Leptin and EPCs in Arterial Injury

Yes, We Can!

Andreas Schober, Christian Weber

Endothelial progenitor cells (EPCs) were introduced to a broad scientific readership in 1997 by Asahara et al, who demonstrated that CD34+ cells from the peripheral blood can adopt an endothelial cell-like phenotype in vitro. This culture-modified cell type (subsequently also termed endothelial outgrowth cells) improved ischemic neovascularization after intravenous transfusion. The prospect of ameliorating tissue ischemia by ex vivo–expanded autologous angioblasts resulted in extensive research activities, including the therapeutic application in patients with myocardial ischemia. However, the results are still conflicting, which is at least partially attributable to the fact that EPCs comprise a heterogeneous pool of subpopulations originating from distinct sources and displaying diverse phenotypes. For instance, the common characterization of EPCs as CD34+CD133+VEGF-R2+ by flow cytometry has been recently questioned in different studies showing that only CD133+CD45− cells differentiate into endothelial cells. Early outgrowth of endothelial-like cells from mononuclear cells cultured for 5 to 7 days in the presence of endothelial growth factors represent a monocyte-like subtype with low proliferative capacity secreting high amounts of angiogenic growth factors. Conversely, late outgrowth EPCs obtained after 14 to 21 days are highly proliferative and present vessel-forming capacity.

Apart from neovascularization of ischemic tissue, EPCs have been involved in endothelial repair in atherosclerosis and neointima formation after endothelial denudation. Although the first evidence for a recruitment of circulating stem cells to sites of plaque progression and thus for a possible contribution to endothelial regeneration in atherosclerosis has been recently provided, treatment of mice with EPCs was associated with accelerated atherosclerosis. In contrast, following balloon- or wire-induced endothelial denudation, EPCs were successfully administered to enhance endothelial recovery through direct incorporation into the endothelial lining. This improved reendothelialization by EPCs is associated with reduced neointima formation and may be a valuable tool to reduce the rate of stent thrombosis after percutaneous coronary interventions. On the other hand, the increased rate of in-stent restenosis in patients with diabetes is associated with functionally impaired EPCs with reduced reendothelialization capability.

In a model of wire injury of the carotid artery, the endothelial recovery by EPCs was delayed in leptin receptor–deficient (db/db) mice with a diabetic phenotype expressing Tie2/LacZ in bone marrow cells. However, this inhibitory effect on reendothelialization was not accompanied by reduced neointima formation, because neointimal hyperplasia was almost completely prevented after wire-induced injury in db/db mice despite hyperinsulinemia and hyperglycemia, suggesting a leptin/leptin receptor–specific effect. Leptin receptor expression on bone marrow cells did not affect neointimal growth excluding the contribution of bone marrow–derived progenitor cells. Accordingly, accelerated neointima formation in hyperlipidemic mice was limited in leptin-deficient (ob/ob) mice after ferric chloride–induced vascular injury, which, in contrast to wire-injury, caused thrombotic occlusion with subsequent recanalization and “organization” of the thrombus. The absence of the prothrombotic activity of leptin appeared to be responsible for the reduction in neointimal hyperplasia after ferric chloride application.

In this issue of Circulation Research, Schroeter et al have now demonstrated that infusion of leptin-stimulated human EPCs reduces neointima formation and enhanced reendothelialization through upregulation of αvβ5- and α4-integrin–dependent adhesion to platelets in ferric chloride–induced vascular injury. With this elegant approach, the effect of leptin on EPC-mediated endothelial recovery can be readily discerned from leptin-enhanced thrombosis. This not only extends the mechanisms by which platelet-derived chemokines, P-selectin, and β2 integrins can support the arrest of EPCs and CD34+ progenitor cells at sites of arterial injury but also adds a new dimension to the functional profile of leptin. Moreover, the authors provide the first evidence for a contribution of EPCs to recanalization of arterial thrombi. Because leptin did not affect EPC proliferation, previously described effects on EPC tube formation may be related to an enhancement of αvβ5- and α4-integrin expression and function in adhesion and migration. In accordance with previous findings in venous thrombosis, leptin-stimulated EPCs were not incorporated into the endothelial lining, suggesting that the secretion of angiogenic growth factors from EPCs is involved in thrombus recanalization, possibly by promoting the recruitment of endogenous endothelial progeny or endothelial cells from local resident sources. Notably, Schroeter et al used early outgrowth EPCs, which are presumed to be monocyte-derived and show significant phenotypic overlap with monocytes. This is also
remarkable because monocytes play a central role in thrombus recanalization, and their differentiation into endothelial-like cells appears to be an important feature in this context. In conclusion, thrombus recanalization by (leptin-assisted) mobilization and recruitment of endogenous EPCs or through the application of leptin-stimulated early endothelial outgrowth cells is an interesting new therapeutic approach and can make a credible change in the EPC field beyond ischemic neovascularization and endothelial recovery resulting from other forms of endothelial damage, eg, after percutaneous interventions and stent implantation.

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