ANTIOXIDANTS & REDOX SIGNALING
Volume 2, Number 3, 2000
Mary Ann Liebert, Inc.

Forum Editorial

Antioxidants: Strategies for Interventions in Aging and Age-Related Diseases

A Workshop Sponsored by the National Institute on Aging and by the Office of Dietary Supplements

VICTOR DARLEY-USMAR[1] and PAMELA E. STARKE-REED[2]

ABSTRACT

The role of free radicals in aging has been a long-standing theory that has now been extended to include both reactive oxygen and nitrogen species. The original concepts that overwhelming oxidative stress depleted antioxidants and thus damaged intracellular targets is being supplanted by the hypothesis that the reactive species play an essential role in signal transduction. The concept that the cell establishes a redox tone that is altered during the aging process places the oxidative and nitrosative modifications that occur during aging in a new and exciting context. Some highlights of this recent workshop convened by The National Institute on Aging and the Office of Dietary Supplements at the National Institutes of Health are discussed. Antiox. & Redox Signal. 2, 375–378.

MEETING COMMENTARY

DISEASES OF AGING and the aging process itself are important areas of research because of both the impact on health economics and the insights into fundamental biological processes such studies can offer. Despite the broad impact of aging on society, the understanding from a biological perspective is only now entering a rapid growth phase. This is being driven by the insights molecular approaches can bring to the understanding of the events that occur at the cellular level. This is, of course, not a unique feature of aging research, but what is different is the need to integrate key elements of research on diet, exercise, and chronic disease into the basic mechanisms that cause the cells in organisms to become "functionally old." It is this need to understand better the interface between the disease process, lifestyle changes, including diet, and the response of the cell at the molecular level that led to this workshop. A small group of investigators expert in a diverse but interrelated range of topics encompassing the metabolism of antioxidant compounds, signal transduction, experimental models of aging, and neurodegenerative diseases was convened to discuss these issues. In the following articles, a sense of the general scientific elements that

[1]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL 35295-0019.
[2]Deputy Director, National Institutes of Health, Division of Nutrition Research Coordination, NIDDK, Bethesda, MD 20892-7973.

frame this debate can be gained. This short overview outlines the overall themes that emerged in the ensuing discussion that may be of interest to aging researchers or, indeed, researchers of the aging process.

The main topics covered by the workshop and some of the general principles that emerged are shown schematically in Fig. 1. This figure is designed to illustrate the interrelationships among topics and potential areas where essential linking elements are either missing altogether or poorly understood. Two critical elements that are emerging in the field of redox signaling that received a great deal of attention in the workshop are highlighted below.

Evaluation of the "oxidative stress" paradigm for aging research

An early question developed in the free radical field is whether a balance exists between the production of oxidants as by-products of oxygen metabolism and their detoxification by endogenous antioxidant defenses. Oxidative stress occurs when oxidant production exceeds the capacity for detoxification and/or repair, resulting in fatal damage to biomolecules such as lipids, proteins, and nucleic acids. *A priori*, this hypothesis ignores the now-emerging and essential role of reactive oxygen (ROS) and nitrogen species in signal transduction. Thus, this perspective has been in a constant state of modification since the discovery that the free radical, nitric oxide (NO), plays an essential role in cell signaling. These concepts are taking time to permeate the oxygen radical field, and the hypothesis that molecules such as superoxide and hydrogen peroxide activate signaling pathways is only recently gaining support. The implication of this is that some cellular antioxidant systems, such as the glutathione peroxidases and superoxide dismutases, regulate peroxide and superoxide levels, and thereby have an impact on signal transduction pathways. In support of this view, it is now clear that the members of these enzyme families are far more extensive than first thought and cellular location is an important factor which is highly controlled. In addition, the regulation and expression of these enzymes are far more complex than would be required for constitutive housekeeping genes. If reactive oxygen/nitrogen species are involved in signaling, it should follow that the formation of these species is also a tightly controlled process. Support for this hypothesis stems from new data identifying a family of oxidases that specifically generate superoxide, and perhaps hydrogen peroxide, in response to changing cellular conditions. The concept that hydrogen peroxide is simply an intermediate in oxidative metabolism in the mitochondrion is also due for revaluation. This is particularly pertinent in understanding the cross talk between nitrosative and oxidative cell signaling, which may be integrated at the mitochondrial respiratory chain.

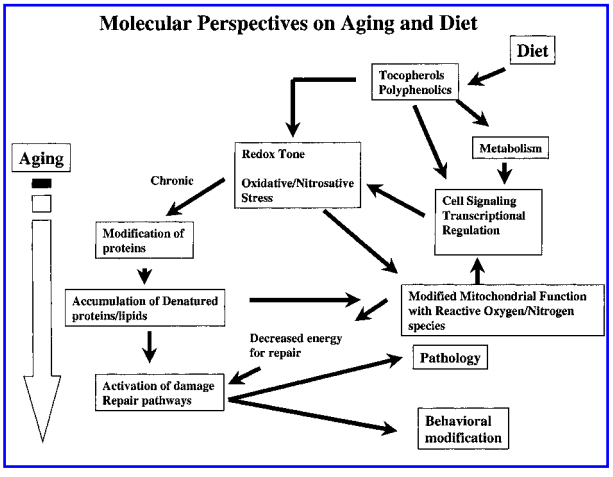

FIG. 1. Molecular perspectives on aging and diet.

