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Amino acid and protein modification by oxygen and nitrogen species

Editorial

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After the success of the first special issue dedicated to *Amino acid and protein modification by oxygen and nitrogen species*, published in *Amino Acids* 25 (2003), I am pleased to follow with this editorial initiative by presenting together with the Guest Editors, Dr. Darley-Usmar (University of Alabama at Birmingham, USA) and Dr. Radi (Universidad de la República, Uruguay), the papers in this issue, contributed by an outstanding panel of authors and dealing with a subject which remains of extreme interest for its exquisite multidisciplinary nature and its contribution to our understanding of specific biological mechanisms.

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Since the origin of free radical research, a variety of reactive species, mostly deriving from molecular oxygen and nitrogen (usually described with the acronyms ROS/RNS), and produced either endogenously by the cell metabolism or exogenously as components or derivatives of environmental pollution, tobacco smoke, drugs, etc., show different degrees of reactivity with virtually all the biomolecules in the cell and in biological fluids. Free amino acids and protein residues are among the targets of this chemistry.

On one hand, this reactivity of ROS/RNS plays a key role in important biological functions such as cell respiration, neurotransmission, and cell signaling. On the other hand, ROS are potentially harmful for living organisms in that they can cause molecular derangement and even destruction of cellular structures. Pathology arises if the output and/or reactivity of ROS/RNS assume overwhelming proportions with respect to the different lines of defence that are present in cells and biological fluids, a condition described with the term of ''oxidative stress''. In addition, loss of control of redox cell signaling pathways is also emerging as a major mechanism leading to cell dysfunction. Adaptation responses and repair systems are also present and may be effective to control the toxic effects of ROS at molecular level. Even this negative aspect of ROS/RNS biology has a positive role, being for instance involved in the cell-mediated immune response against tumor cells and bacteria, but it is more usually described as one of the underlying factors in aging and chronic-degenerative disease states. In this respect, products of the ROS/RNS and biomolecules have been widely used as biomarkers to trace such pathogenetic input of oxidative or nitrosative stress reaction. However, some discussion has arisen on the fact that ROS/RNS overproduction might be a consequence, rather than a cause, of the onset and progression of disease states in which chronic-degenerative events and inflammation take place.

On the side of physiological roles, in the recent years, a series of studies have shown that ROS/RNS contribute to intracellular signaling and intercellular communication. These key homeostatic events control differentiation, proliferation and death processes. At the same time, specific cell pathways finely tune ROS/RNS generation systems as an expression of the control of normal metabolism or

activation events resulting from stimuli of exogenous or endogenous origin. The central role that cellular proteins play on the control of these aspects has been widely recognized and their interaction with ROS/RNS is the subject of an intense research.

The review papers in this issue touch some of these aspects dealing with basic chemistry, analysis techniques and biological implications of protein and amino acid modifications by ROS/RNS.

In the first papers of this issue some aspects of nitric oxide-derived protein modifications are reviewed. Bartesaghi et al. (2007) provide an outstanding overview of protein tyrosine nitration mechanisms, an aspect of central importance in $NO^{\bullet}$ biochemistry and pathophysiology. Mechanisms of protein 3-nitrotyrosine formation are critically analyzed both in vitro and in vivo, considering the individual and/or combined role of redox components such as antioxidants and metals, the assistance of nitric oxide-dependent nitration steps and the facilitation by hydrophobic environments. The review paper also reports on the development and testing of hydrophilic and hydrophobic probes that can compete with endogenous constituents for the nitrating intermediates providing tools to unravel nitration mechanisms in vitro and in vivo.

Trostchansky and Rubbo (2007) have examined the available literature on lipid-protein adduct formation during oxidative and nitrative stress conditions associated with increasing lipid and protein oxidation and nitration. The heart of this paper is the analysis of interactions between oxidative-modified lipids and proteins and how lipid nitration can modulate lipid-protein adduct formation. Two biologically-relevant models were analysed: a) human low density lipoprotein, whose oxidation is involved in the early steps of atherogenesis, and b) the α-synuclein/lipid membranes system, where lipid-protein adducts are now being associated with the development of Parkinson disease and other synucleinopathies.

