

Contents

Preface XV

The Editors XVII

List of Authors XIX

- 1 Introduction** 1
Claus Jacob and Paul G. Winyard
- 2 Biological Systems Relevant for Redox Signaling and Control** 13
Thomas R. Hurd and Michael P. Murphy
- 2.1 Introduction 13
- 2.2 Reactive Oxygen Species 14
- 2.2.1 The Superoxide Radical 14
- 2.2.1.1 Generation of the Superoxide Radical 14
- 2.2.1.2 The Superoxide Radical as a Redox Signal 16
- 2.2.1.3 Decomposition of the Superoxide Radical 17
- 2.2.2 Hydrogen Peroxide 19
- 2.2.2.1 Generation of Hydrogen Peroxide 19
- 2.2.2.2 Mechanisms of Hydrogen Peroxide Signaling 20
- 2.2.2.3 Decomposition of Hydrogen Peroxide 27
- 2.3 Reactive Nitrogen Species 31
- 2.3.1 Nitric Oxide 31
- 2.3.1.1 Generation of Nitric Oxide 32
- 2.3.1.2 Mechanisms of Nitric Oxide Signaling 32
- 2.3.1.3 Decomposition of Nitric Oxide 32
- 2.3.2 Peroxynitrite and Reactive Nitrogen Species 33
- 2.3.2.1 Generation of Peroxynitrite and Other Important Reactive Nitrogen Species 33
- 2.3.2.2 Mechanisms of Peroxynitrite- and Reactive Nitrogen Species-Mediated Redox Signaling 34

2.4	Lipid Peroxidation Products	36
2.4.1	Generation of Lipid Peroxidation Products	36
2.4.2	Mechanisms of Signaling with Lipid Peroxidation Products	37
2.4.3	Decomposition of Lipid Peroxides	38
2.5	Conclusions	39
	References	40
3	Cellular Generation of Oxidants: Relation to Oxidative Stress	45
	<i>Lars-Oliver Klotz and Helmut Sies</i>	
3.1	Introduction	45
3.2	Molecular Oxygen and Reactive Oxygen Species: Biochemical Relations and Endogenous Sources	45
3.2.1	Endogenous Sources of Superoxide and Superoxide-Derived Reactive Oxygen Species	46
3.2.2	Singlet Oxygen	50
3.2.3	“Secondary” Reactive Oxygen Species Generated in Radical Chain Reactions	51
3.3	Generation of Oxidative Stress Under the Influence of Xenobiotics and Stressful Stimuli	53
3.3.1	Quinones and Other Redox Cyclers	53
3.3.2	Antioxidant Depletion by Alkylation: Acetaminophen Toxicity	56
3.3.3	Ultraviolet Radiation	57
3.3.4	Ultrafine or Nanoparticles	57
	References	61
4	The Chemical Basis of Biological Redox Control	63
	<i>Claus Jacob, Mandy Doering, and Torsten Burkholz</i>	
4.1	Introduction	63
4.2	Forms of Elemental Oxygen as Reactive Oxygen Species	67
4.2.1	Reactive Oxygen Species and Related Cellular Oxidants	67
4.2.2	Singlet Oxygen ($^1\text{O}_2$)	67
4.2.3	Ozone (O_3)	71
4.3	Reduced, Yet Oxidizing: the Chemistry of Oxygen in Oxidation States between 0 and -2	72
4.3.1	Superoxide Radicals ($\text{O}_2^{\bullet-}$)	73
4.3.2	The Superoxide to Peroxide Conversion as a Key Event in Redox Signaling	76
4.3.3	Hydrogen Peroxide (H_2O_2)	77
4.3.4	Hydroxyl Radicals (HO^\bullet)	79
4.3.5	Enzymatic Reduction of Hydrogen Peroxide by Peroxiredoxins, Catalase and Glutathione Peroxidase	81
4.4	The Role of Labile Metal Ions in Oxidative Stress	84
4.5	Follow-on Species Generated by Chemical Interactions of Reactive Oxygen Species	85

