Dual Role of Reactive Oxygen Species in Vascular Growth

Kathy K. Griendling, David G. Harrison

In the last decade, it has become clear that virtually all mammalian cells produce reactive oxygen species. It was generally believed that these were by-products of cellular respiration and metabolism, and that they exerted toxic effects, including DNA damage and lipid oxidation. Recent evidence has demonstrated that this concept is incorrect, and that reactive oxygen species are produced in a controlled fashion and likely have critical signaling functions. Likewise, antioxidant defenses play a crucial role in modulating the ambient steady-state levels of reactive oxygen species. Biological or pharmacological manipulation of endogenous antioxidants can have a profound effect on cellular function.

Emerging evidence suggests that hydrogen peroxide (H$_2$O$_2$) plays a particularly important role in signal transduction. H$_2$O$_2$ is uncharged and is freely diffusible within and between cells. Compared with other reactive oxygen species, it is also quite stable. A major source of H$_2$O$_2$ is a membrane-bound NADH/NADPH oxidase, the activity of which is regulated by hormones, growth factors, and physical forces. The primary product of this enzyme system is superoxide (O$_2^-$), which is rapidly dismutated to H$_2$O$_2$ by the superoxide dismutases. Removal of H$_2$O$_2$ is regulated by two important enzymes, catalase and glutathione peroxidase. Reaction products of H$_2$O$_2$, including lipid hydroperoxides, are also biologically active.

Given the fact that the molecule is diffusible and stable and that its production and removal are highly regulated, H$_2$O$_2$ is an obvious candidate as a second messenger. Indeed, many studies have demonstrated that H$_2$O$_2$ mediates intracellular responses to extracellular stimuli. Early work showed that both tyrosine kinases and tyrosine phosphatases were targets of exogenous H$_2$O$_2$, and more recently several groups have demonstrated that agonist-induced activation of these enzymes is redox sensitive. Strong evidence for an involvement of H$_2$O$_2$ in ERK1/2 and p38 MAPK activation by growth factors and angiotensin II has been obtained by treating cells with exogenous catalase or by stably overexpressing catalase. Catalase overexpression of endogenous enzymes, may reduce the level of reactive oxygen species below that necessary for survival, and likely have critical signaling functions. Likewise, treatment with excess antioxidants, either pharmacologically or by overexpression of endogenous enzymes, may reduce the level of reactive oxygen species below that necessary for survival, triggering entry into the apoptotic pathway. Additional ex-

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of ras by reactive oxygen species is also potentially quite important. Recently, it has been shown that catalase, after reacting with H$_2$O$_2$, can activate guanylate cyclase. This seems to occur via a unique mechanism that is quite different from the heme-mediated activation of guanylate cyclase by nitric oxide.

In this issue of Circulation Research, Brown et al. present evidence that overexpression of human catalase has dual effects on vascular smooth muscle cells. Using an adenoviral construct to express up to a 50- to 100-fold excess of catalase, they demonstrate that smooth muscle cells overexpressing catalase have decreased rates of DNA synthesis and cell proliferation and higher rates of apoptosis. Catalase-overexpressing cells also show an induction of COX-2 protein, which may modulate cell growth by increasing the formation of growth-inhibitory prostaglandin, PGE$_2$. This possibility is supported by the observation that a COX-2 inhibitor reversed the reduction in cell number consequent to catalase overexpression.

The study of Brown et al. is in keeping with previous reports that reactive oxygen species mediate the response of smooth muscle cells to growth-promoting agents. Sundaresen et al. showed that not only did PDGF increase intracellular H$_2$O$_2$ but also that incubation of vascular smooth muscle cells with catalase prevented DNA synthesis in response to PDGF. Similarly, stable transfection of rat aortic smooth muscle cells with human catalase blocked angiotensin II–induced H$_2$O$_2$ production and hypertrophy. The concept that reactive oxygen species are growth promoting is further supported by the observations of Tsai et al., who reported that treatment of vascular smooth muscle cells with the antioxidants N-acetylcysteine or pyrrolidine dithiocarbamate dose dependently reduced cell viability and enhanced apoptosis. These findings agree well with observations of Brown et al. that overexpression of catalase, another antioxidant, also increased apoptosis.

Not all studies agree that oxidant stress is growth promoting, and in fact, others have shown that H$_2$O$_2$ actually may enhance apoptosis. Fiorani et al. found that although H$_2$O$_2$ initially increases DNA synthesis, this increase is followed by cell death. Similarly, exposure of vascular smooth muscle cells to glucose/glucose oxidase (which generates H$_2$O$_2$) induces apoptosis via the formation of hydroxyl radicals. The resolution of this apparent paradox is likely related to the levels and identity of the reactive oxygen species and antioxidants under consideration. Thus, although a certain level of oxidant stress appears to be growth promoting, more severe stress may lead to cell death. Similarly, treatment with excess antioxidants, either pharmacologically or by overexpression of endogenous enzymes, may reduce the level of reactive oxygen species below that necessary for survival, triggering entry into the apoptotic pathway. Additional ex-
performation will be necessary to reconcile these disparate observations.

The information presented by Brown et al., together with other recent studies, strongly supports a role of \( \text{H}_2\text{O}_2 \) as an important signaling molecule in vascular smooth muscle. Interestingly, it seems that \( \text{H}_2\text{O}_2 \) shares some similarities to nitric oxide in this regard. Both nitric oxide and \( \text{H}_2\text{O}_2 \) are reactive oxygen species that are freely diffusible between cells. Both nitric oxide and \( \text{H}_2\text{O}_2 \) have different effects depending on their concentration. It has now become clear that \( \text{H}_2\text{O}_2 \) has specific cellular targets, as does nitric oxide, and the biological effects of both of these reactive oxygen species seem critical to normal vascular function. Future studies of the endogenous reactive oxygen species, including \( \text{H}_2\text{O}_2 \), are essential in allowing an understanding of how these small molecules affect vascular cells under normal and pathophysiological conditions.

**References**

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