

Oxidative Stress and Antioxidant Defenses in Biology

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***edited by
Sami Ahmad***



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Preface

The ground-state of molecular oxygen, O_2 , is essential to many indispensable metabolic processes of all aerobic life forms ranging from prokaryotes, protists, plants, and fungi to animals. Research by mammalian toxicologists and clinicians has unravelled persuasive evidence that O_2 dependence imposes universal toxicity to all aerobic life processes. The basis of this paradox is that one-electron reduction of O_2 generates the superoxide anion free radical, O_2^- , from numerous biological sources; for example, redox-active autoxidizable molecules such as catecholamines, oxidoreductases, and subcellular organelles such as mitochondria, endoplasmic reticulum (microsomes), nuclei, and chloroplasts. Oxygen is also activated in biologically relevant photosensitizing reactions to highly reactive singlet oxygen, 1O_2 .

In all biological systems, O_2^- undergoes further reduction to H_2O_2 via Fenton reaction to the hydroxyl radical, $\cdot OH$. These, and some other forms of activated O_2 , constitute reactive oxygen species (ROS) and/or metabolites (ROM). Both $\cdot OH$ and 1O_2 are the most reactive forms of ROS known and among their deleterious reactions are oxidation of proteins, DNA, steroidal compounds, and peroxidation of the cell membrane's unsaturated lipids to form unstable hydroperoxides. Their many breakdown products include malondialdehyde and hydroxynonenals that are themselves highly reactive and threaten cellular integrity and function. More importantly, they decompose to free radicals that can continue to propagate the vicious lipid peroxidation chain reaction. This is the so-called endogenous oxidative stress with which all aerobic organisms must cope.

Thus the evolutionary process that in the first instance harnessed oxygen for the physiological support of aerobic organisms resulted in toxicity as a side effect of ROS attack, rendering them targets for peroxidative attack, cell and tissue degeneration and, ultimately, organismal death. Earlier texts have emphasized the nature of pathological processes mediated by this stress which include the leakage of cell membranes, dysfunction of mitochondria, depletion of glutathione and disturbed redox states of cells, and the depletion of ATP. These processes which affect cells and DNAs lead to aging, tumor promotion and cancer, inflammatory diseases, post-ischemic injury and numerous serious ailments.

Faced with the inevitable consequences of O_2 toxicity, evolution began in the earliest aerobic cells to acquire appropriate defensive strategies. As evolution proceeded towards more complex aerobic life forms, it also favored the appropriate elaboration of antioxidant defenses. The first line of this defensive strategy was the deployment of antioxidant substances such as vitamin C (ascorbic acid), vitamin E (α -tocopherol), urate, glutathione, and carotenoids. In addition, a battery of antioxidant enzymatic defenses prevent the O_2 radical cascade and terminate the lipid peroxidation cycle. The enzymatic defenses are regarded as crucial in that only they can ameliorate O_2 toxicity when the antioxidant molecule supply is meager or exhausted.

With this antioxidant machinery, aerobic cells seem competent to cope with endogenous oxidative stress. Unfortunately aerobic organisms are subject to oxidative injury from prooxidants arising from natural products in dietary sources and from environmental pollutants released by humans as mining and industrial wastes, therapeutic drugs, and agrochemicals of all sorts. These interactions of prooxidants lead to the O_2 radical cascade and lipid peroxidation, thereby exacerbating the endogenous oxidative stress. In turn, the organisms seem to mobilize the very same defenses that in the first place were designed to cope with endogenous oxidative stress. Often, however, despite the induction of chain-terminating antioxidant enzymes, the toll of prooxidative insult is far more severe, resulting in early initiation of the aging process and numerous pathologies including cancer.

The implication of oxidative stress in far more pathologies and disorders than previously imagined has provided the impetus for numerous national and international meetings, symposia, and congresses. In addition, specialized journals have appeared in recent years, which are now major outlets for reports on this subject matter. The field of free-radical based biological and pathological interface is virtually exploding with new discoveries; for example, nitric oxide, NO, is now known to be an endothelial releasing factor with an essential physiological role as a vasodilator. Most volumes on oxyradicals published recently either as symposia proceedings or edited books are devoted to highly specialized topics that are clinically oriented. The effort extended to the fundamental studies of oxidative stress in organisms such as plants, fungi, and invertebrates was never neglected, but it was subordinated to the research effort devoted to mammalian models. That this relative neglect occurred in a field still being primarily driven by medically oriented scientists is hardly surprising. The enormous difficulty attendant upon

accessing and synthesizing the vastly scattered literature on non-mammalian organisms is amply illustrated in this volume and in fact represents its unique character.

