, and molecular levels.

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PI3Kγ Helps an SDF Seeking Home . . . for EPCs: Correction

In the editorial that appears on page 871 of the April 25, 2008, issue, second paragraph of the Introduction, line 15, the sentence should read as follows:

One of the first signaling pathways initiated by SDF-1/CXCR4 leads to activation of the GTPase RAP1 (Figure).

In addition, “cAMP” and “EPAC” should not have appeared in the figure. The arrow should point directly to “Rap1/RapL.” The figure should appear as follows:

![Figure](image)

The authors regret this error. This error has been noted in the online version of the article, which is available at http://circres.ahajournals.org/cgi/content/full/102/8/871

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