Vascular progenitor cells and diabetes: role in postischemic neovascularisation

J.-S. Silvestre

Centre de Recherche Cardiovasculaire INSERM Lariboisière, INSERM U689, Hôpital Lariboisière, 41, bd de la Chapelle, 75475 Paris cedex 10, France

Received: October 23rd 2007; accepted: November 15th 2007

Abstract

Advances in the field of vascular biology lead to the identification of endothelial progenitor cells (EPC) and to the development of EPC-based cell therapy to induce new vessel formation in ischemic tissues and to accelerate re-endothelialisation of injured vessels in human and various animals models. However, recent studies have shown that age and other risk factors for cardiovascular diseases, such as diabetes, reduce the availability of EPC and impair their function to varying degrees, leading to reduction in postischemic vessel growth. This review focus on the cellular and molecular mechanisms governing EPC-related functions and analyzes the impact of diabetes in this setting.

© 2008 Elsevier Masson SAS. All rights reserved.

Keywords: Vasculogenesis; Stem cells; Ischemia; Diabetes

1. Postischemic vasculogenesis

In the past decade, stem or progenitor cells have been identified in various tissues, including bone marrow, peri...
pheral blood, umbilical cord blood, brain, heart, liver and adipose tissue [1-3]. Among these stem cells, EPC have been isolated and characterized as progenitor cells with proliferation capacity and potential to differentiate into endothelial lineage cells. EPC are thought to originate from a common hemangioblast precursor in the bone marrow [2,4]. However, myeloid-monocyte lineage cells (CD14+) can also differentiate into cells with EPC characteristics [5,6]. In addition, some tissues harbor stem cells that may differentiate into various lineages including endothelial cells [3,7]. Typically, these cells are defined on the basis of expression of cell surface markers such as CD34, Flk-1 and CD-133 [1,8]. Recently, CD34+/CD133+ EPC subpopulation has been identified as a precursor of classical CD34+/CD133+ EPC with potent vasoregeneratrice capacities [9]. Both in vitro and in vivo, EPC are able to differentiate into expressing endothelial lineage markers: VE-cadherin, endothelial nitric oxide synthase, von Willebrand factor, PECAM-1 (CD31), uptake of Dil acetylated LDL and binding of lectin. Their high proliferation rate also distinguishes EPC from mature endothelial cells shed from the vessel wall. EPC are then successfully ex vivo expanded with the use of human peripheral blood mononuclear cells.

EPC appear to be a heterogeneous group of cells originating from multiple precursors and present in different stages of endothelial differentiation in peripheral blood. In support of this view, cultured total mononuclear cells from human peripheral blood have been shown to differentiate into both early and late EPC. Early EPC express monocytic lineage markers, display spindle shape, show peak growth at 2 to 3 weeks and die at 4 weeks. Late EPC with cobblestone shape appear late at 2 to 3 weeks, show exponential growth at 4 to 8 weeks, and live up to 12 weeks. Late EPC are different from early EPC in their vasogenic properties and the expression of VE-cadherin, Flt-1, KDR, and CD45 [10]. It is therefore likely that different cells share similar EPC capacity or that appropriate marker(s) defining the effective subpopulation of cells are still missing.

Several lines of evidence suggest that local tissue injury alters the vascular endothelium to arrest EPC in regions where regeneration of endothelium is needed [11]. For example, in the setting of ischemia, the recruitment of CXCR4-positive EPC to regenerate tissues is mediated by hypoxic gradients via hypoxia-induced factor-1-induced expression of stroma-derived factor (SDF-1) [12]. Bone marrow mononuclear cells or EPC of heterozygous CXCR4 (+/-) mice display reduced CXCR4 expression and disclose impaired in vivo capacity to enhance recovery of ischemic blood flow in nude mice [13]. Local hypoxia also releases a soluble factor, or multiple soluble factors, that act as a chemotaxant for circulating EPC. One likely candidate is VEGF, which has previously been shown to be locally elevated in response to hypoxia, and to promote SDF-1 induction in perivascular tissue [14]. Alternatively, chemokines and platelets may also trigger EPC capture at sites of vascular lesions [15-17]. The arrest of EPC in injured microvessels is then mediated by cell-surface vascular adhesion molecules and selectins, such as beta2 integrins or L-selectin [18-20]. After their recruitment within the target tissue, EPC may exert their beneficial effects.

However, a major critical point is the identification of cellular mechanisms governing EPC vasoregeneratrice capacities. EPC have been shown to incorporate into blood vessel and physically contribute to vascular endothelium. However, the relative contribution of circulating EPC to adult organ and tumor vasculature is highly variable and may range from a minor [21-23] to a major contribution [24]. The experimental animal models and the method of EPC isolation may have contributed to these different numbers. Hence, whereas both types of EPC show comparable in vivo vasulagenic capacity, late EPC incorporate more readily into human umbilical vein endothelial cells monolayer, and form capillary tube better than early EPC [10]. In addition, the gradient of hypoxia directs EPC to coalesce into independent vascular structures to restore tissue perfusion in the ischemic region. However, the extent of incorporation is directly proportional to the degree of tissue ischemia [25].

