

Book Review

Redox Regulation of Cell Signaling and Its Clinical Application

Reviewed by EDA T. BLOOM

OXIDATION-REDUCTION (REDOX) REACTIONS are, quite simply, essential to life. At the same time, oxidative stress has been implicated in aging and in the etiology of cancer, cardiovascular disease, and a host of other pathological states. The understanding of redox systems and how redox-based mechanisms regulate cellular functions is key to the eventual understanding of human health and disease. The new volume, *Redox Regulation of Cell Signaling and Its Clinical Application* (Marcel Dekker, New York, 1999; 328 pages), edited by Lester Packer and Junji Yodoi, is one of a series titled, "Oxidative Stress and Disease" (series editors: Lester Packer and Enrique Cadenas). It includes up-to-date information on redox reactions, especially as they pertain to gene transcription. Special attention is given to sulfhydryl-containing compounds, because free thiol groups are involved in multiple crucial cellular processes including catalysis and phosphorylation.

Redox Regulation of Cell Signaling and Its Clinical Application includes twenty-two chapters, written by eminent scientists in the area of redox regulation of signal transduction, in a little more than three hundred pages. Many of the chapters are succinct reviews and often include useful diagrams that summarize pathways or mechanisms in a clear and concise fashion. Others present new research data relevant to redox regulation of signaling. Overall, the book provides a well-balanced group of chapters, dealing with subjects ranging from basic biochemistry to clinically relevant subjects. Signal transduction and gene regulation are addressed in a number of chapters with specific reference to redox regulation, while other chapters discuss redox regulation per-

taining to different physiologic systems or pathologic conditions.

The volume places strong emphasis on a group of thiol-containing natural antioxidants including thioredoxin, glutaredoxin, and peroxiredoxin. Interest in these biological reductants has markedly increased over the past several years, and this volume provides a succinct introduction and updated current knowledge. This is especially true for information on thioredoxin, an evolutionarily conserved protein with two redox-active cysteines. Thus, nearly half of the twenty-two chapters discuss various inter-related aspects of the signaling and biology of the thioredoxin system. Sasada and Yodoi provide a brief yet informative review of thioredoxin as a response to cellular stresses and in the redox control of cell growth and death. Signaling pathways regulated by thioredoxin are also briefly discussed. Qin, Clore, and Gronenborn review the structure of human thioredoxin, and how the structure relates to formation of complexes with certain target molecules, such as another redox protein, Ref-1, and the multifunctional transcription factor, nuclear factor (NF)- κ B. In a later chapter by Hirota *et al.*, data are presented suggesting that the transcriptional activity of nuclear factor AP-1 is regulated by a direct association between thioredoxin and Ref-1. Okamoto, Yoshida, and Tetsuka further review the regulation of NF- κ B by thioredoxin by redox dependent mechanisms. The review is an excellent synopsis of a complicated area and includes a particularly informative diagram. Finally, Holmgren reviews the redox regulation and mechanisms of thioredoxin, including thioredoxin reductase, as well as that of glutaredoxin.

Additional chapters present practical, applied, or clinically relevant material pertaining to thioredoxin. Del Val and colleagues present information about thiolcalsin, an apparently uniquely thioredoxin-dependent protease. These authors further suggest potential ways in which thioredoxins might find technological use, such as for improving human foods. Tanaka *et al.* present new data regarding the possible effect of thioredoxin in protection against pathological processes, in this case, in mice treated with the renal carcinogen nitrilotriacetate. Miyazaki and colleagues provide data suggesting increased serum thioredoxin levels in human patients with hepatocellular carcinoma. In the process of performing their study, the authors developed and used a new enzyme-linked immunosorbent assay (ELISA) for thioredoxin, but point out that the new assay may provide different results in normal controls than data presented by previous authors.

Peroxiredoxins constitute another group of natural antioxidants. Chae, Kim, and Kim discuss the peroxiredoxins, and the relationship of these molecules to signal transduction, while giving special attention to thioredoxin peroxidase, a novel antioxidant enzyme. The oxidative stress-induced expression of MSP23, a mammalian peroxiredoxin, is discussed by Sato, Ishii, and Bannai.

Other biochemical mechanisms in the redox regulation of gene transcription and other signaling pathways are discussed in further chapters. Kuge and Nomoto present data in a study of the regulation by oxidative stress of the transcription factor γ AP-1, an AP-1-binding protein, in *Saccharomyces cerevisiae*. Ohno *et al.* discuss redox regulation of transcription factors and provide data on the role of cysteines in the Runt domain family, a family of phylogenetically highly conserved nuclear factors. Using cells of the immune system as a model, the chapter by Nakashima *et al.* provides both data and a review of redox events in signal transduction, including a discussion regarding genetically controlled and conformation-oriented or environmentally regulated and redox-oriented signaling switches.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are mentioned, partic-

ularly as cellular stressors, throughout the volume. There are at least two chapters that discuss these moieties with major emphasis. Fujii and Taniguchi provide a very nice review, with multiple informative diagrammatic summaries, of specific known or hypothetical effects of these oxidants in selected enzymatic pathways, including glycation and apoptosis. The chapter by Gamou *et al.* elaborates on their earlier observation that reactive oxygen, produced by various means, enhances phosphorylation of the epidermal growth factor (EGF) receptor, thereby activating the receptor.

Mechanisms of lipid oxidation have been studied for some time because of potential involvement in key cellular processes including senescence and death. Two chapters include processes related to lipid oxidation as a major theme. Sen and Packer provide a concise review of redox regulation by α -lipoic acid, which can be used as a therapeutic tool to alter intracellular thiol redox status. They compare the potential clinical relevance of α -lipoic acid with that of N-acetyl-L-cysteine. Uchida and Osawa present data regarding the cellular response to lipid peroxidation products in response to glutathione transferase induction.

Other chapters in the book focus more on the role of redox regulation in particular physiologic systems. Tanaka *et al.* present data on the interaction of glucocorticoid hormone action and the glucocorticoid receptor with cellular antioxidants. Special attention is given in this chapter, too, to thioredoxin as an important cellular reducing agent. Smith, Sayre, and Perry provide a review of the involvement of oxidative stress in neurodegenerative diseases, especially Alzheimer's Disease, and the possible use of various antioxidants in reducing clinical manifestations of such disorders. Two chapters discuss redox regulation of signaling with particular reference to cells of the immune system. Otsuji *et al.* examined induction of structural changes in the T cell receptor-CD3 complex on T cells from tumor-bearing mice, whereas Minami *et al.* discuss the roles of the protein tyrosine kinase Syk in signaling induced by oxidative and osmotic stress specifically in B cells. The chapter by Miyata *et al.* reviews evidence suggesting that the oxidative stress induced in uremia may cause conversion of carbohydrates,

lipids, and ascorbate into toxic carbonyl groups that can react with proteins, forming advanced glycation products. Finally, as mentioned earlier, Miyazaki *et al.* provide data suggesting that serum thioredoxin levels are increased in patients with hepatocellular carcinoma.

Overall, Drs. Packer and Yodoi have done a fine job of integrating a series of excellent chapters, including some that provide concise reviews and others that present new data. The chapters have been well selected and edited to provide a volume of interest on the subject of redox regulation of signal transduction and its implications. Although a less random ordering of chapters might have improved the book from an organizational standpoint, random ordering is typical of this type of publication, and

certainly does not prevent the reader from reading chapters of particular personal interest in a chosen order. Most scientists with interest in redox regulation of cellular functions, particularly those interested in natural antioxidants, would likely find one or more chapters of serious interest.

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