These modulatory roles of reactive species or antioxidants in cell signaling do not preclude protection against excessive oxidative or nitrosative stress. However, it is essential to note that the cell signaling events can occur at extremely low concentrations of reactive species compared to the levels required to cause extensive nonspecific oxidation.

Redox tone and dietary antioxidants

The second related area of discussion is the concept that modulation of cell signaling molecules is responsive to subtle changes in the redox status of the cell within the physiological norm. Specifically this could involve the oxidation of vicinal thiols on a regulatory enzyme

in a signaling cascade by 20–30%. Because the enzyme can amplify the signaling pathway, a modest change in the oxidation of the protein can result in a significant change in cell function. For this reason, the concept of "oxidative stress" hardly applies because the cell is not under stress. A good analogy is the role various vascular mediators play, including free radicals such as NO, in establishing vascular tone with a balance between molecules that control constriction and relaxation in the blood vessel wall. Similarly, the balance between oxidants and reductants in the cell coupled through the activation of redox-sensitive enzymes establishes a "redox tone." In this setting, it is perhaps easier to understand why more care needs to be exercised when classifying dietary components as antioxidants. This is particularly important in the emerging field of research related to polyphenolic compounds in wine, fruits, and vegetables. It is now clear that although these molecules can exhibit antioxidant properties in *in vitro* or cell culture models, bioavailability and metabolism may so severely constrain the available concentrations *in vivo* that these direct relationships remain unclear. This has become a potentially urgent issue because partially purified or highly concentrated extracts of polyphenolics are becoming commercially available and the biological mechanisms underlying beneficial, or detrimental effects, remain poorly understood. Emerging evidence suggests that these molecules can alter the transcriptional regulation of important enzyme systems such as the NO synthases and superoxide dismutases. The mechanisms may remain unclear, but the concept that they indirectly modulate redox tone in the cells is receiving experimental support. Even for molecules such as the tocopherols, tocotrienols, and ascorbate, that have acquired the dogmatic persona of "classical" antioxidants, it is now clear that alternative mechanisms involving signal transduction should be considered.

SUMMARY

The interaction of investigators developing different concepts in closely related fields rarely occurs in the usual tightly focused, but large, meetings, but is often, as in this case, highly stimulating and rewarding. It is important to capitalize on the abundant literature on the direct effects of reactive oxygen and nitrogen species as primary mediators of cell damage and apply this knowledge to biological systems with a recognizable physiological output. One area where this is now happening is the field of redox cell signaling, which now becomes an important focus for future free radical and aging research endeavors. This will necessarily mean a refocus of attention on oxidative or nitrosative modification as modifiers of cell function rather than markers of excessive exposure. This will challenge analytical techniques to their current limits, but with the advent of mass spectrometry capable of analyzing individual modifications of proteins in cells this is becoming feasible.

Address reprint requests to:
Victor Darley-Usmar, Ph.D.
Department of Pathology
Volker Hall G019
1670 University Boulevard
University of Alabama at Birmingham
Birmingham, AL 35295-0019

This article has been cited by:

1. Samanta Di Francescomarino, Adolfo Sciartilli, Valentina Di Valerio, Angela Di Baldassarre, Sabina Gallina. 2009. The Effect of Physical Exercise on Endothelial Function. *Sports Medicine* **39**:10, 797-812. [CrossRef]
2. F FRANZONI, Y PLANTINGA, F FEMIA, F BARTOLOMUCCI, C GAUDIO, F REGOLI, A CARPI, G SANTORO, F GALETTA. 2004. Plasma antioxidant activity and cutaneous microvascular endothelial function in athletes and sedentary controls. *Biomedecine & Pharmacotherapy* **58**:8, 432-436. [CrossRef]
3. Virginia B.C. Junqueira, Silvia B.M. Barros, Sandra S. Chan, Luciano Rodrigues, Leandro Giavarotti, Ronaldo L. Abud, Guilherme P. Deucher. 2004. Aging and oxidative stress. *Molecular Aspects of Medicine* **25**:1-2, 5-16. [CrossRef]
4. Dean P Jones, Vino C Mody, Joanne L Carlson, Michael J Lynn, Paul Sternberg. 2002. Redox analysis of human plasma allows separation of pro-oxidant events of aging from decline in antioxidant defenses. *Free Radical Biology and Medicine* **33**:9, 1290-1300. [CrossRef]