4.5.1	Hypochlorous Acid (HOCl)	86
4.5.2	Peroxynitrite (ONOO ⁻)	88
4.6	Nitrogen Monoxide and Reactive Nitrogen Species	91
4.6.1	Reactive Nitrogen Species	91
4.6.2	S-Nitrosothiols	95
4.7	Sulfur as a Prime Target of Oxidative Stress	98
4.7.1	Thiol Groups in Peptides and Proteins	99
4.7.2	The Concept of Reactive Sulfur Species	101
4.7.3	Sulfur-Centered Radicals	103
4.7.4	Disulfide-S-Oxides (RS(O) _x SR')	106
4.7.5	Sulfenic and Sulfinic Acids (RSOH and RS(O)OH)	108
4.7.6	Oxidation of Methionine: Sulfoxides (RS(O)R) and Sulfones (RS(O) ₂ R')	109
4.7.7	S-Thiolation as Chemical Protection	110
4.7.8	Oxidation of Disulfides	111
4.8	A Brief Overview of Hydroxylation and Nitration Reactions	112
4.8.1	Hydroxylation and Nitration of Aromatic Residues	113
4.8.2	Fatty Acid Chemistry	116
4.9	Conclusion	117
	References	118
5	Protein Glutathiolation	123
	<i>Pietro Ghezzi and Paolo Di Simplicio</i>	
5.1	Introduction: Glutathione – From Antioxidant to Redox Signal	123
5.2	Glutathiolation	124
5.3	Mechanisms of Glutathiolation	127
5.3.1	ROS-Dependent Glutathiolation by Thiol/Disulfide Exchange Reactions	129
5.3.2	ROS-Dependent Glutathiolation via Sulfenic Acid	130
5.3.3	ROS-Dependent Glutathiolation by Radical Reactions	132
5.3.4	ROS-Independent Glutathiolation	133
5.4	Toxicological Aspects of Glutathiolation	133
5.5	Mechanisms of Deglutathiolation	135
5.6	Enzymes Implicated in Glutathiolation	136
5.7	Specificity of Glutathiolation	136
5.8	Genetic Factors Affecting Glutathiolation	137
5.8.1	Mouse Beta-Globin	137
5.8.2	Glucose-6-Phosphate Dehydrogenase Mutations	137
5.8.3	Glutathione S-Transferase Mutations	138
5.9	Future Perspectives	138
	References	139

6	Structure and Function of the Human Peroxiredoxin-Based Antioxidant System: the Interplay between Peroxiredoxins, Thioredoxins, Thioredoxin Reductases, Sulfiredoxins and Sestrins 143
	<i>Katalin É. Szabó, Kirsty Line, Paul Eggleton, Jennifer A. Littlechild, and Paul G. Winyard</i>
6.1	Introduction 143
6.2	Peroxiredoxins 147
6.3	Thioredoxins 158
6.4	Thioredoxin Reductases 159
6.5	Sulfiredoxin and Sestrins 161
6.6	Regulation of the Expression and Activity of the Peroxiredoxin-Based System Enzymes 163
6.7	Cell Signaling and the Peroxiredoxin-Based System: Regulation of Transcription Factors, Cell Cycle and Apoptosis 166
6.8	Peroxiredoxin-Based System in Cells and Organs of the Body 170
6.9	Summary 173
	References 174
7	Hydrogen Peroxide and Cysteine Protein Signaling Pathways 181
	<i>Ewald Schröder and Philip Eaton</i>
7.1	Introduction 181
7.2	Hydrogen Peroxide Production in Cells and Tissues 182
7.3	Sources and Concentrations of Hydrogen Peroxide 183
7.4	Hydrogen Peroxide and the Formation of Secondary Oxidants such as Peroxynitrite 184
7.5	Exogenous Hydrogen Peroxide as an Experimental Tool 186
7.6	Hydrogen Peroxide Sensing and Cysteine Sensors 188
7.7	Low Molecular Weight Oxidized Thiols and S-Thiolated Protein Adducts 188
7.8	Protein Thiol Modifications 189
7.9	Protein Regulation via Sulfination-Dependent Proteolysis 190
	References 192
8	Protein Tyrosine Phosphatases as Mediators of Redox Signaling 197
	<i>Jeroen den Hertog</i>
8.1	Introduction 197
8.2	Protein Tyrosine Phosphatases 198
8.3	Protein Tyrosine Phosphatases are Sensitive to Oxidation 199
8.4	Allosteric Regulation of Receptor Protein Tyrosine Phosphatases by Oxidation 200
8.5	Activation of Sdp1 by Oxidation 202
8.6	Physiological Relevance of Protein Tyrosine Phosphatase Oxidation 203
8.7	Conclusions 204
	References 204

