
CONTENTS

Contributors	xiii
List of Abbreviations	xvii
Preface	xix
1. Redox Metabolism and Life	1
<i>By Ruma Banerjee</i>	
1.1. Redox Biochemistry and the Evolution of Life	1
1.2. Global Redox Cycles	4
1.3. Major Bioenergetic Cycles	6
1.3.A. Photosynthesis	6
1.3.B. Aerobic Respiration	7
2. Antioxidant Molecules and Redox Cofactors	11
<i>Edited by Donald Becker</i>	
2.1. Glutathione	11
<i>By Joseph J. Barycki</i>	
2.1.A. Biological Functions	13
2.1.B. Biosynthesis	14
2.1.C. Degradation	16
2.1.D. Other Thiol-Based Redox Buffers	21
2.2. Ascorbate	22
<i>By Han Asard</i>	
2.2.A. Ascorbate Chemistry	22
2.2.B. Ascorbate Biosynthesis	23
2.2.C. Ascorbate Recycling	25
2.2.D. Ascorbate Transport	26
2.2.E. Importance of Ascorbate in Stress and Disease	26
2.3. Other Antioxidants	27
<i>By Julie M. Stone and Mark A. Wilson</i>	
2.3.A. Lipid-Soluble Antioxidants	28
	vii

viii CONTENTS

2.3.B. Water-Soluble Antioxidants	31
2.3.C. Antioxidants and Human Health	32
2.4. Redox Coenzymes	35
<i>By Ruma Banerjee and Donald F. Becker</i>	
2.4.A. Flavin	35
2.4.B. NAD	39
2.4.C. Quinones	40
2.4.D. Pterins and Molybdopterins	42
2.4.E. Folic Acid	46
3. Antioxidant Enzymes	49
<i>Edited by Vadim Gladyshev</i>	
3.1. ROS-Dependent Enzymes	50
<i>By Irwin Fridovich and Leslie B. Poole</i>	
3.1.A. Catalase	50
3.1.B. Superoxide Dismutase	55
3.1.C. Peroxiredoxins	59
3.1.D. Alkyl Hydroperoxide Reductases	65
3.2. The Thioredoxin System	68
<i>By Arne Holmgren</i>	
3.2.A. Thioredoxin	68
3.2.B. Thioredoxin Reductase	71
3.3. The Glutathione System	74
<i>By Marjorie F. Lou</i>	
3.3.A. Glutathione Reductase	75
3.3.B. Glutaredoxin (Thioltransferase)	78
3.4. Repair Enzymes	84
<i>By Vadim N. Gladyshev, Sheila S. David, and By Leslie B. Poole</i>	
3.4.A. Methionine Sulfoxide Reductases	84
3.4.B. DNA Repair Enzymes	87
3.4.C. Sulfiredoxins	94
3.5. Detoxification Enzymes	97
<i>By Robert L. Osborne, John H. Dawson, and Shelly D. Copley</i>	
3.5.A. Cytochrome P450 Enzymes: Structure, Function, and Mechanism	97
3.5.B. GSH Transferases	104
3.6. Oxidative Folding	113
<i>By Hiroshi Kadokura, Jon Beckwith, and Hiram F. Gilbert</i>	

