## LETTER

## H<sub>2</sub>S and O<sub>2</sub> sensing

Oxygen-sensing cells in the carotid body, blood vessels, airways, and adrenal gland initiate vital homeostatic responses to hypoxia and hypoxemia. Inappropriate activity of these cells is associated with a variety of pathophysiologies, but despite intense research and obvious clinical applicability, there is no consensus regarding the oxygen sensor that directly couples oxygen availability to the eventual physiological response.

In the recent article "H<sub>2</sub>S mediates  $O_2$  sensing by the carotid body," Peng et al. (1) showed that the hypoxic responses of carotid bodies were significantly decreased in mice lacking cystathionine  $\gamma$  lyase (CSE), one of the enzymes involved in H<sub>2</sub>S biosynthesis. They also provided evidence for H<sub>2</sub>S-mediated hypoxic responses in both chemoreceptor and adrenal chromaffin cells. The authors state in their introduction that "given that carotid bodies are peripheral organs and that H<sub>2</sub>S is redox active, we hypothesized that CSE-derived H<sub>2</sub>S plays a role in hypoxic sensing by the carotid body"; in their discussion, they state that the "present study established a physiological role for H<sub>2</sub>S generated by CSE in mediating hypoxic sensing" (1). This leads the reader to believe that the authors have identified a novel oxygen-sensing mechanism. Actually, this is not a novel hypothesis (1).

Peng et al. (1) failed to cite that the concept of  $H_2S$ -mediated  $O_2$  sensing was first proposed by us (2) in 2006. In our model, tissue  $H_2S$  concentration is established by the simple balance between constitutive production and oxygen-dependent in-activation. In subsequent work (reviewed in ref. 3), we showed that  $H_2S$  and hypoxic responses were identical and that the latter could be blocked by inhibitors of  $H_2S$  biosynthesis. We measured  $H_2S$  production in many living tissues in real time

and showed that  $H_2S$  concentration was inversely related to tissue  $Po_2$  at  $Po_2s$  encountered during hypoxia. We also showed that  $H_2S$  was readily consumed by mitochondria, also at physiologically relevant  $Po_2s$ . Clearly, there was substantial evidence for  $H_2S$ -mediated  $O_2$  sensing before the study by Peng et al. (1).

Furthermore, Peng et al. (1) failed to acknowledge that we had previously shown H<sub>2</sub>S-mediated  $O_2$  sensing in fish chromaffin cells (4) and that these cells are homologous to the mammalian cells. In fact, the only reference to any of our papers was this brief sentence: "It is interesting to note that H<sub>2</sub>S has been demonstrated to mediate  $O_2$  sensing by the trout gill chemoreceptors, indicating that it is an ancient wellconserved system across phyla" (1). Actually, this is more than a phylogenetic curiosity. Not only did we present evidence fora H<sub>2</sub>S-mediated  $O_2$  sensing mechanism, we clearly pointed out that these chemoreceptors are homologous to, and the antecedent of, mammalian chemoreceptors (5). In our opinion, our work established the precedent for H<sub>2</sub>S-mediated  $O_2$ -sensing mechanisms in both chemoreceptors and chromaffin cells.

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