9	Hypoxia-Induced Gene Regulation through Hypoxia Inducible Factor-1α	207
	<i>Adam J. Case and Frederick E. Domann</i>	
9.1	Introduction	207
9.2	The Proteins and Mechanism	208
9.3	Hypoxia Inducible Factor Target Genes	213
9.4	Non-Hypoxia-Induced Activation of Hypoxia Inducible Factor	218
9.5	Diseases Involving Hypoxia Inducible Factor	220
9.6	The Promise of Hypoxia Inducible Factor-Targeted Therapies	223
9.7	Conclusions	226
	References	226
10	Eicosanoid-Based Signaling	229
	<i>Valerie B. O'Donnell</i>	
10.1	Introduction	229
10.2	Biosynthesis and Structures of Eicosanoids	231
10.2.1	Lipoxygenases	234
10.2.2	Cyclooxygenases	235
10.2.3	Cytochrome P450	237
10.3	Signaling by Eicosanoids	239
10.4	Metabolism of Eicosanoids	240
10.5	Summary	242
	References	243
11	Redox-Controlled Transcription Factors and Gene Expression	245
	<i>Gregory I. Giles</i>	
11.1	Introduction	245
11.2	Redox Signaling and Gene Microarray Data: The Global Picture	248
11.3	The Antioxidant Response Element	251
11.4	The Transcription Factor Nrf2: The Master Regulator of Antioxidant Transcription	253
11.5	The Keap1–Nrf2 Complex: A Sensor for Cellular Stress	255
11.5.1	Reactive Oxygen Species, Reactive Nitrogen Species and Electrophile Sensing by Keap1	256
11.5.2	Structural Basis for the Sensing Function of the Keap1–Nrf2 Complex	257
11.6	Redox Reactions of Transcription Factors	261
11.6.1	Nuclear Factor κ B: Redox Control of the Immune Response	262
11.6.2	Activator Protein 1 (AP-1): Redox Control of Proliferation and Apoptosis	264
11.6.3	The Role of the Nuclear Redox State in Gene Expression	265
11.7	Summary	266
	References	267

12	Nitric Oxide Regulation in Redox Signaling 271 <i>Dario A. Vitturi, David M. Krzywanski, Edward M. Postlethwait, and Rakesh P. Patel</i>
12.1	Introduction 271
12.2	Nitric Oxide Formation 271
12.3	Factors Affecting Nitric Oxide Reactivity and Signaling 272
12.3.1	Compartmentalization and Diffusion 272
12.3.2	Interaction with Metal Centers 274
12.3.3	Nitric Oxide Reaction with Free Radicals 276
12.3.3.1	Nitric Oxide and Superoxide 276
12.3.3.2	Peroxynitrite 278
12.3.3.3	Nitrogen Dioxide/Dinitrogen Trioxide 281
12.4	Nitric Oxide Signaling Beyond Soluble Guanylate Cyclase 281
12.4.1	Nitric Oxide and Mitochondria 282
12.4.2	S-Nitrosation 282
12.4.3	Nitrated Lipids 283
12.4.4	3-Nitrotyrosine 284
12.5	Redox Derivatives of Nitric Oxide 284
12.5.1	Nitroxyl Anion 285
12.5.2	Nitrite 285
12.5.3	Nitrite – a Potential Reservoir for Nitric Oxide Bioactivity During Hypoxia 286
12.6	Summary 287 References 287
13	Is Hydrogen Sulfide a Regulator of Nitric Oxide Bioavailability in the Vasculature? 293 <i>Matthew Whiteman and Philip K. Moore</i>
13.1	Introduction 293
13.2	Reactive Nitrogen Species 293
13.3	Reactive Nitrogen Species in the Heart and Vasculature 295
13.4	Hydrogen Sulfide Biosynthesis 296
13.5	Hydrogen Sulfide Measurement, Catabolism and Removal 300
13.6	Hydrogen Sulfide in the Heart and Vasculature 305
13.7	What is the Evidence for “Crosstalk” between Nitric Oxide and Hydrogen Sulfide 309
13.8	Nitric Oxide/Hydrogen Sulfide and Evidence for the Formation of A Novel Intermediate 312
13.9	Concluding Remarks 313 References 314
14	Aspects of Nox/Duox Signaling 317 <i>Masuko Ushio-Fukai</i>
14.1	Introduction 317
14.2	The Nox/Duox Enzymes (Expression and Domain Structure) 318

