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Forum Editorial

Redox Control of Protein Processing: From Electrons to Cells

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OXIDATION AND REDUCTION are fundamental chemical reactions, both of which take place always simultaneously; if one molecule is oxidized, its reaction partner must be reduced. Although different side-chains of amino acids could be subject to oxidation under certain conditions, it is cysteine that actively participates in physiological redox reactions of various kinds. Thus, all the reactions of "redox control of protein processing" discussed in this forum issue involve cysteines, whose extraordinary reactivities are introduced by an excellent review by Leichert and Jakob in this issue (9), who summarize proteomic approaches to identifying cysteine modifications of cellular proteins.

Oxidation/reduction occurs so ubiquitously and spontaneously in conjunction with a number of small molecules, including air oxygen and its reactive species. Although proteins are susceptible to such nonspecific redox reactions, recent progress in the studies of proteinaceous redox mediators have revealed that physiological redox reactions proceed in very specific ways without undergoing extensive "cross talks." Although this forum issue only partly covers the diverse redox processes that occur in biological kingdoms, we nevertheless see, from those discussed in this volume, that cells are equipped with a myriad of redox networks wired by specific protein interactions. Sometimes, the direction of the electron flow could be determined upon such interactions that modulate redox properties of individual components. On the other hand, intrinsic potential of each biological molecule to react with oxidizing or reducing agents means that we can face a pitfall of looking into a fortuitous triviality, when it comes to redox biology. It is important to sort out between specific and nonspecific outcomes when we analyze redox processes and also to determine causal relationships among them. In this regard, genetically tractable microorganisms provide model experimental systems, in which we can pursue logical and integrated approaches more easily, while dealing with complex, versatile, and yet precise processes of oxidation/reduction-based cellular events. Incidentally, all the articles in this forum turned out to be focused primarily on studies using microorganisms.

Cellular environments of proteins are actually buffered by small molecule redox-active compounds, the glutathione–glutathione disulfide couple in most cases, which is also utilized by specific proteins to modify some cysteine residues. Thus, Masip *et al.* (11) summarize many faces of glutathione in bacteria. The cytosolic compartments of both prokaryotes and eukaryotes are kept reducing by the actions of NADPH-linked reductases and thioredoxin/glutaredoxin systems, which could be extended to the nucleus of the eukaryotic cell. One important role of these reducing factors is to activate ribonucleotide reductases as discussed by Gon and Beckwith (2) and experimentally examined by Gon *et al*. (3) in this forum. Thus, redox processing of protein has fundamental roles in the replication and maintenance of the DNA-based genome, by providing adequate levels of its building blocks, deoxyribonucleotides, in the cell. It is remarkable that such regulation is so important that DnaA, a crucial replication initiation protein, is recruited as a repressor of synthesis of a ribonucleotide reductase in *E. coli* as introduced here by Gon and Beckwith (2).

Cellular oxygen levels and oxidative stresses are sensed by a number of different mechanisms, leading to altered gene expression as well as altered protein reactivities. Thus, the Arc two-component system regulates a huge variety of cellular processes, either positively or negatively, according to the cellular oxygen concentrations as discussed by Malpica *et al*. (10) in this volume. It is remarkable that ubiquinone acts as a sensor of aerobiosis, thus leading to a disulfide bond formation between the membrane-bound ArcB cytosolic domains and to the inactivation of its kinase.

Introduction of disulfide bonds into proteins is a major subject in the redox processing of proteins. The occurrence of many different ways of disulfide bond formation as addressed by a number of articles in this forum has been introduced and discussed by the co-editor, Kadokura (7). I would like to add a very recent development by Inaba *et al*. (6), who proposed that the *de novo* formation of a disulfide bond by DsbB is mediated by a charge transfer and an adduct complexes between a thiolate anion form of a particular cysteine residue and

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ubiquinone, stabilized by a nearby residue having a positive charge. Similar mechanism may also be operative for FAD-containing Erv1 in the mitochondrial intermembrane space (4, 8) and possibly by Erv2/Ero1 in the ER (12). Whether ArcB uses similar mechanism on the cytosolic side also remains to be seen.

The peculiar maturation processes of superoxide dismutase, involving chaperone-dependent metal loading and disulfide bond formation, are discussed by Furukawa and O'Halloran (1) and introduced by Kadokura (7) in the context of disulfide bond formation. The importance of this enzyme's proper maturation is shown by the disease, ALS, caused by its failure (1).

The importance of metals in the redox biochemistry is introduced by Ilbert *et al*. (5), who also give an excellent overview of oxidative stress responses followed by description of what are known about molecular and structural mechanisms as well as cellular functions of Hsp33, a redox-controlled chaperone. It is remarkable that this chaperone is activated by oxidation to substitute for the general chaperone, DnaK, that is inactivated by oxidative stresses. Undoubtedly, this is one of the best-characterized redox regulation systems.

In conclusion, the articles here indicate the importance of basic and thorough studies of a system to obtain integrated knowledge at the levels of quantum chemistry to supramolecular interaction with other systems in the cell. Such approaches will be beneficial eventually for the medical and industrial applications of the knowledge thus accumulating.

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