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Forum Editorial

The Many Nuances of Oxidative Stress and Proteolysis

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OXIDATIVE DAMAGE IS NOT SYNONYMOUS WITH OXIDATIVE STRESS

Elevations in oxidized macromolecules can promote potentially deleterious alterations in cellular homeostasis, ultimately placing cells in a condition commonly referred to as oxidative stress (2–4, 7). It is becoming increasingly clear that evidence for oxidative stress is found in a variety of paradigms and experimental settings, with oxidative stress likely to play a role in the cellular dysfunction that occurs in those conditions. Because of these observations, understanding the mechanism(s) responsible for inducing oxidative stress, and understanding the downstream events responsible for mediating oxidative stress-induced cytotoxicity, are of fundamental importance.

The role of oxidative stress in mediating cellular dysfunction is not as straightforward, or as simple, as it may first appear. Immediately one must be concerned with the multitude of questions that readily become evident. How much oxidative damage must occur in order to alter the function of a given cellular component? Are elevations in oxidative damage the result of increased reactive oxygen species (ROS) or the result of decreased repair/removal/synthesis? How many macromolecules must be damaged in order to induce oxidative stress? The answer to each of these questions depends on a variety of factors including which cell type is involved, the mitotic status of the cell, and additionally what stressor(s) the cell is encountering. In addition to these relatively straightforward questions, potentially more abstract and difficult questions also arise. For example, is the toxicity of oxidative stress a direct result of the increase in oxidative damage, or is it an indirect result of cells attempting to compensate for the presence of oxidized moieties? Regardless, what clearly emerges from a critical assessment of the field of oxidative stress research, is the fact that oxidative damage is not synonymous with oxidative stress. Clearly, oxidative damage is a component of oxidative stress, but the ultimate ability of oxidative damage to induce oxidative stress is absolutely dependent on a variety of cell type specific factors.

Although there are many types of cellular components which can be oxidized, numerous lines of evidence suggest that protein oxidation may be one of the most important forms of oxidative damage (3, 11). As much as 30%–40% of all proteins may exhibit protein oxidation as part of normal aging (3, 11), and increased protein oxidation being one of the first events observed in a variety of pathological conditions (3, 4, 9), with elevations in protein oxidation tightly linked with increased cellular toxicity. In this line of thinking, the oxidation of proteins is believed to promote the loss of normal protein function, as well as promote a variety of deleterious alterations ranging from protein fragmentation to protein aggregation (3, 4, 9). Yet even with regards to the role of protein oxidation as a mediator of oxidative stress, several nuances and important questions remain. For example, how much oxidation must occur to be deleterious to protein function? Is the elevation in protein oxidation the result of increased ROS or decreased repair/removal/synthesis? How many proteins must be oxidized in order to induce oxidative stress? And perhaps most importantly, is oxidative stress due to increased levels of oxidized proteins, or the cellular attempts to compensate for the presence of oxidized proteins?

OXIDATIVE STRESS AND PROTEOLYSIS

In this collection we focus on the nuances and controversies that surround the current understanding of the role proteolysis plays in oxidative stress, which ultimately is centered on the relationship between altered rates of proteolysis and elevations in protein oxidation. In these articles it is clear that the proteasomal (4–8) and lysosomal (7, 10, 12, 13) proteolytic pathways are critical to regulating oxidative stress, with the

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preservation or enhancement of these proteolytic pathways sufficient to ameliorate increases in protein oxidation and thereby suppress oxidative stress (1, 7, 8, 13). Conversely, inhibition of these pathways appears to be sufficient to induce elevations in protein oxidation and promote oxidative stress (4, 7, 9, 12). As such, it is clear that proteolysis is a central mechanism for both the promotion and inhibition of oxidative stress. Articles within this issue describe evidence for proteasome inhibition alone being sufficient to increase ROS formation (4), while the presence of excessively oxidized proteins is observed to be sufficient to inhibit proteolytic pathways (4, 7, 13), thus clouding the relationship between proteolysis and oxidative stress. Additionally, evidence for cross talk between the proteasomal and lysosomal pathways is emerging, and is discussed in this collection of articles (4, 7, 13).