3.6.A. Disulfide Bond Formation in Bacteria	113
3.6.B. Disulfide Bond Formation in Eukaryotes	120
3.7. Other Antioxidant Enzymes	127
<i>By Vadim N. Gladyshev and Stephen W. Ragsdale</i>	
3.7.A. Selenoproteins	127
3.7.B. Heme Oxygenase	131
4. Redox Regulation of Physiological Processes	135
<i>Edited by Martin Dickman</i>	
4.1. Reactive Oxygen, Nitrogen, and Thiol-Based Signal Transduction	136
<i>By Ilsa I. Rovira and Toren Finkel</i>	
4.1.A. Nitric Oxide Signaling	136
4.1.B. Carbon Monoxide Signaling	141
4.1.C. Superoxide and Hydrogen Peroxide	143
4.1.D. Other Novel Redox Molecules	147
4.2. Role of Nitric Oxide Synthases in Redox Signaling	148
<i>By Bettie Sue Masters</i>	
4.2.A. Characterization of the Nitric Oxide Synthases	149
4.2.B. Regulation of Nitric Oxide Synthases by Intrinsic Elements	150
4.2.C. Extrinsic Regulation of Nitric Oxide Synthases	152
4.2.D. Interactions of NO with Other Proteins and Enzymes	152
4.3. Redox Regulation of Genes	154
<i>By Martin B. Dickman</i>	
4.3.A. MAP Kinase/Cell Cycle	154
4.3.B. Redox Control of Gene Expression	155
4.3.C. Peptide Editing and Thiol-Mediated Redox Regulation	156
4.4. Redox Regulation of Apoptosis	158
<i>By Martin B. Dickman</i>	
4.4.A. Apoptotic Pathways	158
4.4.B. Reactive Oxygen Species and Apoptosis	159
4.5. Metal Homeostasis	162
<i>By Jaekwon Lee</i>	
4.5.A. Physiological Significance of Metal Metabolism	163
4.5.B. Metal Uptake from the Extracellular Environment	164
4.5.C. Intracellular Metal Distribution by Target-Specific Chaperones	165
4.5.D. Subcellular Membrane Metal Transporters	167

x CONTENTS

4.5.E. Heme and Iron–Sulfur Cluster Synthesis	168
4.5.F. Cellular Storage	168
4.5.G. Metal Export	168
4.5.H. Regulation of Metal Metabolism	169
4.5.I. Genetic Disorders in Metal Metabolism	171
4.5.J. Perturbation of Metal Homeostasis and Degenerative Disorders	172
4.6. Redox Enzymology <i>By Stephen W. Ragsdale</i>	173
4.7. Circadian Clock and Heme Biosynthesis <i>By Cheng Chi Lee</i>	177
4.7.A. Cyclic Expression of Heme Binding Proteins	177
4.7.B. Circadian Clock Mechanism	178
4.7.C. PAS Is a Heme Binding Domain	179
4.7.D. Expression of <i>Npas2</i> Is Controlled by mPER2	180
4.7.E. NPAS2 Regulates Expression of Aminolevulinatase Synthase 1	180
5. Pathological Processes Related to Redox <i>Edited by Ruma Banerjee</i>	183
5.1. Protein Modification <i>By Earl R. Stadtman</i>	184
5.1.A. Protein Oxidation and Aging	184
5.1.B. Mechanisms of Protein Oxidation	184
5.1.C. Peptide Bond Cleavage	187
5.1.D. Oxidation of Amino Acid Residue Side Chains	188
5.1.E. Beta Scission of Amino Acid Side Chains	189
5.1.F. Generation of Protein Carbonyl Derivatives	189
5.1.G. Formation of Protein Cross-Linked Derivatives	193
5.1.H. Role of Protein Oxidation in Aging	193
5.2. Oxidative Stress in the Eye: Age-Related Cataract and Retinal Degeneration <i>By Marjorie F. Lou and John W. Crabb</i>	194
5.2.A. Oxidative Stress and Cataract	195
5.2.B. Oxidative Stress and Retinal Pathology	199
5.3. Redox Mechanisms in Cardiovascular Disease: Chronic Heart Failure <i>By George J. Rozanski</i>	204
5.3.A. Excitation–Contraction Coupling in Cardiac Myocytes	204
5.3.B. Role of Oxidative Stress in Chronic Heart Failure	206

