ecSOD Controls the Delicate Balance of Reactive Oxygen Species in Bone Marrow and Ischemic Tissue Needed for Neovascularization

Michael S. Wolin

“...In 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 in 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 species in the extracellular environment toward NO and peroxide. Peroxide appears to be involved in promoting growth of endothelial and vascular smooth muscle cells. As we look further into the potential actions of the balance between ROS and NO-derived species, inhibition of growth and apoptosis are factors to consider. Indeed, increased apoptosis was observed in the ecSOD-deficient hindlimb ischemia model. Observations that a low dose of a SOD mimic (tempol) essentially reversed the effects of a deficiency of ecSOD, further support the key role of the superoxide anion metabolizing activity of this enzyme in the protective effects observed. Thus, it seems quite remarkable that metabolism of superoxide anion by ecSOD in the extracellular region has such an important role of maintaining the balance in ROS-NO signaling needed for neovascularization processes (shown in the Figure).

Based on the observations of improved biosynthesis of nitrite and nitrate decomposition products of NO, one of the actions ecSOD appears to be preventing a decrease in NO biosynthesis. This occurs potentially as a result of increasing nitric oxide synthase activity by hydrogen peroxide or by prevention of the loss of its cofactor tetrahydrobiopterin presumably through oxidation by ONOO⁻. These data suggest that ecSOD is also modulating intracellular processes regulated by ROS and their interaction with the NO system. There is substantial evidence for cellular and subcellular compartmentalization of superoxide-derived ROS regulation. If one hypothesizes how ecSOD alters the metabolism of ROS in a manner which potentially modulates neovascularization, there appear to be many ways it could influence the outcome. Processes such as inflammatory cell recruitment and activation, promoting endothelial and smooth muscle growth, modulating the effect of NO on inflammatory cell activation and vascular cell growth, as well as promoting apoptotic or necrotic cell death, are all regulated by ROS. The dramatic effects of an ecSOD deficiency on all of these processes highlight the biological importance of regulating the balance of individual ROS and NO-derived species.

There are many observations and issues raised by the Fukai study that are likely to influence future work in this area. Because ecSOD enhances NO signaling, this action of increased ecSOD should help promote the mobilization of circulating inflammatory and EPCs from bone marrow, and angiogenesis in ischemic tissue. However, NO is also known to have a role in inhibiting inflammatory responses and the growth of vascular smooth muscle. Thus, one could hypothesize that NO would restrain inflammatory cell recruitment and the arteriogenesis component of neovascularization. Per-
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.6 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 model1 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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