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Special issue: Redox regulation of protein folding

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Thiol groups of cysteine residues are of outstanding physiological relevance for many biological reactions: They coordinate structurally or catalytically important metal ions, such as zinc, copper, and iron; they are involved in the binding of iron sulfur clusters or heme cofactors; and they function as covalent attachment sites of prenyl anchors. Presumably the most important feature of cysteine residues, however, is their unique ability to form intra- or intermolecular disulfide bridges. This ability is of considerable significance for protein folding processes as well as for the dynamic regulation of protein structures in response to changes in cellular redox conditions. Because the function of many proteins is strictly dependent on the redox state of their cysteine residues, a large number of cellular components that are dedicated to precisely control the redox status of these thiol groups have evolved.

Every cellular compartment harbors specific sets of proteins, such as the thioredoxin and glutaredoxin systems, and small molecules that control the redox state of cysteine residues. While the redox components of some bacteria and eukaryotic organelles are relatively well characterized, the redox biology of other compartments remains largely enigmatic. This is well illustrated in mitochondria, where a disulfide relay machinery responsible for catalyzing the oxidation of cysteines in polypeptides has only very recently been discovered in the intermembrane space. The oxidation reaction is kinetically and functionally coupled to the import of newly synthesized proteins across the mitochondrial outer membrane. Although the principle of protein oxidation presumably has been conserved during the evolution from the bacterial periplasm to the mitochondrial intermembrane space, the individual components appear to be unrelated and might differ considerably in their characteristics. It has been proposed that, in addition to its role in protein import, the mitochondrial disulfide relay machinery is used to sense the concentrations of oxygen or oxygen radicals in mitochondria. This proposed regulatory function of thiol oxidation in mitochondria has yet to be tested experimentally.

The increasing role that thiol modifications play as regulatory components in protein structures becomes particularly apparent in plastid proteins. In chloroplasts, the function of many cysteine-containing proteins is reversibly regulated by the redox status of their cysteines and controlled by light-dependent mechanisms. This sophisticated regulation allows chloroplasts to tie redox-mediated functional changes of a variety of different reactions to photosynthetic activity, which leads to entirely different metabolic regimes in plastids during day and night. Other proteins using oxidative thiol modifications to control protein structure and activity have now been also reported to be present in the cytosol and nucleus. Many of these redox-regulated proteins play a role in protecting cells against the lethal effects of oxidative stress.

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This special issue of BBA focuses on the various redox machineries, their specific properties and physiological relevance. The first section highlights the oxidation machinery of the bacterial periplasm. Periplasmic redox components are well studied and understood at high resolution. Extensive biochemical, biophysical, and structural studies over the past few years have provided fascinating insights into the molecular processes controlling the redox state of thiol groups in bacteria. The second part focuses on the endoplasmic reticulum, which contains presumably the most complex system(s) to introduce and isomerize disulfide bonds in eukaryotic proteins. Many different redox proteins cooperate in the folding of a large number of different secreted proteins in an oxidation-driven process. This process is complicated by the fact that secreted proteins often contain numerous cysteine residues, which need to be correctly connected and involve a complex thiol-disulfide reshuffling process. The third section is dedicated to protein oxidation in mitochondria and chloroplasts, focusing on the components that mediate protein oxidation in these organelles as well as on the different substrates oxidized by these systems. Last but not least, the fourth section describes how the oxidation of proteins can be used to regulate protein functions in the cytosol and the nucleus. Recent studies indicate that the functions of glutaredoxins and thioredoxins are not limited to the simple reduction of cysteine residues but that they play active roles in a variety of different biological processes.

With these five sections, we tried to cover many of the exciting aspects of redox biology. However, we are aware that these articles can only provide a snapshot of the rapidly expanding field of thiol oxidation. It is our pleasure to thank the authors, the referees, and the staff of Elsevier for their invaluable work that made this issue possible.