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Invited Commentary

Catalase as a regulator of reactive sulfur metabolism; a new interpretation beyond hydrogen peroxide☆

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Anti-oxidant cellular defenses have typically been considered an obligatory protective response to the Great Oxidation Event (GOE) some 600 million years ago. However, recent evidence suggests that the earliest forms of Life arose sometime between 3.7 and 1.9 billion years ago, long before the GOE [1,2]. The earth's environment during the Arachean and Proterozoic periods contained ferrunginous followed by euxinic oceans characterized by anoxic and sulfidic conditions [3]. Intriguingly, ancient forms of Life, such as arachea prokaryotes, contain anti-oxidant defense enzymes such as catalase that actively decomposes peroxide to water, its presumed primary function [4]. What then would be an evolutionary purpose for selecting peroxidase activity in an organism existing in an anoxic, sulfidic environment long before the abundance of oxygen?

Recent work in the field of hydrogen sulfide chemical biology and its associated metabolites has revealed a rich and complex role of reactive sulfur species (RSS) in regulating numerous cellular oxidation/reduction responses including respiration, signal transduction, gene expression, cell proliferation and death [5]. However, questions remain regarding how sulfide metabolism is regulated in various tissues and under different conditions. The report by Olson and colleagues sheds important new light on the evolutionary question above with the finding that catalase functions not only as a peroxidase to metabolize reactive oxygen species (ROS), but also as a highly effective sulfide-sulfur oxido-reductase regulating RSS metabolism. The authors also provide clear evidence that catalase 'dual' functions depend on both biochemical substrate and environmental conditions [6].

The results from this study are surprising and profound for an enzyme that has classically been attributed to detoxification of peroxide. The data reveal that catalase oxidizes hydrogen sulfide under normoxic conditions, but reduces sulfane sulfur under hypoxia. Interestingly, catalase was found to reduce a wide range of sulfane sulfur species such as dithiothreitol (DTT), garlic oil, diallyl trisulfide (DATS), thioredoxin (Trx), and sulfur dioxide (SO_2). These data suggest that catalase serves as an important sulfide oxidase under normoxic conditions where the action of sulfide would be less desirable or harmful; but acts as a sulfane reductase to generate hydrogen sulfide under hypoxic conditions, which could stimulate cytoprotective responses. However, a limitation of the current study was use of high concentrations of RSS species beyond what has previously been reported in vivo using precise analytical methods [7–10].

Nonetheless, the molecular and cellular physiology implications of this discovery are significant. These findings indicate that catalase might serve as an alternative regulator of hydrogen sulfide production under different oxygen tensions with a predominant oxidase function under normoxic conditions but a sulfur reductase function at hypoxic conditions. This suggests that sulfide quinone reductase (SQR) may not be the only catabolic pathway for hydrogen sulfide metabolism, which could be important in mitigating its toxicological effects. Conversely, catalase may serve as an important sulfane reductase during hypoxia leading to increased hydrogen sulfide levels that would be cytoprotective through various signal transduction, apoptosis, and cell proliferation pathways [5]. The potential role of catalase as a key regulator of these chemical biology responses is underscored by the fact that catalase single nucleotide polymorphisms (SNP's) are associated with chronic disease states influenced by hydrogen sulfide, such as cancer and metabolic disorders [11–13]. However, the impact of these SNP's on catalase sulfide oxidase or sulfur reductase activity requires further study. Moreover, this finding provides an alternative mechanism that may explain catalase protective mechanisms given that hydrogen peroxide reactivity and abundance may be less that previously reported [14,15]; especially as a recent report from the Olson laboratory has convincingly shown that RSS robustly react with known ROS detectors and dyes [16].

As would be expected, these fascinating results lead to many more questions, such as: How prominent is catalase sulfide oxidase activity versus other known sulfide metabolism pathways such as SQR? To what extent does catalase sulfur reductase activity contribute to cellular hydrogen sulfide protection compared to other hydrogen sulfide generating enzymes (e.g. CSE, CBS, or 3-MST)? Which catalase dependent metabolic reactions predominant between reactive oxygen or sulfur species under normoxic or hypoxic conditions? Is catalase enzyme activity important in regulating sulfide/sulfur metabolism during disease states of differential oxygen tensions? Future studies will answer these and many other questions, yet this initial study

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provides provocative and exciting insight into new concepts of redox biology beyond reactive oxygen metabolism.

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