Response to the Letter by Schmidt et al Regarding “Nox4 Is a Janus-Faced Reactive Oxygen Species Generating NADPH Oxidase”

To the Editor:

We thank Schmidt and colleagues for their letter and their interest in our work. We agree with their assessment that ROS have a Janus-faced character and that all NADPH oxidases bear the potential to produce excessive and thus harmful amounts of ROS. In fact, this is clearly mentioned in the discussion section of our study. There we state that excessive induction of Nox4 will probably be harmful, and we even refer to several of the papers quoted in the letter by Schmidt and colleagues.

The decision to choose a title that Schmidt et al consider “assertive” was the consequence of an intense discussion among the authors and also an aspect discussed with the reviewers of the manuscript. Although we all agree that excessive ROS may be harmful, it is a fact that the potential for beneficial effects of NADPH oxidase-derived ROS has been very poorly emphasized to date. We believe that more than 13 years after the discovery of the first Nox homologue, most papers have focused solely on harmful effects of these proteins. It may be necessary to rebalance this point of view, and if our choice of title promotes discussion of this very important issue, then it will have achieved its aim. Thousands of papers have been published linking Nox1, Nox4, and Nox5 to various pathologies but central questions remain unanswered. For Nox4 some of these are: Why is the vascular expression of Nox4 (on the mRNA level) so much higher than that of any other Nox homologues? Why is the enzyme greatly induced in vascular healing and recovery from injury? Why does Nox4 (different to Nox1 and Nox2) produce predominantly $H_2O_2$ rather than $O_2^{-}$ and does not scavenge NO? Why do endothelial cells express more Nox4 than other vascular cells under basal conditions?

We believe that these questions already suggest that Nox4 may have beneficial functions in endothelial cells. Indeed, we found evidence that Nox4 maintains endothelial NO synthase and heme oxygenase-1 expression, both producers of protective gaseous transmitters, especially in the setting of vascular stress.

For Nox1 and Nox2, we have learned over the years that they have functions in growth factor, cytokine, and hormone signaling. These effects, however, are not specific for the endothelium and generally come at the price of NO scavenging and peroxynitrite generation. For Nox4, in contrast, even if overexpressed, peroxynitrite generation does not occur. It is very tempting to speculate that this specific feature of Nox4 evolved to cope with its high endothelial expression and the large amounts of NO present in endothelial cells. Obviously, this also implies that the function of Nox4 in other systems may be different and this is why we stressed the “vascular” aspect in the title of our study. In line with this, studies on smooth muscle cells and fibroblasts have linked Nox4 to cellular differentiation and quiescence, again, rather protective features. In contrast, epithelial cells, which express little Nox4 under basal conditions, respond to its induction with apoptosis.

Despite this, we agree with the assessment of Schmidt and colleagues that more studies will be needed to define the range of functions of Nox4. We are in the lucky situation that for this particular NADPH oxidase, to our knowledge, at least 5 different knockout mice have been independently generated, leading to a broad experimental basis and consensus on its function. This information is urgently needed to make rational decisions on potential indications for isoform-selective Nox inhibitors.

In conclusion, the diverse reports on potential functions of Nox homologues not only ask for more experimental data but also for strong scientific opinions and vivid statements to categorize all the findings and to eventually distill a consensus interpretation on the true roles of this class of enzymes in our body. Highlighting the potential for Nox4 to exert significant protective effects in the vasculature is part of this process.

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References


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