Letter to the Editor

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 In contrast, in a less severe and subacute model of ischemia–reperfusion injury, NOX4 appears to play a protective role.14,15

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 Schroeder article. For example, using NOX4 KO and transgenic animals, 2 independent studies suggest that NOX4 isoform in blood vessels always serves a “protective” function.16–20

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.21–24 It is also unlikely that NOX1 and NOX2 have no physiological or beneficial functions in blood vessels, and, to their credit, Schrör et al acknowledge that other NOX proteins are “important for physiological signaling under normal conditions.”

In short, the results reported by Schroeder 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.

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