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## Protein Oxidative Modifications: Beneficial Roles in Disease and Health

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### Abstract

Protein oxidative modifications, also known as protein oxidation, are a major class of protein posttranslational modifications. They are caused by reactions between protein amino acid residues and reactive oxygen species (ROS) or reactive nitrogen species (RNS) and can be classified into two categories: irreversible modifications and reversible modifications. Protein oxidation has been often associated with functional decline of the target proteins, which are thought to contribute to normal aging and age-related pathogenesis. However, it has now been recognized that protein oxidative modifications can also play beneficial roles in disease and health. This review summarizes and highlights certain positive roles of protein oxidative modifications that have been documented in the literature. Covered oxidatively modified protein adducts include carbonylation, 3-nitrotyrosine, s-sulfenation, s-nitrosylation, s-glutathionylation, and disulfide formation. All of which have been widely analyzed in numerous experimental systems associated with redox stress conditions. The authors believe that selected protein targets, when modified in a reversible manner in prophylactic approaches such as preconditioning or ischemic tolerance, may provide potential promise in maintaining health and fighting disease.

### Keywords

carbonylation; cysteine; glutathionylation; ischemic tolerance; nitrosylation; nitrotyrosine; sulfenation; sulfenic acid; postconditioning; preconditioning; oxidative modifications; reactive oxygen species

## 1. Introduction

In order to cope with environmental challenges, cells rely on a variety of posttranslational modification mechanisms to expand protein function [1-4]. Of all the documented posttranslational modifications, oxidative modification of the side chains of various amino acid residues forms a major category of protein posttranslational modifications [5-7]. Protein oxidative modifications can be generally classified into two categories: irreversible oxidation and reversible oxidation [8-10]; both of which can be selectively induced by reactive oxygen species (ROS) and reactive nitrogen species (RNS) [11, 12].

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Earlier studies of protein oxidation nearly exclusively focused on the detrimental effects of protein oxidation in aging and diseases [5, 9, 13-17]. It has now been firmly recognized, however, that protein oxidation can also play a positive role in many cellular functions. This gradual realization of the beneficial roles of protein oxidation may be attributed to accumulating evidence that ROS and RNS are indispensable for cell survival [18-22] and regeneration [23], and in many cases, they are required for recovery of cellular functions by creating positive stress conditions whereby cell survival mechanisms are reprogrammed to extend life span [24-27] or to withstand severe, or lethal challenges [28-31].

In this article, we review both irreversible and reversible oxidative modifications that are beneficial in health and disease. Modification adducts to be discussed include protein carbonyls, 3-nitrotyrosine, and cysteine oxidation products (Fig. 1). As protein cysteine residue is the one that often undergoes reversible redox modifications by ROS or RNS [32-34], we have inclined to devote more space on cysteine modifications including s-sulfenation, s-nitrosylation, s-glutathionylation, and disulfide formation that are all reversible [35-38]. It should be noted that protein oxidative modifications that have deleterious effects in health and disease are beyond the scope of this review and will only be sporadically mentioned.

## 2. Cellular sources of oxidants

There are many systems inside a cell that can generate ROS. Mitochondria are recognized as the major site for ROS production [39-41]; and both complexes I and III have been established to be the specific sites for mitochondrial ROS generation [42-45]. Besides mitochondria, many enzymes are also capable of producing ROS. These include, but not limited to, NADPH oxidase [46, 47], xanthine oxidase [48, 49],  $\alpha$ -ketoglutarate dehydrogenase complex [50-52], d-amino acid oxidases [53-55], and dihydrolipoamide dehydrogenase [56-62]. On the other hand, nitric oxide production *in vivo* is mainly achieved by nitric oxide synthases [63-65] though under certain conditions deoxygenated myoglobin [66] or xanthine oxidoreductase [67] or cytochrome c oxidase [68] can be involved in NO production; and *in vitro* nitric oxide donors are also frequently used either in experimental systems [69-71] or for therapeutic purpose [72-74]. It should be noted that in the presence of superoxide anion, nitric oxide can rapidly react with superoxide anion to yield peroxynitrite [75-77], a reactive species that is highly reactive toward redox-sensitive amino acid residues including tyrosine and cysteine [78, 79].

## 3. Irreversible protein oxidative modifications

First, we would like to discuss briefly the possible beneficial role of irreversible modifications. These types of modifications include mainly protein carbonylation and tyrosine nitration [11, 80-84]. Both modifications are often associated with oxidative damage and have been used as biomarkers for assessment of oxidative stress in aging and diseases [13, 15-17, 85]. While both carbonylation and nitration can have detrimental effects on the target proteins, evidence has also emerged that such modifications can also play positive roles in cellular function under stress conditions.

