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Redox control of protein degradation

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ABSTRACT

Intracellular proteolysis is critical to maintain timely degradation of altered proteins including oxidized proteins. This review attempts to summarize the most relevant findings about oxidant protein modification, as well as the impact of reactive oxygen species on the proteolytic systems that regulate cell response to an oxidant environment: the ubiquitin-proteasome system (UPS), autophagy and the unfolded protein response (UPR). In the presence of an oxidant environment, these systems are critical to ensure proteostasis and cell survival. An example of altered degradation of oxidized proteins in pathology is provided for neurodegenerative diseases. Future work will determine if protein oxidation is a valid target to combat proteinopathies.

Contents

Abbreviations: Aβ, amyloid beta; AMPK, AMP activated protein kinase; ASK1, apoptosis signal-regulating kinase 1; ATG4, autophagy related protein 4; ATM, ataxia-telangiectasia mutated; BCL-2, B-cell lymphoma 2; CMA, chaperone mediated autophagy; ER, endoplasmic reticulum; GSH, reduced glutathione; GSSG, oxidized glutathione; HIF-1, hypoxia inducible factor-1; IKKB, inhibitor of nuclear factor kappa-B kinase subunit beta; JNK1, c-Jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; NFκB, nuclear factor kappa B; NOX, nicotinamide adenine dinucleotide phosphate oxidase; NRF1/2, nuclear factor (erythroid-derived 2)-like 1/2; PARP1, poly [ADP-ribose] polymerase 1; PDH, prolyl-4-hydroxylase; PDIs, protein disulfide isomerase; PI3K, phosphatidylinositol 3-kinase; PrP, prion protein (PrPc, cellular form, PrPsc, scrapie form); PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species (mtROS, mitochondrial ROS); α-SYN, α-synuclein; mTORC1, mammalian target of rapamycin complex 1; Trx, thioredoxin; TSC2, tuberous sclerosis complex 2; Ub, ubiquitin; ULK1, unc-51 like autophagy activating kinase 1; UPR, unfolded protein response; UPS, ubiquitin proteasome system

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1. Introduction to redox homeostasis (redoxtasis)

Aerobic metabolism has the advantage of a better energy yield, but at the cost of generating reactive oxygen species (ROS). Indeed, the leakage of superoxide from mitochondrial respiratory chain complexes I and III constitutes one of the major sources of ROS production [1]. Other sources of harmful ROS include unfolded protein response at the endoplasmatic reticulum (ER) [2], and oxidant byproducts generated at peroxisomes [3,4]. Moreover, evolution has used oxygen to modify certain proteins, now termed redox switches, as a cell signaling mechanism in survival [5] and regeneration [6] among other pathways. This clever use of ROS is best exemplified by NADPH oxidases (NOX), situated in the plasma membrane, whose main role is to generate superoxide and ultimately hydrogen peroxide (H_2O_2) as second messengers [7].

Cells have efficient enzymatic and non-enzymatic strategies to modulate redox signaling and maintain redox homeostasis [8,9]. In addition, antioxidants are also obtained from exogenous sources, with the diet as the main supplier [10]. However, many pathological conditions or the normal decline in cell homeostasis related to ageing lead to a gradual imbalance between ROS formation and degradation and result in detrimental alterations of macromolecules. Sulfur containing amino acids, cysteine and methionine, are responsible for reversible and irreversible modification of proteins. In addition, proteins can form adducts with oxidizing byproducts. Fig. 1 summarizes oxidative modifications of sulfur containing amino acids.

In this review, we summarize the most relevant findings about the degradation of oxidized proteins, here termed oxyproteins, and the impact of oxidative stress on proteolytic cell systems, and gene expression.

2. The ubiquitin-proteasome system (UPS) in the control of oxyprotein degradation

The UPS participates in the degradation of soluble proteins in cytosol and nucleus [11]. The central core of the UPS is the 20S proteasome, which is present in animals, plants and bacteria. This 700 kDa-multisubunit protease is highly effective in the proteolytic

