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Forum Editorial

Antiaging Medicine: Antioxidants and Aging

VITTORIO CALABRESE[1] and MAHIN D. MAINES[2]

THE AGING PROCESS is a continuous set of events that causes gradual decrements in cellular functions (28). Individual actions of various factors as well as interplay among them are responsible for the cumulative untoward effects of aging. These factors can originate from within the cell or imposed upon it extracellularly. Accordingly, although the process of aging cannot be halted, offsetting the deleterious effects of these factors can significantly decelerate it. A common denominator of aging factors is their association with free radicals and modulation of redox potential of the cell (1, 2, 10, 11).

Oxygen radicals can originate within the cell organelles, as occurs in the course of normal functioning of the mitochondria respiratory chain complexes (11) or extra mitochondrially by redox-available iron generated in the course of heme (Fe-protoporphyrin IX) degradation. The synergistic action of active oxygen species and catalytically active iron on the tissue prominently figure in tissue damage (7, 22). The target organelles for iron-catalyzed oxygen radicals are the mitochondria and the lysosomes, which are particularly targeted in high risk organs—heart, liver, pancreatic β cells (7), and the brain (20), all of which show age-related decrement of functions and are tissues at risk (26). Consistent with this likely association is finding that iron accumulation and oxidative stress-mediated defects in mitochondrial functions are important factors in premature aging and tissue damage in Friedreich's ataxia (13).

The primary source of iron in the cell is the heme iron. The most effective mechanism for degradation of heme is the heme oxygenase (HO) system (15, 16, 18). The heme molecule is degraded isomer-specifically by the heme oxygenase (HO) isozymes, HO-1 and HO-2, a controlled process that for every atom of iron released one molecule of CO and bilirubin IXα are produced. Biliverdin is subsequently reduced to the potent antioxidant, bilirubin IXα, by biliverdin reductase, a dual-specific kinase (17). The heme molecule can also be degraded by nonisomer-specific mechanisms, without production of CO antioxidants (15). It is generally considered that there is a direct correlation between HO activity and cytoprotection afforded to the cell; in fact, the possible utility of degradation products of the porphyrin ring—CO and biliverdin/bilirubin—in therapeutic settings is currently under consideration (17, 28). While bilirubin inactivation of free radicals of oxygen has been known for some time now (27), a newly discovered activity of the bile pigment, that is denoted by Mancuso *et al.* (19), is its interaction with nitric oxide. Nitrogen oxide radicals, particularly peroxyinitrite, are among the most potent oxidizing radicals (1).

Although heme is degraded extramitochondrially, it is synthesized in the mitochondria. Heme synthesis, which is a complex and lengthy chain of reactions, is initiated in the mitochondria by condensation of succinyl-CoA and glycine, undergoes a series of oxidation and condensation steps in the cytosol, and is terminated by chelation of iron into the protoporphyrin IX tetrapyrrole ring. Uroporphyrin and coproporphyrin isomers constitute intermediary compounds in the pathway of protoporphyrin IX synthesis. The porphyrin intermediates as well as protoporphyrin itself in the presence of molecular oxygen produce free radicals that target cellular components (25). In cases when there is deficiency of iron available for heme biosynthesis or deficiencies in micronutrients that are essential for formation of correct intermediates and orderly progression of enzymatic steps, an enlarged pool of oxygen-reactive species will be generated, with resulting damage to the cell (26).

In addition, changes in metabolic processes, when combined with a suboptimal nutritional state, figure prominently in the aging process. The contribution of these factors to aging can clearly be attenuated through enhancement of antioxidant potential of the cell (4) and implementing changes in life style and diet that prevent aging from within the cell (12, 24, 26). The changes may be as small as inclusion of a common spice in the diet (26) or fortifying the diet with antioxidant supplements.