### 3.1. Protein carbonyls

Protein carbonyls formed on several amino acids residues, including arginine, histidine, lysine, proline, threonine and cysteine, are the most widely used biomarker for measurement of protein oxidation and oxidative stress in aging and diseases [5, 8, 11-14, 86-90]. As the modification occurs on multiple amino acid residues on selected protein targets [15-17, 91], its magnitude is much greater than any other modifications that occur only on a specific amino acid residue [11, 12], and thus is more readily detectable. Many studies have

employed protein carbonylation to evaluate the detrimental effects of protein oxidation and oxidative stress [13-16, 87-90]; evidence for positive effects of this modification, however, has started to accumulate. For example, protein carbonylation has been shown to be involved in signal transduction [92-95] and is known to be involved in ischemic preconditioning eliciting protection against reperfusion-induced tissue injuries [96, 97].

### 3.2. Protein nitrotyrosine

Nitrotyrosine, usually 3-nitrotyrosine, is formed between reactive nitrogen species and a protein's tyrosine residue [78, 98, 99]. This modification is a highly selective process as not all proteins or all tyrosine residues on a target protein can get nitrated [100]. Formation of nitrotyrosine is often thought to be accompanied with acute or chronic inflammation disease [101-104], whereby level of nitric oxide is elevated [102, 104-106]. While numerous studies have investigated the deleterious effects of 3-nitrotyrosines [107, 108], concurrent with development of methods for detection and quantitation [109, 110], this modification has been detected under normal physiological conditions such as healthy pregnancy [111, 112], indicating that formation of 3-nitrotyrosine has physiological function.

## 4. Reversible protein oxidative modifications: protein cysteine modifications

### 4.1. Chemistry of protein cysteine residues

At neutral pH under physiological conditions, free cysteine residues have a pKa value that is around 8.5, which makes oxidative modifications impossible [113]. To be susceptible to oxidation, the pKa value of a cysteine residue needs to be lower than the physiological pH value (pH 7.4), a condition under which, the cysteine -SH group becomes thiolated (thiolate anion) [113-115]. It is those thiolated cysteine residues that are redox reactive [35, 116]. This thiolation process, decreasing the pKa value to 7.2 or lower, can be achieved via many factors such as hydrogen bonding [117, 118], the effect of adjacent basic amino acid residues [117], the microenvironment of the target cysteine residues [117], and substrate binding [119]. For example, albumin cysteine 34 has a very low pKa value of 5 [120]. Hence under physiological condition, it exists as thiolate anion and is very reactive towards oxidants, thiols, metals, and disulfides [121-123].

As described above, thiols with low pKa values are more reactive because they are usually deprotonated or thiolated at physiological pH [124-126]. Therefore, oxidation of protein cysteines that are redox reactive is also a highly selective process [127, 128]. As shown in Fig. 2, cysteine oxidation usually starts with the formation of sulfenic acid, from which a variety of oxidation products can be furtherly formed and many of them are reversible and well defined chemically. These cysteine oxidation products include disulfide formation (S-S-), S-glutathionylation (protein-SSG), S-nitrosylation (-SNO), sulfenic acid formation (-SOH, or S-sulfenation) and have all been demonstrated in redox regulation of protein functions by ROS and RNS [35, 129, 130]. Importantly, all of which have been implicated to play beneficial roles in disease and health because they may protect the target proteins from further oxidation that will otherwise permanently damage the target proteins [131-133]. Another mechanism is that these modifications also play a role in redox signaling cascades that boost cellular defense systems to better counteract stress insults [134-136].

### 4.2. Protein sulfenic acid formation (S-sulfenation)

This sulfur-hydroxylation product (P-SOH) possesses powerful redox chemistry and has been demonstrated to play a key redox regulatory role in a growing number of proteins [34, 138-141]. Its formation is mainly induced by ROS such as hydrogen peroxide, alkyl hydroperoxides, and RNS such as peroxynitrite [38, 129, 137, 142, 143]. Although being a

