[文章编号] 1007-3949(2009)17-07-0578-03

Endothelial Damage and Stem Cell Repair in Atherosclerosis

Qingbo Xu

(Cardiovascular Division, King's College London, London, UK)

[KEY WORDS] Endothelial Damage; Stem Cell Repair; Atherosclerosis

Atherosclerosis is an inflammatory disease characterized by leukocyte infiltration, smooth muscle cell accumulation and neointima formation[1]. Activation and damage of the endothelial monolayer seems to trigger the development of the lesions. Initially, it was thought that the damaged endothelial cells were replaced by the adjacent intact endothelium. However, recent studies demonstrated the recruitment and incorporation of vascular progenitor cells into atherosclerotic lesions and thus provided evidence in support of the role of vascular cells in the development of the disease[2,3]. Direct incorporation of circulating stem cells into the vessel wall was detected in

mice[4-7]. For example, conclusive data was obtained using transgenic animals in which expression of LacZ genes was controlled by specific endothelial promoters. This resulted in only the endothelial cells of these mice (TIE2-LacZ) express beta-galactosidase (beta-gal). Using the animal models for vascular grafts[8], we performed vessel grafts in two types of transgenic mice expressing beta-gal in ECs, including TIE2-LacZ, TIE2-LacZ/apoE$^{-/-}$, and wild-type mice[9]. We demonstrated that the endothelium on grafts completely disappeared due to apoptosis or necrosis, and were replaced by stem cells, of which about one-third of cells were derived from the bone marrows[9]. These findings indicate the contribution of circulating stem cells to regenerate damaged endothelium of the vessel wall.

Concerning stem cell homing to the site where endothelium was damaged, multiple molecules, including families of adhesion molecules and chemokines, provide signals for the dynamic trafficking of stem cells to the surface of damaged vessels[10]. Sakihama et al[11] show that SDF-1 is a critical molecular target for the stem cell homing. During the course of arteriosclerosis, intragraft SDF-1 expression was upregulated, and the circulating stem cells expressing its counter-receptor CXCR4 increased in the recipients receiving allografts. CXCR4^{+} stem cells, derived from transplant recipients, migrated into allografts via microvessels in the adventitia and then toward the luminal side. In support of a functional role for these molecules, in vivo neutralization of SDF-1 inhibited stem cell homing[12]. Thus, interaction between SDF-1 and CXCR4 plays a key role in transplant arteriosclerosis development.

Theoretically, adhered stem cells to the surface of damaged endothelium could differentiate into endothelial cells. Obviously, microenvironment of stem cells located in the vessel wall could play a crucial role in determining the fate of the cells. Based on published data, it seems that two signals are required for stem cell differentiation: i) interaction between adhesion molecules/integrin family members and ii) growth factor/shear stress[13, 14]. For example, expression of adhesion molecules by activated endothelial cells of the vessel wall and integrins expressed on the stem cell membrane leads to tethering of stem cells to the surface of the vessel wall and initiates differentiation. The later, growth factor, could be released by activated ECs and/or platelets aggregated on subendothelial matrix.

The microenvironment of the platelet-rich fibrin clot is most supportive for CD34^{+} cell differentiation toward EC phenotype, in which VEGF is abundant[15]. Platelets elaborate an array of factors that are involved in wound healing, of which many factors also play a role in the biology of stem cells. For instance, the potent growth factor VEGF, which is highly accumulated in procoaggulant regions[16], not only leads to recruitment of stem cells into the damaged areas but also stimulates the differentiation of CD34^{+} progenitors into endothelial cells[17]. Once CD34+ progenitors attach to the injured vessel wall, they will be subjected to fluid shear stress, which enhances their VEGFR2 expression, proliferation and tube formation[18, 19]. Additionally, we demonstrated that collagen Ⅳ/intergrin interaction and VEGF stimulation is essential for Sca-1+ progenitor differentiation into endothelial cells[20]. These data provide evidence that may translate to the in vivo situation of stem cell repair to damaged endothelial cells of damaged vessels during development of arteriosclerosis.

As stated above, laminar shear stress, created by blood flow, stimulates stem cell differentiation. Stem cells attached to the damaged surface of vessels are subjected to the shear stress caused by blood flow, which may directly stimulate cell differentiation. Supporting this notion is the fact that shear treatment of stem cells in vitro results in expression of a panel of endothelial markers, including CD31, ICAM-1 and VE-cadherin[18, 19, 21, 22]. Assays for tube formation in the Matrigel showed that the shear-stressed progenitors form tube-like structures and develop an extensive tubular network significantly faster than the static controls[22]. The mechanisms of shear-induced stem/progenitor cell differentiation seem to involve several signal initiators and transducers, as recently identified by Zeng et al[22]. It was shown that histone deacetylase (HDAC) activation is essential in this process. HDACs comprise at least[17] genes, of which HDAC1, HDAC3, and SIRT1 are expressed in human peripheral blood - derived endothelial progenitors, while embryonic stem cells express the majority, if not all of HDAC family genes. We found that shear stress can rapidly activate the VEGF receptor-Akt-eNOS pathway in embryonic stem cell-derived progenitors, in which Akt also induces HDAC3 phosphorylation. One downstream target for HDAC3 is p53 which is upregulated by shear stress[22]. Taken together, shear stress is a positive signal for stem/progenitor cell differentiation into ECs via pathways similar to those used by VEGF.

