Nox4 NADPH oxidase: emerging from the veil of darkness

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Online publish-ahead-of-print 1 October 2015

This editorial refers to ‘The NADPH oxidase Nox4 has anti-atherosclerotic functions†, by C. Schürmann et al., on page 3447.

In Greek and Roman mythology, the Primordial goddess Nox, born out of Chaos, is the goddess of the night. This allegory linking chaos to darkness characterizes our understanding of the Nox4 NADPH oxidase. In the vasculature, the NADPH oxidases are recognized as the predominant source of reactive oxygen species (ROS), which act as second messengers in redox signaling and contribute to the ‘oxidative stress’ in disease. Of the seven Nox isoforms, only Nox1, Nox2, Nox4, and Nox5 are expressed in the blood vessel, ‘oxidative stress’ in disease. Of the seven Nox isoforms, only Nox1, Nox2, Nox4, and Nox5 are expressed in the blood vessel, and each differs in cell-specific expression, mode of activation, intracellular location, and function.1 Although there is strong evidence of increased expression of the Nox isoforms in human atherosclerosis, the change in expression does not necessarily indicate a contribution to disease development. Recently, the availability of genetically modified mice has facilitated the process of defining the role of the specific Nox isoforms in atherosclerosis.

Studies with knockout mice have identified distinct functional roles for Nox1 and Nox2 in atherogenesis. In the hypercholesterolaemic ApoE–/– mouse, Nox1 deficiency decreases atherosclerotic lesion size in addition to reducing collagen content and the number of macrophages in lesions,2 which is consistent with a role for Nox1 in matrix degradation, monocyte recruitment, and adhesion molecule expression. Nox1’s contribution to these phenotypes was confirmed using a diabetes-accelerated model of atherosclerosis.3 Nox2 deficiency in the ApoE–/– mouse also protects against lesion formation and improves endothelial function.4 Nox2 appears to have a more profound effect on plaque burden within the aorta as compared with Nox1,2,4 most probably due to the contribution of Nox2-containing inflammatory cells to atherogenesis. Based on the existing data, Nox1 has emerged primarily as a regulator of vascular smooth muscle cell migration and proliferation and may reduce nitric oxide (NO) bioavailability.5–7 In contrast, Nox2 exerts its greatest effects on endothelial and inflammatory cell function. Despite these assertions, data using similar models have not consistently supported Nox1- or Nox2-dependent acceleration of atherosclerotic lesions.8,9 Since Nox5 is not expressed in rodents, its role in atherogenesis is unknown.

In contrast to the data supporting the direct contribution of Nox1 and Nox2 to the progression of vascular disease, early observations suggest that Nox4 is vasculoprotective and involves mechanisms that include increased bioavailability of NO and regulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a transcription factor that induces several cytoprotective genes.10,11 However, until now, the role of Nox4 in atherogenesis remained unknown. In this issue of the journal, Schürmann et al. define a protective role for Nox4 using two distinct models of vascular injury in hypercholesterolaemic mice and show that in a chronic model (9 months) of atherosclerosis, the global deficiency of Nox4 dramatically increases lesion size.12 Using partial carotid artery ligation as an acute model (28 days) of vascular injury, Nox4–/– mice exhibit accelerated luminal loss and increased intimal area. The deficiency of Nox4 is associated with changes in the vascular expression of multiple genes related to disease progression, including adhesion molecules and proinflammatory factors. Corroborating evidence is provided by showing that endothelial cells deficient in Nox4 exhibit increased leukocyte adhesion.

In a separate study, Craig et al. found that the overexpression of Nox4 in endothelium decreases the atherosclerotic lesion area in ApoE–/– mice.13 They provide evidence that Nox4 regulates the distribution of T cells in the aorta by promoting the immunosuppressive regulatory T-cell population over the proatherogenic effector T cells. Thus, both studies suggest a vasculoprotective effect of Nox4 in atherosclerosis via suppression of inflammatory and proatherogenic processes. However, neither of the two studies provides a direct molecular link between Nox4-derived hydrogen peroxide (H2O2) and specific pathway activation. Based on the evidence, it is our opinion that Nox4 primarily functions to modulate...
compartmental redox states to coordinate multiple signaling pathways.