Oxidative stress is an area of contemporary research that is rapidly gaining momentum, as scientists from diverse disciplines seek more details about the deleterious effects ROS have on cells. It is therefore salutary that an attempt has been made to address in this volume oxidant-induced stress and antioxidant defenses in a broad biological context. Its broad coverage should be highly appealing to biologists as diverse as ecologists, entomologists, microbiologists, mycologists, molecular biologists, animal and plant physiologists, and biochemists. In addition, the specialists will find it a valuable reference source not only because the information is current, but is relevant to the progress made on other organisms, which previously had not received as much attention because of continued emphasis on mammalian species.

For the book to be as thorough in coverage as possible, it comprises of eleven chapters. The progression of chapters is logical, and their combined bibliographies provide a comprehensive view of our current knowledge.

E. Cadenas in chapter 1 describes the chemistry of oxygen activation in a manner that is easily comprehended by non-specialists and specialists alike. The chapter is comprehensive and, aside from the mechanisms of O_2 activation to ROS per se, it also deals with important reactions between ROS with carbon-centered free radicals and antioxidant molecules. In addition, the chemistry of the oxo-ferryl complex, a matter of contemporary interest, is addressed. The origin of these complexes and their connection with the oxidation of cell constituents (distinct from that by $\cdot OH$ radical) and drugs is described. Another novel aspect addressed is the biochemistry of $\cdot NO$ and its reactions with oxyradicals.

In chapter 2, Y. Chen et al. cover the numerous pathologies that seem to be ROS-mediated, which are primarily the outcome of vascular and tissue injury. ROS mediated ontogeny of cancer is also treated. Despite the extensive evidence for these pathologies, the authors are correct in pointing out that many lacunae still exist in defining the extent and particular forms of ROS that have an effect on particular pathologies. Lastly, both E. Cadenas in chapter 1 and Y. Chen et al. in chapter 2 describe the interaction of two radicals, $\cdot NO$ and $O_2^{\cdot -}$, which may react under certain conditions (e.g., pH and the flux of $O_2^{\cdot -}$) to generate the two most reactive free radical species, $\cdot OH$ and nitrogen dioxide (NO_2) radicals, which might be the specific ROS species involved in the microvascular injury pro-

duced during ischemia and reperfusion of various organ systems. Since NO research is new, the involvement of NO in ischemic injury and other pathologies warrants experimental validation.

In chapter 3, B. Kalyanaraman addresses the pathological consequences of oxidation of the low-density lipoprotein (LDL, the major cholesterol and other lipid transport protein). Of several lipids associated with this protein, linoleate is most sensitive to peroxidative damage. A consequence of this damage is the degenerative disease atherosclerosis. LDL interactions involving oxyradicals, peroxy-nitrite (ONOO^-) and metals such as Cu, and phenolic antioxidants, has been discussed at length. The author reaches the conclusion that the oxidation of LDL and food fat can be prevented by vitamins C and E.

Chapter 4 by S.J. Stohs is very comprehensive on oxidative stress exerted by environmental contaminants, including drugs and pesticides. The author emphasizes that not all contaminants act as prooxidants in a similar fashion. Some of these materials are able to exert oxidative stress directly, e.g., therapeutic drugs for malaria, antibiotics such as adriamycin for cancer therapy, and tetracyclines as broad-spectrum antibiotics, may exert O_2 toxicity including photosensitizing reactions. Others such as mercury raise oxidative stress through a pleiotropic response that generates H_2O_2 . In addition, many halogenated compounds such as dioxins release iron from transport or storage proteins. Once iron is released, it leads to the production of the lipid peroxidizing $\cdot\text{OH}$ radical. The chapter also addresses the difficulty in pinpointing whether oxidative stress mediated pathology is an early, mid or late event in defining the sequence of events that lead to cell damage and death. Nevertheless, all compounds listed by Stohs exert oxidative stress, but he is judicious in arguing that more research and information will yield a better picture of the role of ROS in the action of prooxidative xenobiotics.