In summary, following the endothelial injury, stem cells derived from different sources may participate in endothelial repair during development of arteriosclerosis. In this process, the fate of stem cell differentiation into endothelium is a key issue for the progression of arteriosclerosis. Further understanding of the biology of stem cells is essential in order to fully benefit for their regenerative properties and design novel ways to successfully intervene with the progress of the disease.

(This work was supported by Grants from British Heart Foundation and Oak Foundation).

[References]

[1] Ross R. Atherosclerosis--an inflammatory disease [J]. *N Engl J Med*, 1999, **340**: 115-126.

[2] Xu Q. The impact of progenitor cells in atherosclerosis [J]. *Nat Clin Pract Cardiovasc Med*, 2006, **3**: 94-101.

[3] Xu Q. Stem cells and transplant arteriosclerosis [J]. *Circ Res*, 2008, **102**: 1 011-024.

[4] Hillebrands JL, Klatter FA, Rozing J. Origin of vascular smooth muscle cells and the role of circulating stem cells in transplant arteriosclerosis [J]. *Arterioscler Thromb Vasc Biol*, 2003, **23**: 380-387.

[5] Hillebrands JL, Klatter FA, van den Hurk BM, et al. Origin of neointimal endothelium and alpha-actin-positive smooth muscle cells in transplant arteriosclerosis [J]. *J Clin Invest*, 2001, **107**: 1 411-422.

[6] Hu Y, Davison F, Ludewig B, et al. Smooth muscle cells in transplant atherosclerotic lesions are originated from recipients, but not bone marrow progenitor cells [J]. *Circulation*, 2002, **106**: 1 834-839.

[7] Lagaaij EL, Cramer-Knijnenburg GF, van Kemenade FJ, et al. Endothelial cell chimerism after renal transplantation and vascular rejection [J]. *Lancet*, 2001, 357: 33-37.

[8] Dietrich H, Hu Y, Zou Y, et al. Mouse model of transplant arteriosclerosis: role of intercellular adhesion molecule-1 [J]. *Arterioscler Thromb Vasc Biol*, 2000, **20**: 343-352.

[9] Hu Y, Davison F, Zhang Z, et al. Endothelial replacement and angiogenesis in arteriosclerotic lesions of allografts are contributed by circulating progenitor cells [J]. *Circulation*, 2003, **108**: 3 122-127.

[10] Jin DK, Shido K, Kopp HG, et al. Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4+ hemangiocytes [J]. *Nat Med*, 2006, **12**: 557-567.

[11] Sakihama H, Masunaga T, Yamashita K, et al. Stromal cell-derived factor-1 and CXCR4 interaction is critical for development of transplant arteriosclerosis [J]. *Circulation*, 2004, **110**: 2 924-930.

[12] Gao C, Li Y. SDF-1 plays a key role in the repairing and remodeling process on rat allo-orthotopic abdominal aorta grafts [J]. *Transplant Proc*, 2007, **39**: 268-272.

[13] Deb A, Skelding KA, Wang S, et al. Integrin profile and in vivo homing of human smooth muscle progenitor cells [J]. *Circulation*, 2004, **110**: 2 673-677.

[14] Xiao Q, Zeng L, Zhang Z, et al. Sca-1+ progenitors derived from embryonic stem cells differentiate into endothelial cells capable of vascular repair after arterial injury [J]. *Arterioscler Thromb Vasc Biol*, 2006, **26**: 2 244-251.

[15] de Boer HC, Verseyden C, Ulfman LH, et al. Fibrin and activated platelets cooperatively guide stem cells to a vascular injury and promote differentiation towards an endothelial cell phenotype [J]. *Arterioscler Thromb Vasc Biol*, 2006, **26**: 1 653-659.

[16] Lev EI, Estrov Z, Aboulfatova K, et al. Potential role of activated platelets in homing of human endothelial progenitor cells to subendothelial matrix [J]. *Thromb Haemost*, 2006, **96**: 498-504.

[17] Massberg S, Konrad I, Schurzinger K, et al. Platelets secrete stromal cell-derived factor 1alpha and recruit bone marrow-derived progenitor cells to arterial thrombi in vivo [J]. *J Exp Med*, 2006, **203**: 1 221-233.

[18] Yamamoto K, Takahashi T, Asahara T, et al. Proliferation, differentiation, and tube formation by endothelial progenitor cells in response to shear stress [J]. *J Appl Physiol*, 2003, **95**: 2 081-088.

[19] Sho E, Sho M, Nanjo H, et al. Hemodynamic Regulation of CD34+ Cell Localization and Differentiation in Experimental Aneurysms [J]. *Arterioscler Thromb Vasc Biol*, **2004**.

[20] Xiao Q, Zeng L, Zhang Z, et al. Stem cell-derived Sca-**1+** progenitors differentiate into smooth muscle cells, which is mediated by collagen IV-integrin alpha**1**/beta**1**/alphav and PDGF receptor pathways [J]. *Am J Physiol Cell Physiol*, **2007**, **292**: C342-352.

[21] Wang H, Riha GM, Yan S, et al. Shear stress induces endothelial differentiation from a murine embryonic mesenchymal progenitor cell line [J]. *Arterioscler Thromb Vasc Biol*, 2005, **25**: 1 817-823.

[22] Zeng L, Xiao Q, Margariti A, et al. HDAC3 is crucial in shear- and VEGF-induced stem cell differentiation toward endothelial cells [J]. *J Cell Biol*, 2006, **174**: 1 059-069.

(Edited by LI Xiao-Ling)