14.2.1	NOXO1 and NOXA1	322
14.3	Mechanism of the Nox/Duox Activation	322
14.3.1	Nox1	323
14.3.2	Nox3	324
14.3.3	Nox4	324
14.3.4	Nox5	324
14.3.5	Duox	325
14.4	Redox Signaling Activated by NADPH Oxidase	325
14.4.1	Activation of Kinases and Phospholipases	326
14.4.2	Activation of Ion Channels and Calcium Signaling	327
14.4.3	Oxidative Inactivation of Protein Tyrosine Phosphatase	328
14.4.4	Specific Localization of NADPH Oxidase as Mechanism of Activation of Specific Redox Signaling	328
14.5	Transcription Factors and Gene Expression Regulated by ROS	330
14.5.1	NF- κ B	331
14.5.2	AP-1 (c-Jun and c-Fos)	331
14.5.3	HIF-1	331
14.5.4	Ets	332
14.5.5	p53	332
14.6	Functional Role of Nox/Duox in Physiological and Pathophysiological Functions	333
14.6.1	Function of Nox1	333
14.6.2	Function of Nox2	333
14.6.3	Function of Nox3	336
14.6.4	Function of Nox4	336
14.6.5	Function of Nox5	339
14.6.6	Function of Duox	340
14.7	Summary and Conclusions	340
	References	341
15	Photodynamic Therapy with Aminolevulinic Acid and Iron Chelators: A Clinical Example of Redox Signaling	351
	<i>Andrew Pye, Yuktee Dogra, Jessica Tyrrell, Paul Winyard, and Alison Curnow</i>	
15.1	Photodynamic Therapy	351
15.2	The Development of Photodynamic Therapy	352
15.3	Aminolevulinic Acid Photodynamic Therapy	353
15.4	Heme Biosynthesis and Regulation During ALA-PDT	354
15.5	Iron and the Enhancement of ALA-PDT	356
15.6	Redox Signaling in Photodynamic Therapy after Light Irradiation	361
15.7	Photosensitizers as Reactive Oxygen Species Generators in Redox Research	363
15.8	Reactive Oxygen Species Generation and Signaling in Clinical Photodynamic Therapy	364

