Endothelial NADPH oxidase 2: when does it matter in atherosclerosis?

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This editorial refers to ‘Endothelial-specific Nox2 overexpression increases vascular superoxide and macrophage recruitment in ApoE−/− mice’ by G. Douglas et al., pp. 20–29, this issue.

Reactive oxygen species (ROS) act as a double-edged sword in numerous cardiovascular conditions. In addition to their known detrimental effects on all cellular macromolecules, referred to as oxidative stress, lower amounts of ROS also directly modify molecules and thereby modulate their functions - this process has been termed redox signalling.

The picture might be completely different with a high-fat diet, which was not investigated by the authors. Since the high-fat diet stimulates lesion growth by elevated lipid levels, the increased monocyte recruitment in the Nox2-Tg ApoE−/− mice could, under these conditions where oxLDL levels may be higher, result in accelerated plaque progression. The authors demonstrate further that the endothelial-specific overexpression of human Nox2 did not influence angiotensin II-driven atherosclerosis. Finally, it is also possible that endothelial-derived ROS from other sources within the endothelium may be more important, such as uncoupled endothelial nitric oxide synthase, which has been found to be elevated in atherosclerosis progression.

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Why does increased endothelial-derived ROS production not result in changes in angiotensin II-driven atherosclerosis? Unfortunately, the authors did not measure angiotensin II effects on vascular ROS formation in ApoE−/− and Nox2-Tg ApoE−/− mice. It is known from previous studies that angiotensin II increases ROS formation in vascular cells; however, it is unclear whether further elevated ROS levels would be observed in the angiotensin II-treated Nox2-Tg ApoE−/− animals compared with the non-infused mice. One could argue that the levels of ROS produced from the endothelium are already saturated and cannot be further increased. Moreover, the initial recruitment of monocytes is not shown in treated and untreated mice. Thus, one cannot completely rule out a role for endothelial-derived ROS formation in angiotensin II-driven atherosclerosis.

What are the implications of this study for atherosclerosis in humans? Activation of Nox2 in the endothelium increases the monocyte/macrophage recruitment and thereby the initiation of plaque development. Thus, reducing this initial Nox2 activation could delay plaque development. However, one has to take into account that a global inhibition of Nox2 may result in reduced infectious defence. The absence of a role for endothelial, Nox2-derived ROS in plaque progression is supported by findings from Sorescu et al., who found that Nox2 and p22phox are predominantly co-localized in macrophages of human atherosclerotic specimens and that mRNA levels for p22phox and Nox2 correlate with lesion severity. Moreover, increased p22phox has been detected in endothelial cells, smooth muscle cells, infiltrating macrophages, and adventitial fibroblasts of human atherosclerotic coronary arteries. The present study did not investigate the levels of p22phox; however, since the authors demonstrate no atherosclerosis progression in Nox2-Tg ApoE−/− mice compared with ApoE−/− mice, an increase in p22phox levels, as it is found in advanced atherosclerotic plaques in humans, is not expected.

In summary, the study by Douglas et al. importantly contributes further to our understanding of initiation of atherosclerosis and its progression. Overexpression of Nox2 in the endothelium results in increased ROS formation. This ROS formation indeed leads to activation of the endothelial cells and increased monocyte recruitment. However, as long as the lipid composition does not change, the macrophage function is not altered, and inflammatory markers are not elevated, an increase in endothelial-derived ROS formation alone will not result in atherosclerotic plaque progression.

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References