While studying the effects of 2 weeks of angiotensin II infusion in extracellular superoxide dismutase knockout (ecSOD\(^{-/-}\)) mice on increasing superoxide and promoting hypertension, Gongora et al.\(^1\) made the surprising observation that NO production and its associated endothelium-dependent relaxation were actually improved by angiotensin II treatment in aorta from these mice without altering the expression of endothelial NO synthase. The studies were initially designed to further examine in ecSOD\(^{-/-}\) mice the concept that an elevation of superoxide causes a compensatory increase in the expression of ecSOD, which blunts the hypertensive response to angiotensin II and preserves endothelium-dependent vasodilatation. Evidence for this initial hypothesis was seen in measurements of blood pressure and in the response of isolated mesenteric resistance arteries. Angiotensin II treatment was observed to cause the hypothesized greater increase in blood pressure in the ecSOD\(^{-/-}\) mice compared with control animals and a loss of endothelium-dependent relaxation to acetylcholine, associated with the detection of increased superoxide in the resistance arteries. Endothelium-dependent relaxation to acetylcholine was impaired in the aorta of ecSOD\(^{-/-}\) mice even in the absence of angiotensin II treatment. Thus, a dominant effect of depleted ecSOD in resistance arteries and aorta is an attenuation of endothelium-dependent relaxation, which could originate from superoxide scavenging NO and/or impairment of the conversion of superoxide to hydrogen peroxide, a potential alternative mediator of endothelium-dependent relaxation in mouse mesenteric resistance arteries.\(^2\)

The surprising observation made in the study by Gongora et al.\(^1\) was that angiotensin II–elicited impairment of endothelium-dependent relaxation seen in control mice was actually improved in aorta from the ecSOD\(^{-/-}\) animals, associated with increased NO and decreased superoxide detection by spin trapping electron spin resonance methods and decreases in intracellular superoxide measured by dihydroethidine. The properties of superoxide generation and metabolism were investigated to elucidate how angiotensin II could be improving endothelial-dependent relaxation in aorta from ecSOD\(^{-/-}\) mice. Angiotensin II infusion increased reduced nicotinamide-adenine dinucleotide phosphate–dependent superoxide generation and the expression of Nox-1 in aorta from control and ecSOD\(^{-/-}\) mice; however, its effects were greater in the control mice. Aorta from the ecSOD\(^{-/-}\) mice show normal levels of expression of cytosolic Cu,Zn-superoxide dismutase (SOD) and intramitochondrial Mn-SOD and the expected absence of ecSOD. In addition, angiotensin II treatment decreased Mn-SOD and did not alter the expression of Cu,Zn-SOD in the ecSOD\(^{-/-}\) mice. With results like these, one might not want to continue a study of this type. However, these investigators observed that exposure of the ecSOD\(^{-/-}\) mice to angiotensin II increased Cu,Zn-SOD activity by \(\approx 2\)-fold, without altering its expression, an observation that could potentially explain the unusual results that were observed.

A potential explanation for how angiotensin II was stimulating Cu,Zn-SOD activity without increasing expression of this protein evolved from investigating the role of copper chaperone proteins, which is the focus of recent research by Jeney et al.\(^3\) and Qin et al.\(^4\), along with Dr. Fukai, a coauthor of the article discussed in this editorial. His group has been studying how Cu chaperones participate in the regulation of Cu,Zn-SOD expression, and the influence of angiotensin II on Cu,Zn-SOD was subsequently investigated. As discussed in the article by Gongora et al.,\(^1\) it is known that copper chaperone for Cu,Zn-SOD can provide Cu to the Cu-deficient form of this SOD and increase its activity without altering its expression, and oxidant stress conditions could also cause the loss of Cu from SOD.\(^1\) Thus, the delivery of Cu to SOD could be a key factor in controlling its activity. The Cu chaperone for Cu,Zn-SOD was increased by angiotensin II in the aorta but not in mesenteric arteries from the ecSOD\(^{-/-}\) mice. Thus, an elevation of Cu chaperone for Cu,Zn-SOD seems to be the potential origin of increased Cu,Zn-SOD activity and its protective effect on endothelial vascular regulation in aorta of ecSOD\(^{-/-}\) mice in the angiotensin II hypertensive model examined in the study of Gongora et al.\(^1\)

The data in this study highlight how localized activities of different forms of SOD in the vessel wall shown in the Figure are additional key factors that influence vascular function in models of hypertensive disease processes. It is known that Cu,Zn-SOD controls superoxide in the cytosolic region, and it may function to lower the efflux of superoxide from cells in the vessel wall making superoxide. In the absence of pathophysiological stimulation of oxidases, the Cu,Zn-SOD seems to enable NO and hydrogen peroxide to be released from endothelium\(^5\)–\(^7\) and for these mediators to activate soluble guanylate cyclase–elicited relaxation in vascular smooth muscle.\(^7\)–\(^8\) Most of the oxidases in the vessel wall are intracellular, and they are likely to generate superoxide in
regions where the cytosolic Cu,Zn-SOD could function to scavenge superoxide before it is able to be transported into the extracellular region. Although the gp91phox containing oxidase of phagocytic cells (Nox-2), such as neutrophils, is thought to generate superoxide across the plasma membrane of these cells, especially during the phagocytic process, there is little evidence to document that the various forms of Nox found in the cells of the arterial wall, such as endothelium and vascular smooth muscle, function to generate superoxide on the extracellular surface of these cells. Thus, intracellular forms of SOD may be the primary regulators of superoxide levels and its effects on NO regulation in the vessel wall. Under pathophysiological conditions where oxidases are activated, it is well established that superoxide escapes the intracellular environment, and there is significant evidence that ecSOD preserves NO function under these conditions.9 Overall, the ecSOD and Cu,Zn-SOD systems seem to have specialized roles in controlling oxidative stress in vivo.10 The data in the study of Gongora et al1 support and highlight the importance of these mechanisms.

Observations on the influence of angiotensin II on the expression and activity of various forms of SOD in the vessel wall underscore the incomplete understanding we have on what controls the function of the SOD systems. For example, the study of Gongora et al1 contains difficult-to-explain observations associated with why angiotensin II–treated hypertensive animals have elevated Cu chaperone and Cu,Zn-SOD activity in aorta but not in mesenteric resistance arteries. Thus, the study on which this editorial is written has data both advancing our understanding on the roles that different forms of SOD have in modulating the expression of hypertensive disease processes and highlighting areas where further investigation of regulatory mechanisms is warranted.

Model highlighting some of the known roles for Cu,Zn-SOD and ecSOD controlling endothelial regulation of vascular function in mouse mesenteric resistance arteries and aorta that are studied in Ang II–induced hypertensive ecSOD−/− mice. Figure shows how these systems participate in modulating the Ang II–elicited impairment of endothelium-derived NO regulation of resistance artery function. A surprising observation in the study shown was that NO production and endothelium-dependent relaxation were actually improved by Ang II treatment in aorta from ecSOD−/− mice associated with an upregulation of Cu chaperone for Cu,Zn-SOD (CCS), increased Cu,Zn-SOD activity, and decreased detection of superoxide.

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