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EDITORIAL

Endothelial Progenitor Cells and Percutaneous Coronary Artery Intervention

Editorial to: "Effect of High Dose Statin Pretreatment on Endothelial Progenitor Cells after Percutaneous Coronary Intervention (HIPOCRATES Study)" by A. Eisen et al.

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In the HIPOCRATES study Eisen et al. give us important insighths into the effects of statins on endothelial progenitor cells (EPC) levels after percutaneous coronary intervention (PCI) [1]. Pretreatment with high-dose statins given before PCI induces an increase in EPC. In the last decade the understanding of EPC has grown, supporting the important role of these cells for vascular health and adding impetus to the search for ways to upregulate their circulating levels. Although it is clear that the contribution to vascular healing of these circulating progenitors is almost certainly due to their paracrine effects, it is also evident that their function is dependent on both the local microenvironment and a synergy between other populations mobilized in response to the vascular insult.

In the mid 1990s Risau et al. [2] described the origins of endothelial cells within the embryonic vasculogenesis, finding that the endothelial cells derive from a putative common mesenchymal precursor for endothelium and hematopoietic cells named the hemangioblast. In 1997 Asahara and colleagues published a landmark paper [3] showing that bone marrow-derived CD34+ VEGFR-2+ monocytic cells could be isolated from human blood and grown in culture under conditions that yielded cells with endothelial characteristics indicating the contribution of bone marrow-derived putative EPC to adult neoangiogenesis. Two major cell types may be obtained from peripheral blood mononuclear cells: 1) the early-outgrowth EPC, obtained by culturing isolated mononuclear cells for 4–7 days, and 2) the late-outgrowth EPC, that start proliferating only after 2–3 weeks in culture [4]. The early-outgrowth EPC origin from haematopoietic lineage, have a limited proliferative capacity and, differently from mature endothelial cells, present similar features to monocytes since they express the monocytic marker CD14 and the panleucocytic marker CD45 [5]. The early-outgrowth EPCs may have a role as biomarkers. The late out-growth EPC (also called endothelial colony-forming cells [ECFC]) express the endothelial (KDR, CD146 and VE-cadherin), but not the haematopoietic (CD45 and CD14) markers. The late-outgrowth EPC proliferate can form a vascular network, and are probably more related to replacement of defective endothelial cells and vasculogenesis. Circulating late-outgrowth EPC represent <1 % of circulating EPC and are a smaller part of the CD34-positive bone marrow cells used in clinical trials [6]. The level of circulating EPC is low in normal conditions but it rapidly increases in response to physiological and pathological stimuli, including myocardial and peripheral ischemia [7]. The EPC move from the bone marrow and travel to the sites of new vessel growth in the ischemic tissue (injury site): this process called "homing" [8] includes a coordinated sequence of multi-step adhesive and signaling events, including chemoattraction, adhesion, and migration. Some studies report that the EPC number is

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reduced in patients with atherosclerotic disease [9] and that a reduced number of EPCs is associated with the occurrence of ischemic cardiovascular events in patients with angiographically documented CAD [10, 11].

The endothelial damage caused by balloon inflation and/or stent implantation give rise to an intensive local inflammatory response, resulting in neointimal hyperplasia, in-stent restenosis and potentially acute stent thrombosis. Recruitment of EPC to the site of vascular injury has been proposed to promote vascular healing and has been shown to inhibit neointimal proliferation and restenosis associated with PCI [12]. On the contrary, however, Schober et al [13] demonstrated a relationship between the increase in $CD34^+$ cells and the risk of restenosis. Therapies focused on EPC and/or the homing process to the site of stent implantation are attractive and have the potential to improve clinical outcomes after PCI. The mechanisms responsible for the mobilization of EPC have been reviewed extensively elsewhere [14]. Among their pleiotropic effects statins are able to mobilize $CD34^+$ and KDR^+ cells into the peripheral circulation in a dose-dependent manner. Statins also increase the formation of ECFC [15, 16] and can induce in vitro differentiation of $CD14^+$ and $CD34^+$ cells toward an endothelial phenotype [17]. Walter et al. [18] demonstrated an accelerated rate of re-endothelialization and a reduction in neointimal hyperplasia in rats treated with simvastatin after balloon mediated arterial injury.

Further studies are required to elucidate how to use EPC as an effective treatment modality, evaluating not only the target cell type of interest, but also the involvement of the microenvironment on cellular behavior, the best mode of delivery of cells and defined paracrine factors to the site of injury and the need for adjunctive therapy to optimize EPC function. All strategies effective in increasing the EPC level should be tested in order to assess whether they are useful in reducing disease progression and therefore events at follow-up.

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