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COMMENTARY

Oxidants and antioxidants revisited. New concepts of oxidative stress

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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 the regulation of signal transduction and gene expression, activation of receptors and nuclear transcription factors, oxidative damage to cell components, the antimicrobial and cytotoxic action inherent in immune system cells, as well as in ageing 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).

Understanding oxidative stress

Oxidative stress is 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.

In recent years, the research disciplines interested in *oxidative stress* have grown and remarkably increased our knowledge of the importance of the cell redox status and the recognition of oxidative stress as a process with implications for many pathophysiological states. From this multi- and interdisciplinary interest in oxidative stress emerges a concept that attests to the vast consequences of the complex and dynamic interplay of *oxidants* and *antioxidants* in cellular and tissue settings. Consequently, our view of *oxidative stress* is growing in scope and new future directions. Likewise, the term 'reactive oxygen species', adopted at some stage in order to highlight non-radical oxidants such as H_2O_2, peroxynitrite and $^1O_2$, fails nowadays to reflect the rich variety of other reactive species in free radical biology and medicine, i.e. encompassing nitrogen-, sulphur-, oxygen-, and carbon-centred radicals. With the discovery of nitric oxide, nitrogen-centred radicals gathered momentum and has matured into an area of enormous importance in biology and medicine. Nitric oxide or nitrogen monoxide ($^{\bullet}NO$), a free radical generated by a variety of cell types by nitric oxide synthases (NOS), is involved in a wide array of physiological

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and pathophysiological phenomena, such as vasodilation, neuronal signalling and inflammation. Of great importance is the radical–radical reaction of nitric oxide with superoxide anion: this is among the most rapid non-enzymatic reactions in biology (at nearly the diffusion limit) and yields the potent non-radical oxidant, peroxynitrite. The involvement of this species in tissue injury through oxidation and nitration reactions is well documented.

Virtually all diseases thus far examined involve free radicals. In most cases, free radicals are secondary to the disease process, but in some instances causality is established by free radicals themselves. Thus, there is a delicate balance between oxidants and antioxidants in health and disease. Their proper balance is essential for ensuring healthy ageing.

Both reactive oxygen and nitrogen species are involved in the redox regulation of cell functions. Oxidative stress is increasingly viewed as a major upstream component in the signalling cascade encompassed by inflammatory responses, stimulation of cell adhesion molecules and chemo-attractant production and as an early component in age-related neurodegenerative disorders, such as Alzheimer's, Parkinson's, Huntington's disease and amyotrophic lateral sclerosis. Hydrogen peroxide is probably the most important redox signalling 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 signalling and gene expression was a significant breakthrough in the field of oxidative stress: hence, the classical assessment of oxidative stress as an *imbalance between the production of oxidants and the occurrence of cell antioxidant defenses* proposed by Sies [1] 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 signalling and control events occur through discreet redox pathways rather than through global balances, a new definition of oxidative stress was advanced in 2006 by Jones [2,3] as a *disruption of redox signalling and control* that recognizes the occurrence of compartmentalized cellular redox circuits. Recognition of discreet thiol redox circuits led Jones to provide this new definition of oxidative stress. Measurements of GSH/GSSG or cysteine/cystine, $\text{thioredoxin}_{\text{reduced}}/\text{thioredoxin}_{\text{oxidized}}$ provide a quantitative definition of redox status from which an assessment of oxidative stress can be made. Moreover, the dynamic ratio of glutathionylated/deglutathionylated proteins (Prot–SSG $\leftrightarrow$ Prot-SH) is also a valuable marker of oxidative stress and is thought to protect temporarily cysteine residues from reversible or irreversible modifications, such as S-nitrosylation and oxidation to sulphonic acid. 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 prevent oxidative damage. In this reducing environment, disulphide bonds (S—S) do not spontaneously form because sulphydryl groups are maintained in the reduced state, thus preventing protein misfolding or aggregation. The thiol/disulphide balance is maintained by metabolic and redox pathways entailing compounds such as glutathione, thioredoxin, vitamins E and C and enzymes such as superoxide dismutases, catalase and the thioredoxin, glutaredoxin and peroxiredoxin systems. Also of importance is the recognition of the existence of many tissue- 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 showing that an enhanced antioxidant status is associated with reduced risk of several diseases.

Of high importance is the role that micronutrients play in modulation of redox cell signalling: this establishes a strong link between diet and health and disease, which results from the ability of micronutrients to regulate redox cell signalling and modify gene expression.

These new concepts of oxidative stress serve as a platform for development of tissue-specific therapeutics tailored to discreet, compartmentalized redox circuits. In essence, this dictates the principles of *nutrient modulation* of oxidative stress as well as of drug development targeted towards regulation of oxidative stress. Hence, successful interventions should take advantage of new knowledge of redox control and free radical scavenging.

Acknowledgements

Adapted from *Oxidative Stress and Disease* Series Introduction, Taylor & Francis CRC Press. Editors: Lester Packer and Enrique Cadenas.

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