The review of Mannick (2007) describes the mechanisms of regulation of apoptosis by S-nitrosylation/denitrosylation of critical cysteine residues on cell proteins. These represent redox switches along the cell signaling selectively sensitive to endogenous $NO^{\bullet}$ production which operates to fine tune the responses to apoptotic signals.

In the review paper of Voss and Grune (2007) the proteasomal system developed by mammalian cells to selectively degrade damaged and miss-folded proteins at cellular level is described. This prevents the accumulation of oxidative stress-derived protein damage which is known to be linked to cell aging and some severe neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease. The authors focus on the nuclear proteasomal system and its specific role in the degradation of nuclear proteins under oxidative conditions.

An overview of EPR spin-trapping methodology and application to investigate protein radicals during oxidative mechanisms has been contributed by Augusto and Muntz Vaz (2007). This technique can provide relevant insights into the biological reactivity of known and emerging biological oxidants and into signaling mechanisms involving specific residues of proteins.

Carballal et al. (2007) describe the role of sulfenic acid as an intermediate of both the reversible and irreversible redox modulation by ROS of an increasing number of proteins involved in signal transduction and enzymatic pathways. In this paper the authors focus on the formation and stabilization of sulfenic acid after oxidation of the free thiol Cys34 of human serum albumin through one- or two-electron mechanisms as an appropriate model to examine protein sulfenic acid biochemistry.

The last three review papers deal with clinical aspects of oxidative stress and protein/amino acid chemistry. Polidori et al. (2007) have reviewed protein oxidative damage in Alzheimer's disease mostly focusing on the role of oxidatively modified proteins as hallmarks of the imbalance between pro-oxidant and antioxidant species or repair and removal systems in this neurodegenerative condition and brain aging overall.

In the paper of Perła-Kaján et al. (2007) the toxicity mechanisms of homocysteine are reviewed in the context of endothelial dysfunction as well as on protein metabolism with a special respect to posttranslational modification of protein involving homocysteine thiolactone. These aspects may help to understand the possible role of this non-protein amino acid as a risk factor for ischemic heart disease and stroke in humans being proposed as pro-thrombotic and pro-inflammatory factor, and endoplasmatic reticulum-stress inducer. The authors describe the chemistry of the incorporation of Hcy into proteins via disulfide or amide linkages (S-homocysteinylation or N-homocysteinylation) as mechanisms that can take place in vivo and affect protein structure and function.

Piroddi et al. (2007) have critically examined the literature on the pathogenetic role that protein glycation and oxidation have in the inflammatory syndrome of end stage renal disease. In this review paper the authors systematically describe the hallmarks of protein damage in the

uremic blood mainly focusing on those that have been now recognized as high molecular weight uremic toxins. The authors propose an hypothesis model to explain the multifactorial (and self-feeding) pro-inflammatory nature of these modified proteins.

The present issue includes also two regular papers. The study by Miller et al. (2007) focuses on the effect that S-nitrosoglutathione have on the kinetic and proteomic characteristics of the glycolytic enzyme hexokinase. A possible role of S-nitrosoglutathione-dependent modulation of hexokinase activity in the control of energy metabolism of cancer cells is proposed. The paper by Oien and Moskovitz (2007) used the model of senescing *msrA* knockout mother yeast cells to describe a role of the methionine sulfoxide reductase system in protein damage accumulation during aging and exposure to H_2O_2. In this study the authors propose that a compromised MsrA activity may serve as marker for non-replicative aging.

In closing, I would like to thank the authors for their cooperation and diligence in summarizing their studies, which advance our understanding of protein modification by ROS/RNS. Finally, I would like to thank the Guest Editors, Dr. Victor Darley-Usmar and Dr. Rafael Radi, and the external (anonymous) reviewers for the valuable assistance in manuscript revision and contribution to the preparation of this special issue.

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