FUTURE DIRECTIONS

It is hoped that these articles will stimulate an intelligent, critical, and careful analysis of the interplay between proteolysis and oxidative stress. The ultimate goal of this forum is to stimulate many investigators to pursue research that ultimately answers the many important questions that remain in this active area of research. In particular it is hoped that studies in the near future will elucidate how proteolysis is impaired by oxidative stressors, and how the inhibition of these proteolytic pathways contributes to altered turnover (i.e., degradation) of specific proteins. Once these protein targets of proteolysis are identified (both oxidized and nonoxidized), it is likely that a new and more accurate picture of oxidative stress-induced toxicity will emerge. For example, it is likely that such studies will identify new cellular pathways and cellular functions which are negatively impacted by oxidative stressors. Such findings may then open the door to new therapeutic interventions designed to maintain proteolysis during conditions of oxidative stress, or therapies designed to specifically address the protein targets of proteolysis which exhibit altered turnover during conditions of oxidative stress. Additionally, such studies may allow for the identification of novel biomarkers, which can be used in a variety of disorders to identify the onset of the earliest stages of pathology. I want to personally thank each of the authors who contributed to this collection, and the timely efforts of the many reviewers without whom this collection could never have been possible.

ABBREVIATIONS

CNS, central nervous system; ROS, reactive oxygen species.

REFERENCES

1. Bulteau AL, Moreau M, Saunois A, Nizard C, and Friguet B. Algae extract-mediated stimulation and protection of proteasome activity within human keratinocytes exposed to UVA and UVB irradiation. *Antioxid Redox Signal* 8: 136–143, 2006.
2. Butler D and Bahr B. Oxidative stress and lysosomes: CNS-related consequences and implications for lysosomal enhancement strategies and induction of autophagy. *Antioxid Redox Signal* 8: 185–196, 2006.
3. Davies KJ. Oxidative stress: the paradox of aerobic life. *Biochem Soc Symp* 61: 1–31, 1995.
4. Ding Q, Dimayuga E, and Keller JN. Proteasome regulation of oxidative stress in aging and age-related diseases of the CNS. *Antioxid Redox Signal* 8: 163–172, 2006.
5. Ding Q, Martin S, Dimayuga E, Bruce-Keller AJ, and Keller JN. LMP2 knock-out mice have reduced proteasome activities and increased levels of oxidatively damaged proteins. *Antioxid Redox Signal* 8: 130–135, 2006.
6. Farout L and Friguet B. Proteasome function in aging and oxidative stress: implications in protein maintenance failure. *Antioxid Redox Signal* 8: 205–216, 2006.
7. Kiffen R, Bandyopadhyay U, and Cuervo AM. Oxidative stress and autophagy. *Antioxid Redox Signal* 8: 152–162, 2006.
8. Pettinari A, Amici M, Cuccioloni M, Angeletti M, Fioretti E, and Eleuteri AM. Effect of polyphenolic compounds on the proteolytic activities of constitutive and immunoproteasomes. *Antioxid Redox Signal* 8: 121–129, 2006.
9. Poppek D and Grune T. Proteasomal defense of oxidative protein modifications. *Antioxid Redox Signal* 8: 173–184, 2006.
10. Potashkin JA and Meredith GE. The role of oxidative stress in the dysregulation of gene expression and protein metabolism in neurodegenerative disease. *Antioxid Redox Signal* 8: 144–151, 2006.
11. Sohal RS. Role of oxidative stress and protein oxidation in the aging process. *Free Radic Biol Med* 33: 37–44, 2002.
12. Squier TC. Redox modulation of cellular metabolism through targeted degradation of signaling proteins by the proteasome. *Antioxid Redox Signal* 8: 217–228, 2006.
13. Terman A and Brunk UT. Oxidative stress, accumulation of biological 'garbage', and aging. *Antioxid Redox Signal* 8: 197–204, 2006.

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2. Anne-Laure Bulteau, Andrew Dancis, Monique Gareil, Jean-Jacques Montagne, Jean-Michel Camadro, Emmanuel Lesuisse. 2007. Oxidative stress and protease dysfunction in the yeast model of Friedreich ataxia. *Free Radical Biology and Medicine* **42**:10, 1561-1570. [CrossRef]