Chapter 5 by M.R. Berenbaum tackles a unique aspect of either behavioral escape or metabolic resistance to naturally occurring prooxidants. Some specialized feeders are capable of rapidly metabolizing photodynamic prooxidants with cytochrome P-450, and an assortment of other detoxification enzymes. While many redox-active compounds are well tolerated by herbivores including man (e.g., the flavonol quercetin), others are not. The compounds not well tolerated are highly redox-active and react with O_2 to generate ROS. The metabolism of these compounds is not well studied. Clearly then, more research is needed in this interesting area despite the

fact that as the author states, “. . . unifying themes in the disposition of prooxidants is not an easy task.”

Chapter 6 by R.A. Larson serves as an overview of antioxidant molecules that are components of natural products. Larson provides a good account of the initiation of the lipid peroxidation chain reaction and of termination processes involving vitamins C and E, flavonols, β -carotene, tertiary amines, bilirubin and metal complexing compounds. He addresses this subject well with kinetics and rate constants for interactions of various ROS with different antioxidants, and processes associated with the antioxidant action. For example, these molecules are effective via their reducing property and radical and excited-state quenching, which may be via physical or chemical interactions. He cites the novel aspect of naturally-occurring compounds such as phytic acid which complex with metals, such as iron, that are known to generate ROS.

Chapter 7 by S. Ahmad reviews the antioxidant defenses of enzymes and proteins. Substantive coverage is given to a group of antioxidant enzymes which act in a concerted or sequential manner to prevent the O_2 radical cascade and to terminate the lipid peroxidation chain reaction. Where the available information is considered authentic, Ahmad has provided the reaction schemes and kinetics of these enzymes, the preference for and range of substrates attacked, inhibitors, molecular weights of native proteins and subunits, and their isoenzymes. The coverage of ancillary antioxidant enzymes and proteins is brief, since D.A. Dalton and G.W. Felton, in their respective chapters, have provided an in-depth account of these processes.

Chapter 8 by R.P. Cunningham and H. Ahern provides an account of the antioxidant defenses of prokaryotes using the bacterial species *Escherichia coli* and *Salmonella typhimurium* as prime examples. It is evident that prokaryotes share many if not most of the same antioxidant defenses as eukaryotes which leads to the conclusion that countermeasures against O_2 toxicity are of ancient evolutionary origin. The chapter delves further into other repair mechanisms of oxidized lipids, proteins, and especially of DNA. The prokaryotic model provides insight into the mechanisms whereby oxidative lesions are indirectly repaired by an arsenal of enzymes that degrade oxidized molecules. The degraded products are either released for excretion or are conserved for reutilization. Recent evidence suggests that these indirect mechanisms of repair are also operative in eukaryotic systems.

Chapter 9 by D.A. Dalton on alleviation of oxidative stress in plants and fungi is notable for its pioneering coverage. He identifies cellular locations in plants such as chloroplasts and nodules where the generation of ROS is higher. He discusses oxidative stress as it arises normally and in conditions of nitrogen fixation, and also points to the benefits of ROS production. Plants' antioxidant machinery is essentially similar to that of other organisms with the exception of the absence of selenium-dependent glutathione peroxidases typical of vertebrates. He argues that an ascorbate-specific peroxidase is more crucial for the destruction of H_2O_2 than catalase. He provides a thorough account of the enzymes, ascorbyl free radical reductase and dehydroascorbate (DHA) reductase. Respectively, these enzymes regenerate ascorbate from ascorbyl free radical and DHA, which result from ascorbate reactions with ROS. Based on his own research, Dalton describes a fascinating interaction among ascorbate peroxidase, DHA reductase, and glutathione reductase. Dalton also ponders the functional roles of many peroxidases present in plants. Peroxidase (horseradish peroxidase) is an enzyme of ubiquitous occurrence, and is abundant in plants. Dalton traces the origin and homologies of the various peroxidases, and concludes that in plants the crucial form is ascorbate peroxidase. The account of antioxidant defenses of fungi is relatively meager because of the paucity of data. Nonetheless, according to Dalton, a cytochrome-*c* peroxidase is crucial in fungi for the destruction of H_2O_2 . This enzyme is associated with the fungal wall, where the generation of ROS is apparently highest and the necessary co-substrate cytochrome *c* is in abundant supply.