15.9	Apoptosis in Photodynamic Therapy	364
15.10	Subcellular Localization of Reactive Oxygen Species Production	365
15.11	Changes in Transcription Factor and Protein Levels Following Photodynamic Therapy	366
15.12	Iron and Iron Chelation Post Light Activation of Photosensitizer	367
15.13	Vascular Damage, Hypoxia and Hypoxia Inducible Factor	368
15.14	Conclusion	369
	References	370
16	Oxidative Stress and Apoptosis	373
	<i>Silvia Cristofanon, Mario Dicato, Lina Ghibelli, and Marc Diederich</i>	
16.1	Apoptosis, The Programmed Destiny of a Cell	373
16.2	Historical Overview of the Relation Between Oxidative Stress and Apoptosis	378
16.3	Oxidative Stress as a Mediator and Inducer of Apoptosis	378
	References	382
17	Redox Regulation of Apoptosis in Immune Cells	385
	<i>Edith Charlier, Jacques Piette, and Geoffrey Gloire</i>	
17.1	Apoptosis, Necrosis and Autophagy	385
17.2	Apoptosis	386
17.2.1	Morphological and Biochemical Features of Apoptosis	386
17.2.2	Molecular Mechanisms of Apoptosis	386
17.2.2.1	The Major Players in Apoptosis	386
17.2.2.2	Main Pathways of Apoptosis	392
17.3	Redox Regulation of Apoptosis in Immune Cells	395
17.3.1	Induction of Apoptosis by Exogenous Reactive Oxygen Species	396
17.3.1.1	Reactive Oxygen Species Targets	396
17.3.1.2	Reactive Oxygen Species-Induced Apoptosis in Immune Cells	397
17.3.2	Control of Apoptosis by Endogenous Reactive Oxygen Species Production	398
17.3.2.1	Cytokine Stimulation	398
17.3.2.2	Immune Receptor Stimulation	399
17.3.2.3	Granzyme A Delivery	402
17.3.2.4	Spontaneous and Bacteria-Induced Neutrophil Apoptosis	403
	References	405
18	Redox Control in Human Disease with a Special Emphasis on the Peroxiredoxin-Based Antioxidant System	409
	<i>Katalin É. Szabó, Nicholas J. Gutowski, Janet E. Holley, Jennifer A. Littlechild, and Paul G. Winyard</i>	
18.1	Introduction	409
18.2	Inflammatory Diseases	410

18.3	Neurodegenerative Diseases	414
18.4	Diseases of the Eye	418
18.5	Blood Disorders	419
18.6	Atherosclerosis and Cardiovascular Disease	420
18.7	Infections and Parasitic Diseases	421
18.8	Cancer	422
18.9	Proteins of the Peroxiredoxin-Based System as Diagnostic and Prognostic Tools, and Potential Drug Targets	424
18.10	Conclusions	426
	References	427
19	Free Radicals and Mammalian Aging	433
	<i>Alberto Sanz, Gustavo Barja, Reinald Pamplona, and Christiaan Leeuwenburgh</i>	
19.1	Introduction	433
19.2	The Mitochondrial Free Radical Theory of Aging	434
19.3	Why are Long-Lived Animals so Long-Lived? Four Correlations to Explain Longevity	435
19.3.1	Mitochondrial Free Radical Generation	436
19.3.2	Is Complex I the Major Determinant of Aging Rate?	438
19.3.2.1	Decrease in the Concentration of Respiratory Complexes	440
19.3.2.2	Modification of the Amino Acid Composition of Respiratory Subunits	440
19.3.2.3	Posttranslational Modification of Specific Subunits	441
19.3.2.4	Changes in mtROS Production Without Altering the Electron Transport Chain	442
19.3.3	The Unsaturation Degree of Membrane Fatty Acids	442
19.3.4	Methionine Content in Proteins	443
19.3.5	G + C Content in mtDNA	444
19.3.6	In Summary: Why are Long-Lived Animals So Long-Lived?	444
19.4	Oxidative Damage to Macromolecules	446
19.4.1	Oxidative Damage to Carbohydrates	446
19.4.2	Oxidative Damage to Lipids	447
19.4.3	Oxidative Damage to Proteins	448
19.4.4	Oxidative Damage to DNA	449
19.4.5	The Importance of Mitochondrial DNA	450
19.5	Effects of Mitochondrial DNA Mutations on Cellular Function	452
19.5.1	Are There Exponential Increases in Free Radical Production With Age?	452
19.5.2	Apoptosis	453
19.5.3	ATP Production	454
19.6	Trying to Increase the Maximum Life Span	456
19.6.1	Antioxidants: The Great Hope, The Great Deception	456
19.6.2	Dietary Restriction: The Cheapest, The Best	458
19.6.3	Dietary Restriction and Reduction in Oxidative Stress	458

XIV | *Contents*

- 19.6.4 How are Mitochondrial ROS Regulated During Dietary Restriction? 460
 - 19.6.4.1 Hormonal Regulation 461
 - 19.6.4.2 Regulation of Mitochondrial ROS Production by Specific Dietary Components: The Role of the Dietary Proteins and Methionine 462
- References 464

Index 473