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 subserves 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 isoforms 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 therapy.7,8 The latter study specifically 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.

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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Harald H.H.W. Schmidt, Kirstin Wingler, Christoph Kleinschnitz and Greg Dusting

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