Chapter 10 by G.W. Felton on antioxidant defenses of vertebrates and invertebrates is contemporary and comprehensive in its coverage. The fundamental processes of oxidant-induced disease states are the same in all aerobic organisms, but many invertebrates do not live long enough to exhibit the typical diseases of vertebrates. Using insects as examples, he shows how ROS affect nutrition with severe reduction in growth rate and lifespan resulting ultimately in death. Fortunately, invertebrates are also endowed with an elaborate system of antioxidant defenses to avoid oxidative stress. Invertebrates resemble in this respect both vertebrates and plants except the selenium-dependent glutathione peroxidases are absent, but in these animals the peroxidase activity of glutathione transferase has been elaborated for the removal of lipid peroxides. H_2O_2 destruction follows the same path as described for plants. Felton also claims the existence of an ascorbyl free radical reductase. There is

evidence to support this contention, although the animal enzyme may not be homologous to the plant enzyme. Another strength of this chapter are details on antioxidant proteins and proteases that degrade oxidized proteins. The latter aspect has been receiving considerable scrutiny, but as of this writing the specifics were unfortunately not worked out.

In the last chapter, chapter 11, H. Ahern and R.P. Cunningham describe the genetic regulation of the antioxidant defenses based on extensive work with *E. coli* and *S. typhimurium*. Genetic responses to ROS-mediated stress are complex and multi-layered, involving stimulons, regulons, regulatory circuits, and specific genes for transcriptional processes. H_2O_2 and O_2^- are the two ROS to which the genetic machinery responds, especially the H_2O_2 stimulon and oxyR regulon, and the O_2^- stimulon and soxRS regulon. The authors account for the induction of antioxidant enzymes and for the repair of proteins and enzymes targeted as oxidatively damaged macromolecules including DNA. Many other proteins are also transcribed in this process, but their role remains to be defined. The genetic regulation area is bound to be an area of research thrust. Since the antioxidant defenses of both prokaryotic species are remarkably similar (chapter 8) to those of eukaryotes, it seems logical to conclude that eukaryotes possess similar genetic machinery for the regulation of antioxidant defenses.

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April 1994

Sami Ahmad

List of Abbreviations

A; dehydroascorbate
A[•]; ascorbyl radical
AH⁻; ascorbate mono-anion
AH₂; ascorbic acid
ACON; acetone
ACT; acetaldehyde
ADP; adenosine diphosphate
AFR; ascorbate free radical reductase
AHP/AHP reductase; alkyl hydroperoxidase
AP; ascorbate peroxidase
5-ASA; 5-aminosalicylic acid
ATP; adenosine triphosphate
ATPase; adenosine triphosphatase
BCNU; bischloronitrosourea
CAT; catalase
CCP; cytochrome-c peroxidase
CD18; cluster of differentiation
CoQ; Co-enzyme Q (UQ₁₀)
CoQH₂; reduced CoQ (UQ₁₀H₂)
CP; ceruloplasmin
CuDIPS; copper di-isopropyl salicylate
CuZnSOD; copper and zinc SOD
D; oxidized DH₂
DCFH; 2',7'-dichlorofluorescein
DDT; 1,1,1-dichloro-2,2-bis(p-chlorophenyl) ethane
DFX/desferal; desferrioxamine
DH₂; hydrogen donor
DHA; dehydroascorbate (A)
DHA reductase; dehydroascorbate reductase
DMPO; 5,5-dimethylpyrrolidone-(2)-oxyl-(1)
DMSO; dimethylsulfoxide
DT; di- or triphosphopyridine nucleotide
DT-diaphorase; quinone reductase
e⁻; electron
EC-SOD; extracellular SOD
EDRF; endothelium derived relaxing factor
ESR; electron spin resonance

