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Editorial

Antioxidants: GRABbing new headlines

A great many small-molecular-weight compounds have been touted as scavengers of oxidants and proposed as cure-alls for a large variety of pathologies in which oxidative stress plays a significant role. But, although these compounds may work in test tube experiments, efficient radical scavenging in cells, with the notable exception of vitamin E, is unlikely because of the inability to reach significantly high concentrations to compete with all the potential targets in the cell. Furthermore phytochemicals have relatively slow rate constants for reaction with oxidants in two-electron reductions compared with enzymes.

Despite this inability to scavenge oxidants, the epidemiological evidence strongly suggests that many phytochemicals have protective effects against oxidative stress. Although some of these “antioxidant” compounds have potential as drugs, they cannot be claimed to be so because they have yet to be shown to cure or prevent specific diseases as demonstrated through clinical trials. But, as many other drugs were grandfathered into the pharmacopeia because they were “generally regarded as safe,” we propose that many phytochemicals should be “Generally Regarded as Beneficial” (or GRAB).

But, the big question is how dietary “antioxidants” actually work. With this in mind, we invited experts in the field to contribute to this special issue of *Free Radical Biology & Medicine* to address several questions: How does vitamin E work in vivo? How do polyphenols and other phytochemicals (or their metabolites) act as “antioxidants”? How and where do antioxidant enzymes and their mimics act to protect cells and organisms? Are there alternatives, including chemical modification of natural antioxidants or dietary alterations, that can also improve antioxidant defenses?

In this special issue are 11 reviews in three sections. The first section primarily concerns vitamin E and radical scavenging. It begins with an article by Niki [1] on how vitamin E functions as a hydroperoxyl radical scavenger. This explains how α-tocopherol can be the exceptionally effective nutritional antioxidant. Lebold and Traber [2] describe how vitamin E also interacts with polyunsaturated fatty acids and lipoxygenases. They provide a specific example of these interactions during embryogenesis. Murphy [3] then describes how molecules can be modified to overcome the problems that other natural antioxidants have in effectively scavenging oxidants in vivo.

The second section focuses on the mechanisms through which the phytochemicals and some potential drugs activate the Nrf2 signaling system that controls enzymatic antioxidant defense. Forman, Davies, and Ursini [4] provide a combined historical and chemical perspective on the mechanism through which phytochemicals drive the Nrf2-dependent induction of protective oxidoreductases and their nucleophilic substrates. Maintenance of this “nucleophilic tone” is regulated by physiological nontoxic concentrations of nonradical oxidant electrophiles derived from phytochemicals in a process named “parahormesis.” Niture, Khatri, and Jaiswal [5] describe some of the more recent findings on the mechanism underlying the activity of Nrf2, including interactions with vitamin E. Particular emphasis is put on how Fyn activation leads to the export of Nrf2 from the nucleus and its subsequent degradation. Satoh, McKercher, and Lipton [6] describe a specific example of how the phytochemicals carnosic acid and carnosol, which come from rosemary, are oxidized to electrophiles, which then activate Nrf2 signaling. Mechanisms underlying how these compounds can be developed to combat neurodegenerative diseases are also provided. The potential downside of how increased antioxidant defenses from Nrf2 activation can protect cancer cells from chemotherapy is addressed by Surh [7]. The dramatic role in cancer cell resistance of heme oxygenase-1, one of the most responsive genes to Nrf2 activation, is emphasized.

In the final section, the recent reconsideration of the pros and cons on the utility of antioxidant enzyme mimics as well as the mechanisms through which the enzymes that remove superoxide and hydroperoxides are described. Day [8] discusses the abnormal biology of oxygen and the dependence of antioxidant defense on NADPH. But, he also warns that antioxidants may interfere with normal processes depending on oxidant production. Orian and Toppo [9] then describe how mimics of glutathione peroxidases have been designed to take advantage of the unique mechanism these enzymes use to accelerate the reduction of hydroperoxides by thiols. They also warn about the unintended consequences of such compounds in modulating thiol-dependent cell processes. The thioredoxin antioxidant system is described by Lu and Holmgren [10]. Included in their discussion is the cross talk between the glutathione and the thioredoxin systems, roles of thioredoxin in cancer and immune responses, and a thorough discussion of the importance of thioredoxin in bacterial physiology. The final article, by Walsh, Shi, and Van Remmen [11], provides insight into an alternative dietary means for lowering oxidative stress. Rather than increasing phytochemicals, dietary restriction seems to decrease oxidative injury and possibly affect aging by elevating glutathione levels.

The goal of this special issue is to provide new insight into how antioxidants affect physiology. We hope the readers will agree that these 11 review articles succeed in achieving that goal.

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References

[1] Niki, E. Role of vitamin E as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence. *Free Radic. Biol. Med.* **66:**3–12; 2014.

[2] Lebold, K. M.; Traber, M. G. Interactions between α-tocopherol, polyunsaturated fatty acids, and lipoxygenases during embryogenesis. *Free Radic. Biol. Med.* **66:**13–19; 2014.

[3] Murphy, M. P. Antioxidants as therapies: can we improve on nature? *Free Radic. Biol. Med.* **66:**20–23; 2014.

[4] Forman, H. J.; Davies, K. J. A.; Ursini, F. How do nutritional antioxidants really work: nucleophilic tone and para-hormesis versus free radical scavenging in vivo. *Free Radic. Biol. Med.* **66:**24–35; 2014.

[5] Niture, S. K.; Khatri, R.; Jaiswal, A. K. Regulation of Nrf2—an update. *Free Radic. Biol. Med.* **66:**36–44; 2014.

[6] Satoh, T.; McKercher, S. R.; Lipton, S. A. Nrf2/ARE-mediated antioxidant actions of pro-electrophilic drugs. *Free Radic. Biol. Med.* **66:**45–57; 2014.

[7] Surh, Y. J. Oncogenic potential of Nrf2 and its principal target gene heme oxygenase-1. *Free Radic. Biol. Med.* **67:**353–365; 2014.

[8] Day, B. J. Antioxidant therapeutics: Pandora's box. *Free Radic. Biol. Med.* **66:**58–64; 2014.

[9] Orian, L.; Toppo, S. Organochalcogen peroxidase mimetics as potential drugs: a long story of a promise still unfulfilled. *Free Radic. Biol. Med.* **66:**65–74; 2014.

[10] Lu, J.; Holmgren, A. The thioredoxin antioxidant system. *Free Radic. Biol. Med.* **66:**75–87; 2014.

[11] Walsh, M. E.; Shi, Y.; Van Remmen, H. The effects of dietary restriction on oxidative stress in rodents. *Free Radic. Biol. Med.* **66:**88–99; 2014.

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