N ew blood vessel formation is required to increase blood supply to the myocardium or other tissues after critical ischemia. Capillary formation after ischemia can be achieved by the sprouting of preexisting vessels, a process named angiogenesis. However, in the last few years it has become evident that bone marrow–derived circulating endothelial progenitor cells (EPCs) can contribute to and amplify neovascularization. EPCs significantly contribute to adult vessel formation by physically incorporating and promoting vessel growth by paracrine mechanisms.

Injected EPCs improve neovascularization of ischemic hind limbs and ischemic hearts in animal models (for review see reference 2). Moreover, initial clinical trials demonstrate that the infusion or injection of bone marrow–derived or circulating progenitor cells augment perfusion and increase the ejection fraction in patients with ischemic heart disease (for review see reference 3). To contribute to tissue repair, EPCs, and stem cells in general, have to be equipped with antioxidative defense systems to survive in necrotic and ischemic tissues. Interestingly, a high resistance to oxidative stress has been considered a characteristic feature of stem cells. Protection against oxidative stress by reactive oxygen species is accomplished by a complex defense system composed of several antioxidative enzymes that reduce the damaging effects of reactive oxygen species (for review see reference 6). The most vulnerable organelles to oxidative stress are the mitochondria, because of the permanent potential for the production of superoxide anions. Superoxide anions are converted to hydrogen peroxide by superoxide dismutases, whereas hydrogen peroxide is detoxified by the enzymes catalase and glutathione peroxidase. Because of the localization of manganese superoxide dismutase and glutathione peroxidase-1 (GPx-1) in the matrix of the mitochondria, in close proximity to the production of reactive oxygen species by the electron transport chain, these two enzymes are believed to be the primary antioxidant defense systems in the mitochondria. Recently, two in vitro studies demonstrated that EPCs express higher levels of manganese superoxide dismutase and GPx-1.

In this issue of Circulation Research, Galasso et al addressed for the first time the role of one of the antioxidative enzymes, namely GPx-1, for the functional capacity of EPCs in vivo. The authors of this study investigated ischemia-induced neovascularization in GPx-1–deficient mice and assessed the number and functional activity of EPCs. GPx-1–deficient mice showed a reduced blood flow recovery after hindlimb ischemia compared with their wild-type littermates. This was accompanied by reduced EPC levels in response to ischemic injury, or to VEGF administration, and a reduction of the functional capacity of EPCs to migrate and promote angiogenesis in vitro. These novel findings support the knowledge that EPCs require antioxidative enzymes, specifically GPx-1, for their functional capacity (for summary see the Figure). However, is the reduction of EPCs in GPx-1–deficient mice caused by increased cell death or decreased differentiation or mobilization? Galasso et al demonstrated that EPCs derived from GPx-1–deficient mice show increased apoptosis sensitivity and decreased expression of the endothelial marker Flk-1. At first glance one could surmise that both processes—increased apoptosis sensitivity and decreased expression of Flk-1—are involved in the reduction of EPC levels from GPx-1–deficient mice. However, a reduced Flk-1 expression was demonstrated before and after ischemia, supporting the hypothesis that interfering with the antioxidative defense systems of cells may influence differentiation. Likewise, the increase in EPC numbers after ischemia or VEGF was inhibited, indicating an influence on mobilization. In contrast, the basal apoptosis rate is similar in EPCs derived from wild-type and from GPx-1–deficient mice, despite the fact that the EPCs were isolated after ischemia. Only after treatment with H2O2 were EPCs derived from GPx-1–deficient mice more prone to apoptosis. Overall, these data would suggest that apoptosis may not be the most important mechanism for reduced EPC levels. What is the specific mechanism by which reactive oxygen species affect mobilization and progenitor cell differentiation toward the endothelial lineage? Although the molecular mechanisms are unknown so far, one may speculate that the reduced bioavailability of nitric oxide reported for the GPx-1–deficient mice may contribute to the phenotype of the mice. It is also important to note that eNOS-deficient mice show a similarly impaired capacity to mobilize EPCs combined with a systemic dysfunction of isolated EPCs.

One important issue to note is the dual role of reactive oxygen species. Although reactive oxygen species in high concentrations are toxic, low levels of reactive oxygen species can serve as intracellular signals stimulating mechanisms that prevent tissue injury and promote angiogenesis. In line with these findings, Tojo et al demonstrated that ischemia-induced neovascularization is impaired in mice lacking a subunit of the NADPH oxidase, the gp91phox. Thus, reactive oxygen species from inflammatory cells, as well as from endothelial cells, appear to be essential to the complete development of angiogenesis in response to ischemia. In contrast, Galasso et al demonstrated here that an increase in reactive oxygen species in EPCs from GPx-1–deficient mice results in a functional impairment of these cells, and GPx-1–deficient mice show a selective sensitivity toward different types of oxidative stress.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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pro- and antioxidative enzymes for classical angiogenesis and the EPC-mediated vasculogenesis would help to better define the complex role of reactive oxygen species in neovascularization.

The finding that GPx-1 expression is essential for EPC functions may also have clinical implications, given that patients with chronic heart failure17 and with type 2 diabetes18 showed a downregulation of GPx-1. This in turn may contribute to the reduced EPC numbers and functions in patients with coronary artery disease and severe heart failure.19,20 However, other antioxidative enzymes such as superoxide dismutases and catalases are also downregulated in these patients.17,18 Thus, it seems mandatory to understand the specific role of the various antioxidative enzymes for EPC functions. In the future, a specific interference with the expression and activity of antioxidative enzymes in progenitor cells from patients might be a therapeutic strategy to improve their regenerative potential.

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References


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