It is seemingly paradoxical that the Nox isoform that primarily generates H$_2$O$_2$ is beneficial in atherosclerosis, whereas the Nox enzymes that generate superoxide, which is enzymatically dismutated to H$_2$O$_2$, are detrimental (Figure 1). Currently, we can only speculate that there is essential specificity in the subcellular distribution of the different isoforms, in the signaling molecules that associate with the Nox isoforms upon activation, and in the cellular responses to the duration of ROS release (e.g. inducible with Nox1/2 and constitutive with Nox4). Furthermore, the interplay of Nox isoform activation and signaling is probably highly dynamic and varies widely in terms of specific cell types and along the spectrum of disease development. Future insights into Nox function in the complex multifactorial disease of atherosclerosis will require experimental approaches that assess the spatial—temporal aspects of Nox activation.

It should not be surprising that several inhibitors of NADPH oxidases are currently under development for the treatment of vascular disease. Schürrmann et al. have demonstrated that treatment with one such inhibitor, GKT137931, attenuates early atherosclerosis development in ApoE$^{-/-}$ mice but accelerates later stages of disease progression. This is a potentially important finding and is consistent with the interpretation that this mixed Nox1/4 inhibitor prevents the proatherogenic effects of Nox1 early in disease and subsequently blunts the protective effects of Nox4. However, further research is warranted to determine whether Nox4 inhibitors should be used clinically, especially in light of the considerable ambiguity in Nox4 function as evident by other studies suggesting that it has a detrimental role in cardiovascular disease. While Nox4 still shares some of the ambiguous qualities associated with its namesake, the goddess of the night, the study conducted by Schürrmann et al. marks an important step toward removing the veil of darkness surrounding Nox4’s role in vascular disease.

**Acknowledgements**

The author thanks Kristina Thiel for assistance in manuscript preparation.

**Conflict of interest:** none declared.

**References**

Editorial


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CARDIOVASCULAR FLASHLIGHT

Cardiac sarcoma causing mechanical tamponade: a radiological dilemma!

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A 39-year-old gentleman presented with an acute cardiac tamponade secondary to a malignant sarcoma of the heart. He was admitted to a district general hospital 6 months earlier with a 2 L pericardial effusion. Cytological examination demonstrated a low background cellularity, with no malignant cells, and bacterial cultures were negative. He had a history of alcohol misuse with withdrawal seizures.

He was admitted with shortness of breath at rest, an elevated JVP and distant heart sounds on auscultation. Bedside echocardiogram demonstrated an 8 cm pericardial effusion causing external compression of the right atrium. Computed tomography suggested a large circumferential pericardial effusion that was compressing the cardiac structures (Panels A and B).

He underwent decompressive pericardiotensis but the drain eventually entered the RV when it failed to aspirate the radiologically suggested fluid; necessitating emergency surgery to remove the drain. On sternotomy an invasive cardiac tumour was found to have infiltrated through the pericardium with complete encasement of the heart. No differentiation could be made between heart muscle and tumour and therefore careful debulking of the tumour was performed to relieve the mechanical compression and to improve haemodynamics (Panel C). Histopathology confirmed an undifferentiated sarcoma comprising highly pleomorphic spindle-shaped tumour cells (Panel D).

Differentiation of an effusive constriction from a tumour with similar densities is extremely difficult on both CT and echocardiography. In non-emergent cases, one can proceed to cardiac MRI to aid in the differential diagnosis, but ultimately the management of such patients will be determined by the immediate clinical presentation.

doi:10.1093/eurheartj/ehv165

Online publish-ahead-of-print 5 May 2015