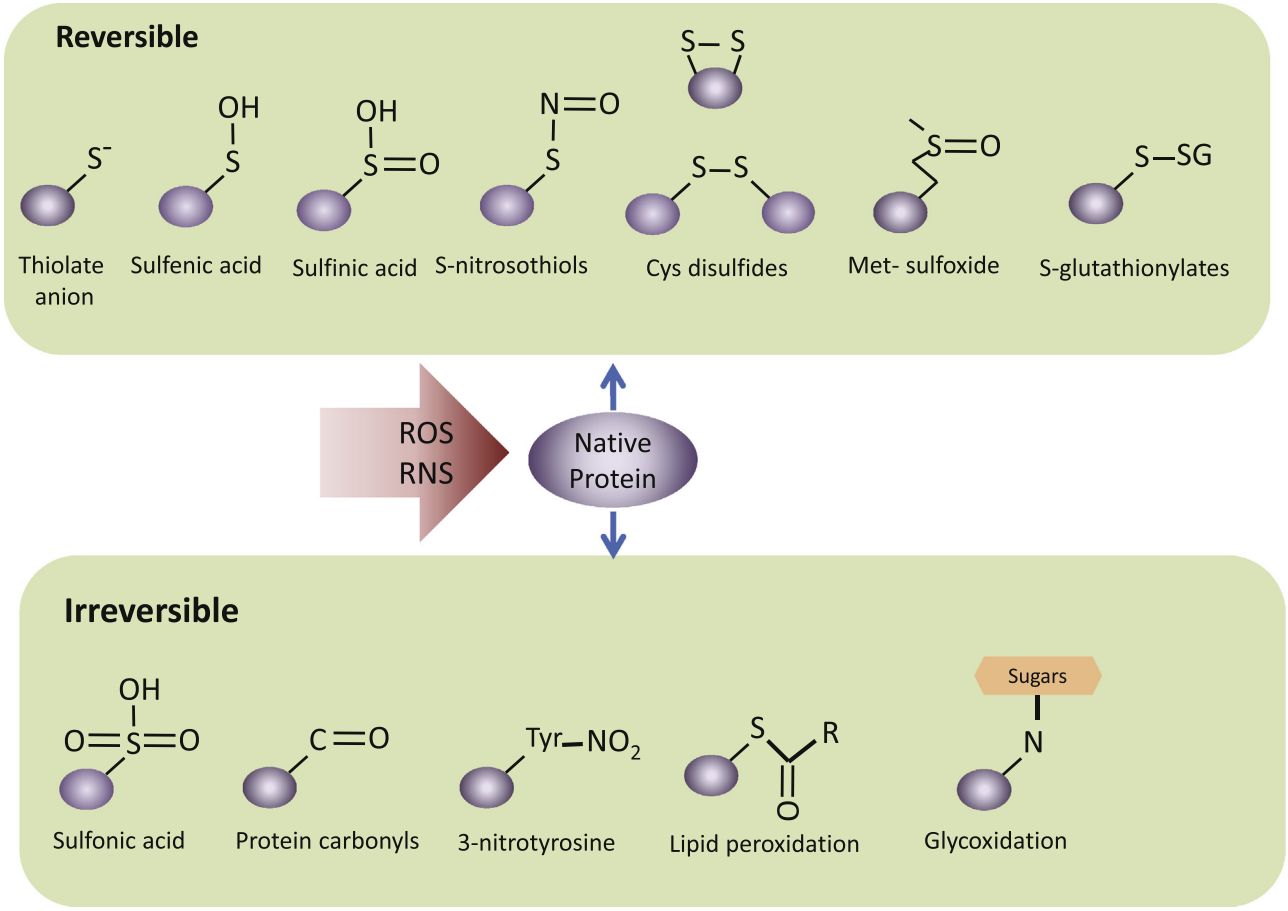

Fig. 1. Oxidation of sulfur containing amino acids. A, Reversible modifications modulate physiological protein functions that act as molecular redox switches. The sulfur-containing amino acids methionine (Met) and cysteine (Cys) may undergo oxidation to generate Cys disulfides, S-thiolates, S-sulfenates, Met-sulfoxides, S-glutathionylates and S-nitrosothiols. B, Sulfur-containing amino acids can be further oxidized to irreversible sulfonic acid. Irreversible oxidative modifications, typically occur under the conditions of oxidative stress and lead to structural changes, protein inactivation and ultimately require protein degradation. Irreversible modifications lead to cleavage of the protein backbone by hydroxyl radical or direct oxidation or adduct formation of the side chain amino acids. Oxidative modifications to amino acids include the hydroxylation of aromatic groups and aliphatic amino-acid side chains, nitration of aromatic amino-acid residues, oxidized lipid adduction, conversion of amino-acid residues to carbonyl derivatives and glycoxidation (adduction of advanced aged glycation end products) (this figure has been adapted from [156] and [157]) .