This issue of Circulation Research, Tohru Fukai and colleagues (1) provide evidence from a mouse hindlimb ischemia model indicating that the superoxide anion scavenging activity of the secreted extracellular form of superoxide dismutase (ecSOD) has an apparently essential role in enabling neovascularization to occur. Both reactive oxygen species (ROS) and nitric oxide (NO) appear to be part of many of the signaling mechanisms in individual cell types and subcellular environments influencing key processes (shown in the Figure) that both enable and prevent the restoration of impaired blood flow to ischemic tissue through neovascularization. Thus, it seems rather remarkable that the ecSOD system has such an important role in controlling the balance of processes involved. Moreover, ecSOD appears to be a key regulator of the mobilization of circulating inflammatory and endothelial progenitor cells (EPCs) from bone marrow, which are major contributors to inflammation driven vascular growth promoting processes involved in neovascularization.

Hindlimb ischemia is shown in the Fukai study to increase the expression of ecSOD both in the ischemic muscle tissue and in bone marrow. The importance of this observation is highlighted by data showing that exposure of mice deficient in ecSOD to hindlimb ischemia was associated with decreased NO-cGMP signaling in both the ischemic skeletal muscle and bone marrow, suggesting that the well established role of ecSOD in protecting NO signaling is likely to be an important factor. Some of the key processes associated with neovascularization, including the mobilization of EPCs and angiogenesis, are thought to be regulated by NO. In addition, the gp91phox or Nox2-containing NAD(P)H oxidase appears to have an important role in the angiogenesis response to hindlimb ischemia. This suggests that the superoxide anion and peroxynitrite (ONOO−) lowering and hydrogen peroxide increasing actions of ecSOD may also be a contributing factor. The observation that ecSOD expression is increased in the region of macrophages in ischemic tissue also suggests that it may function to shift the balance of radical-related processes towards NO synthesis.

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haps enhancement of peroxide formation by ecSOD is also a factor in its effect on the balance of ROS regulation that permits these processes to occur. Once arteriogenesis has occurred, it seems that the endothelium-derived NO-mediated vasodilation may contribute to the increase in blood flow associated with neovascularization. The role of ecSOD in increasing NO and to modulate oxidative stress may also help control the balance of redox processes needed for neovascularization through feedback regulatory mechanisms that further enhance the expression of ecSOD and prevent the activation additional sources of ROS. Bone marrow transplant rescue studies in the hindlimb ischemia model also highlight the great importance of ROS regulation by ecSOD for the release of inflammatory cells and EPCs in the neovascularization process. Thus, observations made in this study of the effects of an ecSOD deficiency on neovascularization may contribute to developing a better understanding of sequential changes in signaling mechanisms controlled by the balance of local levels of ROS and NO-derived species which regulate processes that enable this repair mechanism to function.

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References

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