Editorial

SOD Isoforms and Signaling in Blood Vessels
Evidence for the Importance of ROS Compartmentalization


Over the last decade, there has been a growing body of evidence defining the importance of reactive oxygen species (ROS) in the development of cardiovascular diseases. In blood vessels, ROS have not only been found to be involved in pathologic processes like hypertension, atherosclerosis, restenosis, and diabetic vascular disease, but they also have been shown to work as intracellular messengers that regulate several physiological mechanisms, such as modulation of vessel tone, vascular smooth muscle cell (VSMC) and endothelial cell (EC) apoptosis, VSMC proliferation, hypertrophy, and migration. The level of ROS in cells depends on a delicate balance between their production and destruction. A major source of ROS in VSMCs is the mitochondrial NADPH oxidase, but other sources like complex III of the electron transport chain in mitochondria may play an important role in their production.

As a result of its short half life (≈10^-4 seconds), its low diffusivity through lipid membranes, and its ability to quickly react with NO to produce peroxynitrite (ONOO^-), superoxide is the most likely ROS to have distinct effects depending on its subcellular localization. Moreover, VSMCs produce several different superoxide scavenger enzymes located in different areas of the cell: SOD1 (Cu/ZnSOD), which accounts for 50% to 80% of total SOD in blood vessels and is localized primarily in the cytosol and nucleus; SOD2 (MnSOD), expressed in smaller quantities in VSMCs, more abundantly in ECs, and localized to the mitochondria; and SOD3 (ecSOD) which is bound to the cell membrane through its heparin-binding domain and is located extracellularly.

Recent evidence has shown that each SOD isoform may have important effects on vascular pathophysiology. SOD1-deficient mice have been found to produce more superoxide than their wild-type controls and have decreased endothelium-dependent and -independent vasodilation. SOD1 overexpression in mice causes a decrease in VSMC proliferation in response to EGF, but no change in the aortic hypertrophic response to Angiotensin II. A separate study with mice overexpressing SOD1 on the apoE background showed no significant effect on aortic atherosclerotic lesion area. Total SOD2 deficiency is lethal in mice, and although partial SOD2 deficiency has been shown to cause an increase in atherosclerotic lesion formation at arterial branch points, there was no effect on vasomotor responses to serotonin, PGF2α, or acetylcholine at baseline or after inhibition of SOD1 and SOD3 with diethyldithiocarbamate. The second most abundant SOD isoform in blood vessels is SOD3, which is predominantly produced by VSMCs, but because its location in the interstitium between ECs and VSMCs it is thought to be essential for endothelium-dependent vasodilation by protecting NO as it diffuses from the ECs to the VSMCs. These differences in the regulation of vascular tone or in the formation of atherosclerotic lesions indicate the potential importance of the subcellular localization of antioxidant systems in the modulation of local oxidant signaling.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Madamanchi et al use VSMCs partially deficient in SOD1 or SOD2 and present exciting new data that explore the concept of compartmentalization of ROS signaling. The VSMCs were exposed to thrombin, which has been previously reported by the same group to stimulate NADPH oxidase activity through a G-protein–coupled receptor PAR-1 and thus increase intracellular superoxide and H2O2 production. Interestingly, superoxide production was significantly higher with SOD2 than SOD1 deficiency, despite a lower total SOD activity in the latter. This finding implies that SOD2 has a central role in metabolizing superoxide, probably because of its proximity to an important source of production like the mitochondria.

Furthermore, SOD1 deficiency promoted proliferation and protein synthesis through activation of extracellular signal regulated kinase (ERK)1/2 and p38 MAPK MAP kinases. SOD2 deficiency resulted in preferential activation of the JAK/STAT pathway with similar effects on cell function. This is an interesting finding that raises important questions. First, is it an increase in superoxide or a decrease in H2O2 production that is the cause of the activation of these pathways? Previous studies in VSMCs have shown that ERK1/2 is activated by superoxide, but H2O2 has had variable effects on its stimulation. Moreover, both p38 MAPK and JAK/STAT pathways are activated by H2O2 in VSMCs. Second, how does an increase in superoxide in the mitochondria and not in the cytosol cause phosphorylation of JAK2? JAKs have been shown to be spatially associated with multiple cell surface receptors, and JAK2 specifically has been shown to associate with the G-protein–coupled receptors for angiotensin II and thrombin. This may indicate either a novel association of JAK2 with mitochondrial signal transduction or the presence of intermediate steps between the production of mitochondrial ROS and the modulation of intracellular signaling through these receptors.
activation of JAK2 independent of cytosolic ROS production. Other signaling pathways like the activation of JNK and Akt by H$_2$O$_2$ have been found to be mitochondria-dependent. Finally, but more importantly, because both the increased activation of p38 MAPK and ERK 1/2 with SOD1 deficiency and the increased activation of the JAK/STAT pathway in SOD2-deficient VSMCs caused similar effects on cell proliferation and protein synthesis, is there an impact in the overall vascular phenotype between these partially SOD-deficient mice at baseline or after exposure to oxidative stress? Further studies characterizing and comparing the vasculature of mice partially deficient in SOD1 or SOD2 will likely be of great significance.

References

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