Introduction to the Thematic Minireview Series

REDOX SENSING AND REGULATION

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The cache of coupled reduction-oxidation (i.e. redox) reactions in mammals is ultimately enabled by the cellular nicotinamide currency, i.e. the NAD+/NADH and NADP+/NADPH redox couples. Oxidative metabolism, which results in the capture of reducing equivalents primarily as NADH, represents capital investment, while biosynthetic reactions, which utilize NADPH, represent expenditures. From the central nicotinamide warehouse, conversion to alternative currencies diversifies the cellular energy portfolio. The mitochondrial membrane is the site of currency conversion to ATP, which occurs via the electron-transfer chain and involves a four-electron reduction of oxygen to water. The oxidative-phosphorylation process is, however, leaky, and reactive oxygen species (ROS), representing incomplete oxidation products of this pathway, are side products. ROS are also generated at other loci, such as NADPH oxidase, by metabolic enzymes, such as lipoxygenase, and in response to extracellular signals, such as growth hormones and cytokines. Long viewed as noxious, ROS are produced in a controlled manner that is now recognized as critical for signaling within and between cells. ROS are crucial for regulating such processes as cell division, circadian rhythms and the immune response. On the other hand, uncontrolled ROS levels spell death.

The intracellular redox “climate” is varied and influenced by multiple regulators. In the cytoplasm, protein regulators such as thioredoxin and small-molecule antioxidants such as glutathione and cysteine maintain distinct redox potentials, revealing that the various redox nodes are not in equilibrium with each other (1). Within organelles, the potentials of the very same redox couples vary; the redox poise setting is more oxidizing in the endoplasmic reticulum but more reducing in the mitochondrion, for instance. Outside the cellular “box,” i.e. in the extracellular space, the redox environment is far from fully oxidized and inert as commonly supposed. Instead, it is dynamically shaped by intracellular redox metabolism and is the subject of the minireview by Ruma Banerjee (2).

Redox changes are sensed and relayed by various cellular transducers. Protein redox sensors such as thioredoxin and peroxiredoxin play important roles in this regard and are responsive to redox changes by virtue of reactive cysteines. A conserved cysteine in peroxiredoxins is oxidized by hydrogen peroxide to form a sulfenic acid. While the peroxidase activity confers an antioxidant function, interactions with other proteins that are intrinsically less sensitive to oxidation, e.g. those involved in oxidative protein folding in the endoplasmic reticulum, confer a peroxide sensor function to peroxiredoxins. The minireview by Sue Goo Rhee and co-workers discusses the role of peroxiredoxins in peroxide regulation and signaling (3).

The modification of reactive cysteine residues with nitric oxide gives S-nitrosocysteine. This reversible post-translational modification has pleiotropic effects in cellular signaling pathways and overlaps in some instances with other central mechanisms for signal transmission, e.g. phosphorylation and ubiquitylation. Regulation of protein function by S-nitrosylation is the subject of the minireview from Jonathan Stamler’s group (4).

Cysteines are not particularly abundant in proteins and at physiological pH not particularly reactive. Hence, the use of cysteines for sensing and signaling changes in cellular redox state rely on mechanisms for modulating their reactivity in protein microenvironments. The physicochemical properties of and computational
methods for identifying reactive cysteines at a genomewide level are the subject of the minireview from Vadim Gladyshev’s laboratory (5). The article also includes discussion of bioinformatics approaches for identifying reactive cysteines and predicting their functions in metal binding, structure stabilization, regulation or catalysis.

Finally, two minireviews focus on aspects of redox regulation in the mitochondrion. The majority of mitochondrial proteins synthesized in the cytosol and destined for the intermembrane space lack an N-terminal leader sequence. Instead, these proteins are imported by an oxidation-driven mitochondrial disulfide relay reaction. This disulfide relay apparatus is functionally related to the disulfide bond system of the bacterial periplasm, but is structurally distinct and is the subject of the minireview from Johannes Herrmann’s laboratory (6). The mitochondrion is a hotbed of ROS production used for signaling and regulation of diverse biological activities. Toren Finkel reviews the role of mitochondrial oxidants in the hypoxic response, in regulation of autophagy, in stem-cell self-renewal capacity and in innate immunity (7).

In summary, the six minireviews in this issue provide glimpses into the field of redox sensing and regulation. They illustrate how redox potential setting at a compartmental level is important for enabling/disabling cellular functions and, at a molecular level, reveal that a battery of sensors and carriers convey redox information within signaling networks.

References

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