CONTENTS **xi**

5.3.C. Redox Modulation of Ca ²⁺ Handling Proteins	206
5.3.D. Hypertrophy and Cell Death	209
5.3.E. Extracellular Matrix Remodeling	209
5.4. Role of Reactive Oxygen Species in Carcinogenesis <i>By Suresh Veeramani and Ming-Fong Lin</i>	212
5.4.A. ROS Act as Growth Signaling Messengers	212
5.4.B. Phosphatases Are Prime Targets for ROS During Growth Stimulation	212
5.4.C. Uncontrolled Production of ROS is Carcinogenic	214
5.4.D. ROS Can Induce Carcinogenic DNA and Protein Adducts	215
5.4.E. ROS Can Affect DNA Methylation and Gene Expression	216
5.4.F. Mitochondrial DNA Mutations Are Induced by ROS	216
5.4.G. Clinical Trials on Antioxidant Supplementation Against Cancer	216
5.5. Oxidative Stress and the Host–Pathogen Interaction <i>By Greg A. Somerville</i>	218
5.5.A. Neutrophils and the Innate Immune Response	219
5.5.B. Bacterial Targets of Oxidative Damage	220
5.5.C. Regulating the Oxidative Stress Response	221
5.5.D. The Oxidative Stress Response	223
5.5.E. Evasion of the Innate Immune Response	223
6. Specialized Methods	227
<i>Edited by Stephen Ragsdale</i>	
6.1. Mass Spectrometry Applications for Redox Biology <i>By Ashraf Raza and John R. Engen</i>	228
6.1.A. Mass Spectrometer	228
6.1.B. Applications of Mass Spectrometry	231
6.1.C. Hydrogen Exchange Mass Spectrometry	236
6.2. Electron Paramagnetic Resonance (EPR) for the Redox Biochemist <i>By Stephen W. Ragsdale and Javier Seravalli</i>	237
6.2.A. Introduction to Magnetic Resonance Spectroscopy	237
6.2.B. Basic EPR Theory	239
6.2.C. Appearance of the EPR Spectrum	240
6.2.D. The EPR Experiment	240

xii CONTENTS

6.2.E. The Conventional EPR Spectrometer: Detection of the Signal	241
6.2.F. Sensitivity and Saturation in EPR	244
6.2.G. Measuring the Concentration of Spins	244
6.2.H. Nuclear Hyperfine and Spin–Spin Interactions	246
6.3. Redox Potentiometry <i>By Donald F. Becker</i>	247
6.3.A. Midpoint Potential	247
6.3.B. Redox-Linked Processes	248
6.3.C. Potentiometric Technique	249
6.4. Bioinformatics Methods to Study Thiol-Based Oxidoreductases <i>By Dmitri E. Fomenko and Vadim N. Gladyshev</i>	251
6.4.A. Identification of Redox-Active Cysteines in Proteins	251
6.4.B. Cysteine-Based Redox Motifs	253
6.4.C. Conserved Cysteines in Metal-Binding Proteins	253
6.4.D. Secondary Structure Context of Redox-Active Cysteines	253
6.4.E. Structure Modeling	255
6.4.F. Comparative Sequence Analysis of Thiol-Based Oxidoreductases	255
6.5. Electrophysiology <i>By Mark P. Thomas and Harold D. Schultz</i>	256
6.5.A. Electrophysiology Part I: Ion Channel Physiology	256
6.5.B. Electrophysiology Part II	263
6.6. Methods to Detect Reactive Metabolites of Oxygen and Nitrogen <i>By Matthew B. Grisham</i>	272
6.6.A. Detection of the Superoxide Anion Radical	273
6.6.B. Detection of Hydrogen Peroxide	274
6.6.C. F2-Isoprostanes as Indicators of Lipid Peroxidation <i>In Vivo</i>	276
6.6.D. Measurement of the GSSG/GSH Redox Couple in Cells and Tissue	277
6.6.E. Methods to Detect NO and Its Oxidized Metabolites <i>In Vitro and In Vivo</i>	277
6.6.F. Detection of <i>S</i> -Nitrosothiols by Colorimetric and Fluorimetric Methods	281
6.6.G. Is the Presence of 3-Nitrotyrosine a Specific Footprint for Peroxynitrite?	283
Index	285