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Review

Radiation-induced reductive modifications of sulfur-containing amino acids within peptides and proteins

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ABSTRACT

The complex scenario of radical stress reactions affecting peptides/proteins can be better elucidated through the design of biomimetic studies simulating the consequences of the different free radicals attacking amino acids. In this context, ionizing radiations allowed to examine the specific damages caused by H-atoms and electrons coupled with protons, thus establishing the molecular basis of reductive radical stress. This is an innovative concept that complements the well-known oxidative stress also in view of a complete understanding of the global consequences of radical species reactivities on living systems. This review summarizes the knowledge of the chemical changes present in sulfur-containing amino acids occurring in polypeptides under reductive radical conditions, in particular the transformation of Met and Cys residues into α-amino butyric acid and alanine, respectively. Reductive radical stress causing a desulfurization process, is therefore coupled with the formation of S-centered radicals, which in turn can diffuse apart and become responsible of the damage transfer from proteins to lipids. These reductive modifications assayed in different peptide/protein sequences constitute an integration of the molecular inventories that up to now take into account only oxidative transformations. They can be useful to achieve an integrated vision of the free radical reactivities in a multifunctional system and, overall, for wider applications in the redox proteomics field.

Contents

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1. Introduction

Oxidation and reduction of protein thiol moieties represent the major mechanism by which reactive oxygen species (ROS) and reactive nitrogen species (RNS) integrate into cellular signal transduction pathways [1]. These signaling oxidants/nitrosants, which include nitric oxide ($NO^{\bullet}$), S-nitrosothiols (SNO), hydrogen peroxide (H_2O_2) and superoxide anion ($O_2^{\bullet-}$), are produced mainly by NADPH-dependent enzymes, whose expression is tightly controlled, compartmentalized and tissue-specific [2]. Signaling by these reactive molecules is mainly carried out by targeted modification of Cys residues in proteins, including S-nitrosylation and S-oxidations. Protein SNO derivatives are generally not highly stable and may convert into oxidized Cys derivatives, namely sulfenic (SOH) and sulfinic (SO_2H), as well as intra- and inter-molecular disulfides [2,3], which are also produced by direct amino acid oxidation. These modifications may transform thiol moieties essential for protein catalysis or generate non-native disulfide bonds perturbing final three-dimensional polypeptide structure, thus ultimately affecting protein function (Fig. 1) [4,5]. With the exception of sulfonic acids and sulfinic acids (not including 2-Cys peroxiredoxins), all these oxidized derivatives can be reverted into the original reduced Cys residue by dedicated enzymatic machineries, which include thioredoxin, glutaredoxin, protein disulfide isomerase, sulfiredoxin and GSNO reductase [2]. Protein Met residues may also be oxidized by ROS to sulfoxide [6,7]. The two-epimeric forms of the sulfoxide (*i.e.*, *R* and *S* epimers) can be reverted into the original Met residue by methionine sulfoxide reductases (Msr A and B) (Fig. 1) [4,8]; a specific enzyme is active on each epimer. For this reason, Met residues in proteins are suggested to act as an antioxidant pool and several studies support this vision [9]. Oxidatively-modified forms of Met and Cys residues accumulate in living systems, also due to the impairment of the turnover and defense systems mentioned above; this is clearly involved in a number of degenerative processes during aging and pathological conditions [10].

Exposure to irradiation conditions, such as radiolysis, has been largely used for the study of oxidative stress, thus providing a very useful tool for investigating mechanistic and structural features of the damages to amino acids [11,12]. Reductive stress has been less widely investigated than the oxidative one [13]; in fact, most organisms live under aerobic conditions where oxidative challenges can often occur and affect/modify their biomolecules [14]. However, strong reductive stresses may also alter cellular redox homeostasis, eventually determining specific pathological states [15,16]. Reductive radical species, like hydrated electrons and H-atoms derived from the ionizing irradiation of water, have been the subject of research activity within various groups, including our one. Initially, the reaction of these reducing species with sulfur-containing residues in peptides and proteins has been studied in connection with biomimetic chemistry on tandem protein/lipid damages under reductive radical stress [17–19]. A detailed description of the modifications induced in the protein structure was obtained by combining different spectrometric and spectroscopic techniques. This multidisciplinary approach allowed important chemical changes to be envisaged and the inventory of protein modifications induced by radical stress to be enriched by novel mechanisms and functionalities. In the following sections, the main achievements in the area of reductive radical stress of polypeptide species are reported.

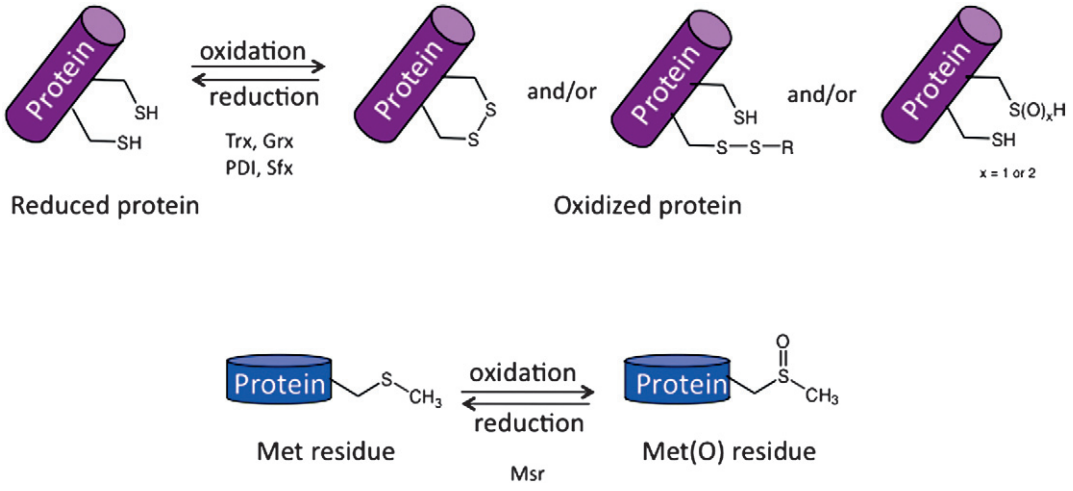

Fig. 1 – Oxidative modifications that have been proved as being repaired enzymatically are those involving sulfur-containing amino acids. Trx, thioredoxin; Grx, glutaredoxin; PDI, protein disulfide isomerase; Sfx, sulfiredoxin; Msr, methionine sulfoxide reductases; and R, protein or glutathione.