Series Preface

OXYGEN BIOLOGY AND MEDICINE

Through evolution, oxygen—itself a free radical—was chosen as the terminal electron acceptor for respiration. The two unpaired electrons of oxygen spin in the same direction; thus, oxygen is a biradical. Other oxygen-derived free radicals, such as superoxide anion or hydroxyl radicals, formed during metabolism or by ionizing radiation, are stronger *oxidants*, i.e., endowed with a higher chemical reactivity. Oxygen-derived free radicals are generated during metabolism and energy production in the body and are involved in regulation of signal transduction and gene expression, activation of receptors and nuclear transcription factors, oxidative damage to cell components, antimicrobial and cytotoxic action of immune system cells, as well as aging and age-related degenerative diseases. Conversely, the cell conserves antioxidant mechanisms to counteract the effect of oxidants; these *antioxidants* may remove oxidants either in a highly specific manner as, for example, by superoxide dismutases or in a less specific manner (for example, small molecules such as vitamin E, vitamin C, and glutathione). *Oxidative stress* as classically defined is an *imbalance between oxidants and antioxidants*. Overwhelming evidence indicates that oxidative stress can lead to cell and tissue injury. However, the same free radicals that are generated during oxidative stress are produced during normal metabolism and, as a corollary, are involved in both human health and disease.

Oxygen is a dangerous friend and virtually all diseases thus far examined involve oxygen free radicals and redox reactions. In most cases, free radicals are secondary to the disease process, but in some instances, causality by free radicals themselves is known. It has been established that low levels of oxygen free radicals and reactive oxygen species are essential for some cell signaling pathways Thus, a delicate balance among oxidants, antioxidants, and redox status is essential for healthy aging.

Reactive oxygen species, i.e., nonradical oxidants such as H_2O_2 and $^1O_2$, and other species reflect the rich variety of reactive species in free radical biology and medicine, i.e., encompassing nitrogen-, sulfur-, oxygen-, and carbon-centered radicals. With the discovery of nitric oxide, nitrogen-centered radicals gathered momentum and have matured into an area of enormous importance in biology and medicine. Nitric oxide or nitrogen monoxide (NO), a free radical generated in a variety of cell types by nitric oxide synthases (NOS), is involved in a wide array of physiological and pathophysiological phenomena, such as vasodilation, neuronal signaling, and inflammation. Of great importance is the reaction of nitric oxide with superoxide anion: this is among the most rapid nonenzymatic reactions in biology (well over the diffusion-controlled limits) and yields the potent nonradical oxidant, peroxynitrite, involved in tissue injury through oxidation and nitration reactions.

Gaseous species such as hydrogen sulfide and molecular hydrogen produced at low levels in tissues by enzymes and by intestinal and tissue microbiota (microbiome)

are also recognized as important regulators of oxidative stress and in maintaining tissue homeostasis.

Reactive oxygen and nitrogen species and the hydrogen gases are involved in the redox regulation of cell function. Oxidative stress is increasingly viewed as a major upstream component in the signaling cascade involved in inflammatory responses, stimulation of cell adhesion molecules, and chemoattractant production and as an early component in age-related neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's disease and amyotrophic lateral sclerosis. Hydrogen peroxide is probably the most important redox signaling molecule that, among others, can activate NF-κB, Nrf2, and other universal transcription factors. Increasing steady-state levels of hydrogen peroxide have been linked to the cell's redox status with clear involvement in adaptation, proliferation, differentiation, apoptosis, and necrosis. The identification of oxidants in regulation of redox cell signaling and gene expression was a significant breakthrough in the field of oxidative stress: the classical definition of oxidative stress as an *imbalance between the production of oxidants and the occurrence of cell antioxidant defenses* proposed by Sies in 1985 now seems to provide a limited concept of oxidative stress, but it emphasizes the significance of the cell's redox status, because individual signaling and control events occur through discreet redox pathways rather than through global balances.

Thus, a new definition of oxidative stress was advanced by Dean P. Jones (*Antioxidants & Redox Signaling*, 2006) as a disruption of redox signaling and control that recognizes the occurrence of compartmentalized cellular redox circuits. Measurements of GSH/GSSG or cysteine/cystine, thioredoxin$_{reduced}$/thioredoxin$_{oxidized}$ provide a quantitative definition of oxidative stress. The redox status is thus dependent on the degree to which tissue-specific cell components are in the oxidized state. In general, the reducing environment inside cells helps to prevent oxidative damage. In this reducing environment, disulfide bonds (S—S) do not spontaneously form because sulfhydryl groups are maintained in the reduced state (SH), thus preventing protein misfolding or aggregation. The reducing environment is maintained by metabolism and by the enzymes involved in maintenance of thiol/disulfide balance and substances, such as glutathione, thioredoxin, vitamins E and C, and enzymes such as superoxide dismutases, catalase, and the selenium-dependent glutathione reductase and glutathione and thioredoxin-dependent hydroperoxidases (peiredoxins), which serve to remove reactive oxygen species (hydroperoxides). Also of importance is the recognition of the existence of many tissue-specific and cell compartment–specific isoforms of antioxidant enzymes and proteins.

Compelling support for the involvement of free radicals in disease development originates from epidemiological studies that show that an enhanced antioxidant status is associated with reduced risk of several diseases. Of high significance is the role that micronutrients play in modulation of redox cell signaling: this establishes a strong link between diet and health centered on the ability of micronutrients to regulate redox cell signaling and modify gene expression.

These concepts are anticipated notions to serve as a platform for the development of tissue-specific therapeutics tailored to discreet, compartmentalized redox circuits. This, in essence, dictates principles of drug development guided knowledge of

mechanisms of oxidative stress. Hence, successful interventions will take advantage of new knowledge of compartmentalized redox control and free radical scavenging.

In this series of books, the importance of oxidative stress and disease associated with organ systems of the body is highlighted by exploring the scientific evidence and clinical applications of this knowledge. These books are intended for researchers in the basic biomedical sciences, health professionals, and clinicians. The potential of such information for healthy aging and disease prevention warrants further knowledge about how oxidants and antioxidants modulate cell and tissue function.

"The Role of Nutrition and Metabolism on Epigenetic Regulation" by Emily Ho and Frederick Domann

Jean-Baptiste Larmar proposed a popular idea in the early nineteenth century, which advanced the idea that characteristics acquired during a lifetime of an organism could be passed on to future generations. The concept was largely dismissed later in the nineteenth century with the origin of the Mendelian inheritance conceived by the work of Gregor Johann Mendel. However, since the twentieth century, environmental effects on genes, epigenetics research, and the role of the epigenome have dramatically changed our modern concepts of inheritance where the human diet plays an important role.

To appreciate this rapidly developing and important area of research requires a book that brings together and highlights the major nutrients and their epigenetic relevance to health and disease. The editors of this volume and the internationally renowned authors who have contributed are to be congratulated for bringing together "the most important dietary factors and specific nutrients that can modulate epigenetic alterations and their susceptibility to disease" as stated by the editors.

Lester Packer
Enrique Cadenas