



# Introduction to the Thematic Minireview Series: Redox metabolism and signaling

Published, Papers in Press, August 24, 2017, DOI 10.1074/jbc.R117.814160

Ruma Banerjee<sup>1</sup>

From the Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan 48109-0600

Edited by Chris Whitfield

Life on oxygen predisposes cells to reactive oxygen species (ROS) generation by electron slippage in the electron transfer chain. Aerobic metabolism also generates superoxide ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ) as *bona fide* products in reactions involving 1- or 2-electron reduction of  $O_2$ . Although often viewed as dangerous, ROS are now recognized as important messengers in redox signaling pathways. A delicate balance between needed *versus* excessive ROS production distinguishes health from an array of disease states. A collection of provocative reviews in this thematic series discusses the relative importance of mitochondrial sites for ROS production, ROS signaling-mediated regulation of cellular stress responses and thermogenesis, and how  $O_2$  deficiency leads to metabolic reprogramming in cancer.

In the first review, Wong, Dighe, Mezera, Monternier, and Brand (1) describe the mitochondrial sites of  $O_2^-$  and  $H_2O_2$  generation under different bioenergetics conditions. Experiments with isolated mitochondria have led to estimates of the magnitude and relative contributions of seven sites in the electron transfer chain to  $O_2^-/H_2O_2$  production. These vary with the substrate being oxidized and with conditions simulating rest *versus* mild or intense exercise. Under the conditions tested, succinate was the most prolific inducer of  $H_2O_2$  production and ~5-fold higher than palmitoylcarnitine/carnitine or glutamate/malate. Determining the relevance of these observations to intact cells and tissues is an important gap that remains to be filled, as is elucidating the modulation of mitochondrial ROS<sup>2</sup> production in the context of caloric restriction and pathological states. To this end, the development of tools such as small molecule inhibitors that suppress site-specific electron leakage promises to move studies away from isolated mitochondria to intact cells.

In the second review, Chouchani, Kazak, and Spiegelman (2) discuss the role of ROS signaling in regulating thermogenesis with a focus on uncoupling protein 1 (UCP1), which dissipates the mitochondrial proton motive force, generating heat. The

authors elegantly describe the challenges associated with faithful modeling of ROS signaling in experimental systems, as well as ascribing the precise ROS involved in driving a physiological response via modification of specific cellular targets. In the case of thermogenesis, elevated  $O_2^-$  or a general oxidative shift in thiol redox metabolism, be it via Nrf2 (nuclear factor-erythroid 2-related factor), isocitrate dehydrogenase 2, or superoxide dismutase 2 ablation, activates UCP1. This redox effect is transduced in part via sulfenylation of a specific cysteine that sensitizes UCP1 to activation by fatty acids during adrenergic stimulation of thermogenic respiration. The molecular details of how redox signaling, metabolism, and gene expression converge to activate the thermogenic program await further elucidation.

Focused on the Keap1 (Kelch-like ECH-associated protein 1)–Nrf2 system, the third article, by Suzuki and Yamamoto (3), describes this major axis of cellular oxidant and stress response. In this protein pair, Nrf2 is a transcriptional factor that induces cytoprotective gene expression and represses inflammatory cytokine gene transcription. Keap1 is a Nrf2 regulator and sensor of oxidative and electrophilic stress. Keap1 marks Nrf2 for proteasomal degradation, albeit only in the absence of stress, and loses this control when it is itself marked by oxidants or electrophiles. Modification of a critical cysteine residue in Keap1 in response to various electrophiles is implicated in modulating ubiquitination of Nrf2. However, the picture is not quite so simple as other cysteines on Keap1 can also be targeted, revealing a possible “cysteine code” that allows for a nuanced response to various chemical and oxidative insults. Mouse models of Nrf2 hyperactivation (by Keap1 gene disruption) reveal a wider role for this stress-response system in organismal homeostasis and in cell fate determination.

In the final article in the series, Xie and Simon (4) discuss the broad impacts that  $O_2$  insufficiency has on metabolic reprogramming in cancer cells, which is mediated in large part by hypoxia-inducible factor (HIF). Under hypoxic conditions, diminished  $O_2$ -dependent hydroxylation of HIF stabilizes it against proteasomal degradation and induces transcription of a massive gene set. Rewiring of central carbon metabolism and other major metabolic arteries ensues through up-regulation of transporters and enzymes. The effect of HIF on glucose metabolism appears to be a two-way street. Although HIF induces an adaptive transcriptional response, it is in turn regulated by direct protein–protein interactions with some gene products whose synthesis it induces, *e.g.* pyruvate kinase M2. HIF regulates  $O_2$  metabolism by both direct and indirect means. Thus, HIF down-regulates several components of the electron trans-

This work was supported by National Institutes of Health Grants DK45776, HL58984, and GM112455 (to R.B.). The author declares that she has no conflicts of interest with the contents of this article. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

<sup>1</sup> To whom correspondence should be addressed: 4220C MSRB III, 1150 W. Medical Center Dr., University of Michigan, Ann Arbor, MI 48109-0600. Tel.: 734-615-5238; E-mail: rbanerje@umich.edu.

<sup>2</sup> The abbreviations used are: ROS, reactive oxygen species; HIF, hypoxia-inducible factor.

This is an open access article under the [CC BY](#) license.

16802 *J. Biol. Chem.* (2017) 292(41) 16802–16803



fer chain, directly impacting O<sub>2</sub> consumption. HIF also inhibits pyruvate dehydrogenase via up-regulation of an inhibitory kinase. This disconnects glycolysis from oxidative mitochondrial metabolism and suppresses ROS production. The review concludes by discussing HIF-independent metabolic adaptations to low O<sub>2</sub> tension. For instance, hypoxia-induced acidification, as well as subsequent promiscuous activation of lactate dehydrogenase, leads to enhanced synthesis of L-2-hydroxyglutarate. Like the oncometabolite D-2-hydroxyglutarate, the L-isomer is an inhibitor of histone demethylases and leads to epigenetic dysregulation.

**References**

1. Wong, H.-S., Dighe, P. A., Mezera, V., Monternier, P.-A., and Brand, M. D. (2017) Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions. *J. Biol. Chem.* **292**, 16804–16809
2. Chouchani, E. T., Kazak, L., and Spiegelman, B. M. (2017) Mitochondrial reactive oxygen species and adipose tissue thermogenesis: Bridging physiology and mechanisms. *J. Biol. Chem.* **292**, 16810–16816
3. Suzuki, T., and Yamamoto, M. (2017) Stress-sensing mechanisms and the physiological roles of the Keap1–Nrf2 system during cellular stress. *J. Biol. Chem.* **292**, 16817–16824
4. Xie, H., and Simon, M. C. (2017) Oxygen availability and metabolic reprogramming in cancer. *J. Biol. Chem.* **292**, 16825–16832