Alternatively, EPC may serve as building blocks for neovascularisation. The plasticity of EPC could be insufficient to ensure their differentiation into mature endothelial cells but may explain their ability to mimic the activities of endothelial cells and to participate in processes such as neovascularisation. This ability has been termed ‘vasulogenic mimicry’ in certain types of cancer cell and may also exist for EPC [26]. Finally, primary role of progenitor cells may be to deliver angiogenic growth factors to pathological tissues and contribute to neovascularisation and tissue/vessel remodeling by paracrine effects. EPC secrete the angiogenic growth factors: vascular endothelial growth factor (VEGF), hepatocyte growth factor, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor [6,27]. In addition, EPC also release proteases, such as cathepsin L, and promote a concomitant increase in matrix degradation that enables endothelial cell migration and vascular remodelling [28].

2. Diabetes and postischemic vasculogenesis

However, recent studies have shown that age and other risk factors for cardiovascular diseases reduce the availability of EPC and impair their function to varying degrees, leading to reduction in postischemic vessel growth. For example, patients with coronary artery disease showed reduced levels and functional impairment of EPC, which correlated with risk factors for coronary artery disease [29]. Patients with peripheral obstructive arterial diseases (PAD) may also have lower angiogenic potential because of decreased expression of EPC specific molecules in their marrow and blood [30].
Diabetes is a major risk factor for coronary and peripheral artery diseases. Diabetes has been shown to impair endogenous neovascularisation of ischemic tissues. This impairment in new blood vessel formation may result from reduced expression of VEGF and cytokine supplementation achieved by intramuscular adeno-VEGF gene transfer restores neovascularisation in a mouse model of diabetes [31,32,33]. The cellular response of monocytes to VEGF-A is attenuated in diabetic patients because of a downstream signal transduction defect suggesting that abrogation in monocytes migration may be involved in the problem of impaired collateral formation in diabetic patients [34]. Hyperglycemia is also associated with a marked accumulation of advanced glycation end products (AGE). Plasma AGE levels were strongly elevated in diabetic mice when compared with control mice. Treatment with aminoguanidine reduced AGE plasma levels and completely normalized ischemia-induced angiogenesis in diabetic mice. This effect is probably mediated by restoration of matrix degradation processes that are disturbed as a result of AGE accumulation [35].

Diabetes may also hamper EPC-related functions. Hence, EPC decrease is related to PAD severity and that EPC function is altered in diabetic subjects with PAD, strengthening the pathogenetic role of EPC dysregulation in diabetic vasculopathy [36].

Similarly, type I and II diabetes, are associated with reduced EPC numbers and angiogenicity [25,37,38]. Diabetes also decreased the ability of adherent bone marrow-derived mononuclear cells (BM-MNCs) to differentiate into endothelial progenitor cells. Treatment with NAC, apocynin, or p38MAPK inhibitor up-regulated the number of endothelial progenitor cell colonies derived from diabetic BM-MNCs. In the ischemic hindlimb model, injection of diabetic BM-MNCs isolated from NAC-treated or gp91 (phox) -deficient diabetic mice increased neovascularisation by approximately 1.5-fold greater than untreated diabetic BM-MNCs. Thus, inhibition of NADPH oxidase-derived reactive oxygen species overproduction improves the angiogenic and vasculogenic processes and restores postischemic neovascularisation in type 1 diabetic mice [39]. Glucose-mediated EPC dysfunction was protein kinase C dependent, associated with reduced intracellular BH (4) (tetrahydrobiopterin) concentrations, and reversible after exogenous BH (4) treatment. Subsequently, eNOS was uncoupled resulting in eNOS-mediated O (2) (-) production and impairment of EPC function in diabetic patients [40].

Alternatively additional factors may be involved in the diabetes-induced EPC dysfunction. Notably, thrombospondin-1 mRNA expression is significantly up-regulated in diabetic EPC, in relation with the decreased EPC adhesion activity in vitro and in vivo [41]. Diabetic mice showed impaired phosphorylation of BM eNOS, decreased circulating EPCs, and diminished SDF-1alpha expression in cutaneous wounds leading to impaired EPC homing in diabetic mice [42]. Finally, activation of the Akt/p53/p21 signaling pathway and accelerated onset of senescence are also detectable in EPC from diabetic patients. Diabetic EPC depleted of endogenous p53 do not undergo to senescence-growth arrest and acquire the ability to form tube-like structures in vitro, identifying the activation of the p53 signaling pathway as a crucial event that can contribute to the impaired neovascularisation in diabetes [43].

Therefore, diabetes reduce the availability of EPC and impair their function to varying degrees, leading to reduction in postischemic vessel growth. In addition, the reduction in EPC pro-angiogenic effect associated with diabetes may limit their therapeutic usefulness in these patients population. Furthermore, the relative scarcity of circulating EPC and their finite proliferative potential limits the ability to expand these cells in sufficient numbers for some therapeutic applications. Strategies to improve homing, survival and therapeutic potential of EPC need to be developed to improve therapeutic effect and counteract EPC dysfunction in diabetic patients.

No potential conflict of interest revealant to this article was reported.

References
