NOX4 Is a Janus-Faced Reactive Oxygen Species Generating NADPH Oxidase

To the Editor:

Hardly any chemical factor in biology serves only good or bad purposes in the body, and this is particularly true for some of the simplest biologically active molecules, the reactive oxygen species (ROS). As our understanding of their functions deepens, it is becoming apparent that ROS subserve both protective and damaging functions, depending on the actual reactive species, the amounts formed, and their subcellular locations.1–3 This Janus-faced role for ROS extends to their enzymatic sources and particularly applies to the only dedicated source of ROS, the NADPH oxidases. We were therefore surprised to read the article by Schröder et al in Circulation Research4 with the assertive title: “NOX4 Is a Protective Reactive Oxygen Species Generating Vascular NADPH Oxidase,” which implies that the NOX4 isoform in blood vessels always serves a “protective” function. We need to consider whether or not NOX4,5,6 should indeed be excluded from the general principle above and be regarded as always and entirely beneficial. The growing body of literature tells us that we should be more cautious than to paint NOX4 as a key signaling system that is universally cytoprotective or beneficial and NOX1 and 2 as negative counterparts.

First, NOX4 may not be universally beneficial. Although the authors present interesting evidence for previously unrecognized roles of NOX4 in 2 rodent models of cardiovascular disease, several other studies have reported a damaging influence of NOX4 in other disease models. Importantly, the data on a deleterious or pathological influence of NOX4 are neither cited nor discussed in sufficient detail in the Schröder article. For example, using NOX4 KO and transgenic animals, 2 independent studies suggest that NOX4 appears to play a major role in neurodegeneration after ischemia and reperfusion injury and thus could be a target for stroke therapy7,8; the latter study specifically portrays that it is endothelial NOX4 that mediates this detrimental effect on infarct size.8 Furthermore, in a severe and acute model of ventricular pressure overload (induced by thoracic aortic constriction) and a type 1 diabetes model, NOX4 appears to contribute to cardiomyocyte damage9 and diabetic cardiomyopathy.10 In contrast, in a less severe and subacute model of abdominal aortic banding, NOX4 facilitates angiogenesis and improves cardiac function.11 Thus, there appear to be mechanisms by which NOX4 can both harm and protect the cardiovascular system under stress. Moreover, deleterious roles for NOX4 have been shown for the induction of lung12,13 renal14 and cardiac fibrosis as well as heart failure.15 Even physiological vascular functions may not be regulated by NOX4 as simply as portrayed. Schröder et al report that NOX4 increases eNOS expression, suggesting enhanced NO-cGMP signaling. However, NOX4 also upregulates phosphodiesterases (PDE) 4A, B, and D, which increases hydrolysis of cAMP, a mechanism that might be central to vasculopathies associated with endothelial dysfunction,16 and as well inhibits NO in arterial smooth muscle of the prediabetic Zucker rat.17

Second, the inference that the NOX1 and NOX2 isoforms represent the vascular dark side of NADPH oxidases is not totally supported by the published literature. With respect to angiogenesis the literature is at least discrepant, with several proangiogenic effects reported for these isoforms as well.18–21 It is also unlikely that NOX1 and NOX2 have no physiological or beneficial functions in blood vessels, and, to their credit, Schröder et al acknowledge that other NOX proteins are “important for physiological signaling under normal conditions.”

In short, the results reported by Schröder et al are interesting but raise a lot of questions. We would argue that more studies on the role of NOX4 in different disease settings, using various animal models, are required to fully elucidate the likely diverse roles of NOX4. One of the most fascinating questions to answer may be why evolution has preserved such a potentially dangerous enzyme family. Based on the current published data, it seems that not only NOX4, but also NOX1 and NOX2, can be helpful in some settings and damaging in others.

Disclosures

None.

References


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