FA; formaldehyde
 $\text{Fe}^{\text{IV}}=\text{O}$; oxoferryl complex in ferrylmyoglobin or ferrylhemoglobin
 FeSOD; iron SOD
 GPOX/Se-GPOX; selenium-dependent glutathione peroxidase
 GPOX-GI; gastrointestinal GPOX
 GR; glutathione (GSSG) reductase
 GSH; glutathione (reduced form)
 GS $\cdot$; glutathionyl radical
 GSSG; glutathione disulfide (oxidized form of GSH)
 GSSG $^{\cdot-}$; glutathione disulfide (anion) radical
 GSOH; sulfenic acid of glutathione
 GST; glutathione transferase
 GST_{px}; GST's peroxidase activity
 Hb; hemoglobin
 HOO $\cdot$ /HO₂ $\cdot$; hydroperoxyl radical
 HP; hydroperoxidase
 HPETE; ((S)-5-hydroperoxy-6-trans-8,11,14-*cis*-eicosatetranoic acid)
 HETE; metabolite of HPETE where hydroperoxy group is reduced
 to a hydroxyl group
 HRP; horseradish peroxidase
 HSP; heat shock protein
 HX- $\text{Fe}^{\text{IV}}=\text{O}$; ferrylmyoglobin or ferrylhemoglobin
 HX- Fe^{III} ; metmyoglobin or methemoglobin
 HX- $\text{Fe}^{\text{II}}\text{O}_2$; oxymyoglobin
 IBD; inflammatory bowel disease
 IOM; inside out membrane
 I/R; ischemia/reperfusion
 LH/RH; unsaturated lipid/organic compound
 L $\cdot$ /R $\cdot$; lipid/organic radical
 LOH/ROH; lipid/organic alcohol
 LOOH/ROOH; lipid/organic hydroperoxide
 LOO $\cdot$ /ROO $\cdot$ (LO₂/RO₂); lipid or peroxy radical
 LO $\cdot$ /RO $\cdot$; alkoxyl radical
 LDL; low-density lipoprotein
 LT; leukotriene
 LTB₄; leukotriene B₄
 MDA; malondialdehyde
 MnSOD; manganese SOD
 NMR; nuclear magnetic resonance
 MPO; myeloperoxidase
 NASA; N-acetyl-5-ASA

$\cdot\text{NO}$ (or NO); nitric oxide
 NO_2 ; nitric dioxide
 $\text{NPh}\cdot\text{O}$; 1-naphthoxyl radical
 NPhOH ; 1-naphthol
 $^1\text{O}_2$; singlet oxygen
 O_2 ; molecular oxygen
 O_2^- ; superoxide anion radical
 $\cdot\text{OH}/\text{HO}\cdot$; hydroxyl radical
 PA ; D-penicillamine
 PAF ; platelet activating factor
 $\text{PBB}'\text{s}$; polybromobiphenyls
 $\text{PCB}'\text{s}$; polychlorobiphenyls
 PG ; prostaglandin
 PGD_2 ; prostaglandin D_2
 PGE_2 ; prostaglandin E_2
 PGG_2 ; prostaglandin G
 PGH_2 ; prostaglandin H_2
 PG/PS ; peptidoglycan/polysaccharide
 PH-GPOX ; phospholipid hydroperoxide GPOX
 PL-GPOX ; plasma GPOX
 PMNs ; polymorphonuclear leukocytes
 POD ; peroxidase (also HRP)
 PUFA ; polyunsaturated fatty acid
 Q ; quinone
 $\text{Q}\cdot^-$; semiquinone (radical)
 QH_2 ; hydroquinone (dihydroquinone)
 RBC ; red blood cell
 ROMs ; reactive oxygen metabolites (=ROS)
 ROS ; reactive oxygen species
 RSH ; thiol compound
 RS^- ; thiolate anion
 $\text{RS}\cdot^-$; thiyl radical
 RS_2 ; aliphatic dithiol (e.g. α -dihydrolipoic acid)
 $\text{RSSR}\cdot^-$; disulfide anion radical
 SAZ ; sulfasalazine
 SOD ; superoxide dismutase
 SP ; sulphapyridine
 TBHQ ; 2 (3)-tert-butyl-4-hydroquinone
 TCDD ; 2,3,7,8-tetrachlorodibenzo-p-dioxin
 TCP ; tetrachloro-1,4-benzoquinone
 TEMPO ; 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl

α -T-OH/ α -TH; α -tocopherol
 α -T-O $\cdot$ / α -T $\cdot$; α -tocopheroxyl radical
 γ -TH; γ -tocopherol
 γ -T $\cdot$; γ -tocopheroxyl radical
U; uric acid
U $\cdot$; uric acid radical
UH $^-$; urate
UQ₁₀; ubiquinone-10
UQ₁₀ $^-$ /UQH $\cdot$; ubi-semiquinone radical
UQ₁₀H₂; ubiquinol-10
Vitamin C; ascorbic acid
Vitamin (vit) E; α -tocopherol
Vit E $\cdot$; α -tocopheroxyl radical
XD; xanthine dehydrogenase
XO; xanthine oxidase