The deleterious effect of oxygen radicals on the tissue, the cumulative effect of which is a presentation of aging process, does not go on in total absence of cellular offenses against them. An evolutionary conserved cytoprotection mechanism against oxidative stress includes activation of those genes that serve as chaperones and cytoprotectants (i.e., stress re-

[1]Department of Chemistry, Section of Biochemistry, University of Catania, Catania, Italy.
[2]Department of Biochemistry and Biophysics University of Rochester, School of Medicine, Rochester, New York.

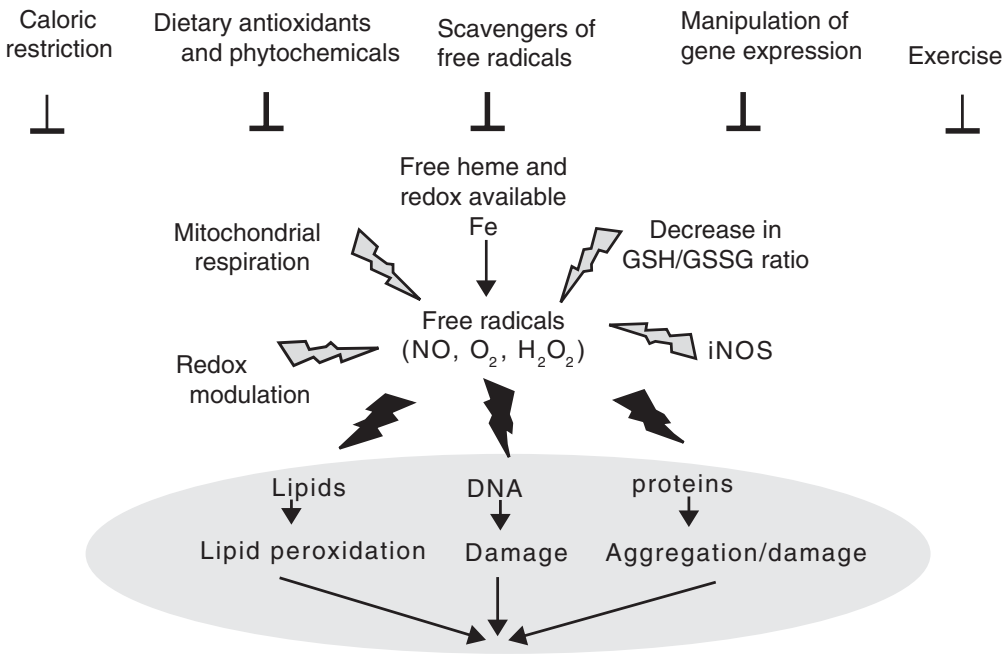

FIG. 1. Mediators of aging and factors that counter the process.

sponse/heat shock proteins). In aging cells, however, particularly in the brain and testes, response to stress is attenuated as exemplified by that of HO enzymes (8) and an altered response of other stress/heat shock proteins (23). In the case of the HO enzymes, because the gaseous product of their activity, CO, is a signaling molecule for neuronal activity (5, 6, 14), decrease in its formation could represent a demise of aging.

At present, although it is only at the level of *in vitro* experimentation, the prospect of manipulation of expression of genes that are directly involved in cell death or survival as anti-aging medicine is becoming increasingly plausible. For instance, attenuation of genes such as NFκB, which is activated in several types of cancer, may impact chemotherapy (21); similarly, induction of Nrf2 (NF-E2), the expression of which enhances expression profile of various genes with antioxidant potential, as well as HO-1 (18), is a promising approach (9) (Fig. 1).

In sum, based on the increasing understanding of the molecular basis for activity of factors that promote tissue damage and ultimately aging, and the rapid development of approaches to retard their advancement, the prospect of significant increase in longevity with maintenance of optimum cellular functions in the future is bright.

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ABBREVIATIONS

CO, carbon monoxide; HO, heme oxygenase; NFκB, nuclear factor-κB; Nrf2 (NF-E2), nuclear factor erythroid 2-related factor.

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Address reprint requests to:
Mahin D. Maines
Department of Biochemistry and Biophysics
University of Rochester Medical Center
Rochester, NY, 14620–2945

E-mail: Mahin_maines@urmc.rochester.edu

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