Editorial Comment

The Renin-Angiotensin System: A Potential Modulator of Endothelial Progenitor Cells

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A growing body of evidence suggests that circulating endothelial progenitor cells (EPCs) participate in vascular healing and remodeling under physiological and pathological conditions (*1*, *2*). It is believed that the majority of EPCs originate in the bone marrow (BM). EPCs are mobilized into systemic circulation in response to specific stimuli (Mobilization) and recruited at the site of vascular repair or neovascularization (Homing), where they differentiate into endothelial-like cells (Differentiation) and proliferate (Proliferation). Recently, it was reported that cardiovascular risk factors inversely correlate with the number of EPCs (*3*). Statin therapy was suggested to promote mobilization of EPCs after vascular injury, leading to accelerated reendothelialization and reduced neointima formation (*4*). Other factors, such as estrogen (*5*) and physical activity (*6*), have been demonstrated to improve the quantity and quality of EPCs, presumably causing vascular protective effects. Thus, it is clinically relevant to understand the molecular mechanisms that regulate the kinetics of EPCs.

In this issue of *Hypertension Research*, Yao *et al*. demonstrate that the proliferation and function of EPCs are impaired in spontaneously hypertensive rats (*7*). The authors report that losartan, an angiotensin II (Ang II) type 1 receptor blocker (ARB), improves the function of EPCs. It has previously been reported that Ang II accelerates EPC senescence by a gp91phox-mediated increase of oxidative stress, resulting in EPC dysfunction (*8*). Consistently, ARBs have been reported to increase the number of EPCs in patients with type 2 diabetes mellitus (*9*). These results suggest that inhibitors of RAS may have beneficial effects on EPCs, contributing to their efficacy in the prophylactic treatment of vascular diseases.

The renin-angiotensin system (RAS) is a circulating hormonal system that regulates blood pressure and flow. In addition, the RAS is reported to be involved in the maintenance of cell proliferation and organ remodeling in various tissues other than those of the cardiovascular system (*10*). Recent reports suggest that a local RAS in BM contributes to the regulation of both normal and malignant hematological processes (*11*). It has been demonstrated that Ang II and angiotensin peptides promote hematopoietic progenitor cell proliferation and hematopoietic recovery after radiation therapy and chemotherapy (*12*). Murohara and his colleagues reported that the Ang II–AT1 receptor pathway plays important roles in angiogenesis associated with ischemia and tumor (*13*, *14*). These results appear to be contradictory to the finding by Yao *et al*. (*7*). Recent studies suggest that the intracellular redox state is a critical modulator of the balance between self-renewal and differentiation in dividing precursor cells and that anti-oxidants may preserve their stemness (*15*). It is plausible that a reduction in oxidative stress resulted in restoration of the impaired function of EPCs in spontaneously hypertensive rats, although it remains to be determined whether RAS inhibition stimulates EPC function under physiological conditions in healthy subjects.

After the discovery of EPCs, a number of studies documented that transplantation of exogenous EPCs isolated from adult peripheral blood, cord blood or BM cells augments collateral development to ischemic tissues (*1*). A number of groups have begun clinical investigations of the safety and efficacy of EPC transplantation for the treatment of ischemic

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diseases. Although most of the studies have reported positive effects with few adverse effects (*16*), there is clinical evidence that some patients, unlike healthy experimental animals, fail to develop spontaneous collateral circulation in response to tissue ischemia and appear to be refractory to exogenous administration of EPCs isolated from their own BM or peripheral blood (*17*). The presence of metabolic disorders, such as diabetes and hypercholesterolemia, appears to impair EPC function. Yao *et al*.'s findings suggest that pharmacological modification of EPCs might improve the efficacy of cell transplantation for therapeutic angiogenesis (*7*). Clinical studies are warranted to determine whether similar favorable effects could be obtained in patients with metabolic diseases.

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