



Introduction to the Thematic Minireview Series: Redox metabolism and signaling

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In this sequel to the thematic collection of Minireviews on redox metabolism and signaling published last year, five articles plumb the redox metabolic pathways relevant to cell proliferation, stress response, and survival post-detachment from the extracellular matrix. The sixth article provides unexpected insights into the hepatic NAD(P)ome, revealing that more than half of these proteins reside outside the cytoplasmic and mitochondrial compartments, pointing to the paucity of knowledge on their functions. Collectively, these articles highlight the metabolic adaptability of proliferating cells to meet redox needs, the use of lipids to mediate mitochondrial stress responses, and the need for tools to interrogate compartment-specific pool sizes and oxidized/reduced ratios of antioxidants and lipids involved in redox homeostasis.

In the first review (1), Hosios and Vander Heiden discuss the integration of redox cofactor requirements with metabolic activity needed to support mammalian cell proliferation. Biomass synthesis during cell proliferation requires redox equivalents to convert nutrients to lipids, proteins, and nucleotides. The NAD⁺/NADH and NADP⁺/NADPH ratios are tightly regulated to serve their primary roles in nutrient oxidation and biosynthesis, respectively. Transamination reactions, although redox-neutral, link to the cellular redox status, interconverting the more oxidized keto to the less oxidized amino acid. One-carbon metabolism connects amino acid, redox, and nucleotide metabolism and is key to sustaining proliferation. This excellent overview of metabolism from a redox perspective highlights the metabolic adaptability of proliferating cells to nutrient availability and growth conditions.

In the second review (2), Kong and Chandel discuss mechanisms for regulating reactive oxygen species (ROS)² in cancer and T cells, which interact in the context of antitumor immunity. The mitochondrial electron transfer chain and NADPH oxidases are the major sites of ROS generation. A host of factors, including metabolic activity and cellular signaling path-

ways, can activate ROS production, while an army of antioxidant defenses, localized in all the major cellular compartments, counters ROS. Paradoxically, cancer cells exhibit expanded pro- and antioxidant capacity induced by mutations in oncogenes or tumor suppressors. The spatiotemporal control of pro-tumorigenic ROS signaling with concomitant protection of collateral oxidative damage of cellular targets is poorly understood. ROS signaling is also crucial for T cell activation and expansion, as is an enhanced capacity to limit ROS-dependent damage at distal sites. The review concludes with a discussion of the therapeutic potential of antioxidants with spatial and temporal targeting in immune and/or cancer cells.

In the third review (3), Goodman, Calvo, and Mootha discuss challenges with studying the spatiotemporal compartmentalization of NAD(P)H metabolism. The paucity of information on compartment-specific pyridine nucleotide pool sizes and their oxidized/reduced ratios limits interpretation of redox metabolic data. Using bioinformatic analysis, the authors report a set of 426 NAD-linked gene products, of which 352 are expressed in human or murine liver. A subset of these enzymes, which are involved in NAD(P)⁺ biogenesis, is highly enriched in liver, suggesting a role for this organ in systemic NAD(P) metabolism. Surprisingly, less than half (~40%) of the hepatic NAD(P)ome is predicted to localize to the cytosol or mitochondria, with organelles such as the nucleus, peroxisome, and endoplasmic reticulum hosting a number of these proteins. Overlay of the NAD(P) proteome data with transcriptome datasets reveals differential gene expression between fasting *versus* feeding states and during the circadian cycle. The development of genetic tools for measuring and modulating pyridine nucleotide pools and their reduced-to-oxidized ratios is opening doors to distinguishing whether they drive or merely report on metabolic changes and to determine their roles in disease.

In the fourth review (4), Nielson and Rutter discuss the involvement of lipids in mitochondrial stress signaling pathways. Diverse functions ranging from protein complex assembly and electron transfer activity to mitophagy are regulated by lipids. In response to damage, cardiolipin relocates from its almost exclusive presence in the inner to the outer mitochondrial membrane where, together with ceramide, it recruits autophagosomes for mitophagic elimination of mitochondria. Ceramides are also implicated in apoptosis, forming stable outer membrane channels with BAX and allowing escape of cytochrome *c*. Sphingosine 1-phosphate in complex with prohibitin, a mitochondrial chaperone, is important for assembly of complex IV. Oxidation of ergosterol in the outer membrane

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² The abbreviations used are: ROS, reactive oxygen species; ECM, extracellular matrix; TCA, tricarboxylic acid.

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to its peroxide derivative induces mitochondrial associated protein degradation via recruitment of the VMS1–CDC48 complex or the ribosome quality control system. Technological advances that enable identification of lipid–protein interactions and assessment of lipid abundance and localization will continue to shape our nascent understanding of how lipids mediate cell signaling.

In the fifth review (5), Solmonson and DeBerardinis discuss the understudied role of lipoate-dependent 2-ketoacid dehydrogenases in both modulating and being modulated by mitochondrial redox metabolism. The mitochondrial lipoate-dependent multienzyme complexes, pyruvate dehydrogenase, branched chain amino acid dehydrogenase, 2-oxoadipate dehydrogenase, and α -ketoglutarate dehydrogenase, generate products, *i.e.* acetyl-CoA or succinyl-CoA, which are TCA cycle intermediates. Hence enzymatic reactions dependent on lipoate, which is derived from the octanoic acid, link fatty acid synthesis to the oxidative capacity of the TCA cycle. The FAD-containing E3 subunit (dihydrolipoamide dehydrogenase) regenerates reduced lipoate and is shared between the various 2-ketoacid dehydrogenases. E3 activity is sensitive to the mitochondrial NAD^+/NADH ratio, and electrons can leak from FADH_2 to O_2 , forming superoxide when NAD^+ levels are low. ROS production is reversibly inhibited by glutathionylation of the lipoyl moiety in the E2 subunit. Interaction of the E3 subunit with thioredoxin 2 links the activities of these dehydrogenases to yet another cellular redox system.

In the sixth review (6), Hawk and Schafer discuss the pertinence of redox metabolism to survival of cancer cells detached from the extracellular matrix (ECM). Successful metastasis

relies upon evasion of cell death by anoikis, autophagy, or entosis. Detachment from the ECM induces a variety of metabolic changes that impact ROS levels. Depending on the oncogenic background, ROS can promote or inhibit survival of ECM-detached cells. Antioxidants such as NADPH, ascorbate, and GSH, as well as antioxidant systems such as thioredoxin, superoxide dismutase, and NAD(P)H-quinone oxidoreductase-1, can contribute to anchorage-independent survival. Furthermore, amino acid metabolism (*e.g.* proline catabolism, glutamine-dependent reductive carboxylation, and serine-dependent one-carbon metabolism) also modulates cellular redox capacity. Much remains to be learned about the contributions of these redox metabolic pathways to driving the metastatic cascade and promoting survival of cancer cells.

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