simple chemical modification, sulfenic acid formation can have a dramatic effect on protein function [130, 137, 144]. It was for a long time regarded as an intermediate, unstable cysteine oxidation product, which may still be true for many proteins [137, 145, 146]. Growing evidence, however, has demonstrated that stable-SOH indeed exists, making trapping, labeling, detecting, and quantitating possible for further evaluation of the formed –SOH [142, 147-150]. A beneficial effect of protein SOH formation has been elegantly demonstrated in studies whereby s-sulfenation of aldose reductase protects the heart against ischemic/reperfusion injury [151-153]. Specifically, these studies found that cys-298's sulfenation of aldose reductase by peroxynitrite shows great protection against cardiac ischemic injury; and administration of peroxynitrite scavengers not only eliminates cys-298's sulfenation, but also abolishes cardiac protection against ischemic injury. In unrelated studies, Michalek *et al.* demonstrated that protein sulfenation is indispensable for T-cell growth and proliferation as arrest of sulfenic acids greatly impairs T cell maturation [154]. Another example of a beneficial role of P-SOH is that of the sulfenation of nitrile hydratase; sulfenic acid formation on this enzyme's Cys114 residue is absolutely essential for the enzyme's catalytic activity [155].

#### 4.3. Protein s-nitrosylation

Protein s-nitrosylation can be induced by nitric oxide, nitroxyl, and peroxynitrite [156, 157]. This modification has been regarded as functionally equivalent to protein phosphorylation and dephosphorylation [158-160]. Besides occurring on cysteine residues other than on tyrosine, serine, or threonine residues, s-nitrosylation is also potentially different from phosphorylation in that nitrosylation may not involve a delicate network consisting of kinases or enzymes that catalyze, respectively, nitrosylation and denitrosylation, though the existence of denitrosylases, including Cu,Zn-superoxide dismutase and bilirubin, has been reported [161-165]. Nonetheless, s-nitrosylation has been demonstrated to be a key modification of cysteine residues under a variety of physiological and pathophysiological conditions [157, 166, 167]. In particular, in connection with nitric oxide-based redox regulation of protein function, s-nitrosylation has been found to be involved in protective mechanisms in many disorders [157, 168-170]. For example, Sheng *et al.* have demonstrated that chemically-enhanced s-nitrosylation can improve recovery from subarachnoid hemorrhage [171], and Penna *et al.* have demonstrated that protein s-nitrosylation is favorably produced during cardiac postconditioning [172].

#### 4.4. Protein s-glutathionylation

Protein cysteine residues can also undergo s-glutathionylation under oxidative stress conditions [173-175]. Glutathione (GSH) is the major cellular antioxidant, yet, it can also modify proteins via mixed disulfide formation (P-S-S-G), leading to functional changes of the target proteins [176]. This reversible oxidation of critical cysteine residues on proteins has been found to be involved in oxidative signal transduction, control of gene expression, cell proliferation, apoptosis, and cellular responses to protecting key regulatory molecules from oxidative insults [173, 176-178]. Similar to s-sulfenation and s-nitrosylation, protein-S-S-G is also often associated with a detrimental effect on the target protein's function [179-182], but can also protect the target protein from irreversible and permanent damage [183-186]. Therefore, protein glutathionylation has increasingly gained great attention as a possible means of redox regulation of protein functions in response to oxidative stress under physiological and pathophysiological conditions [185, 187]. For example, actin glutathionylation regulates actin dynamics in polymorphonuclear neutrophils [188], manipulation of uncoupling protein 2's glutathionylation may provide a strategy for cancer treatment [189], and glutathionylation of adenine nuclear translocase induced by preconditioning can prevent mitochondrial membrane permeabilization and apoptosis [190].

#### 4.5. Protein disulfides

This is different from protein s-glutathionylation, where a mixed disulfide between GSH and a protein-linked cysteine residue is formed [191-193]. Native disulfide bond formation is usually involved in correct protein folding and is catalyzed by disulfide isomerase in the endoplasmic reticulum and the mitochondrial intermembrane space [194-197], and should be considered different from those formed under oxidative stress or pathophysiological conditions. Hence herein, disulfide formation is strictly meant to reflect inter- or intra-protein disulfide formation that is caused by ROS or RNS [198-205]. Disulfide bonds formed between free cysteine residues upon oxidative stress have been reported to play a beneficial role in cellular defense systems against a variety of stress challenges [191, 206-210]. For example, intra-protein disulfide formation in Cdc25c upon hydrogen peroxide exposure regulates the stability of the protein [211], and in the brain type creatine kinase, disulfide formation between two cysteine residues (cys74 and cys254) can serve as a cellular defense mechanism [212]. Additionally and importantly, it is well established that formation of disulfide linkage within Keap1 in response to cellular stimuli by electrophiles and oxidants [213-217] is essential for activation of the NF-E2-related factor 2 (Nrf2) that then upregulates the expression of phase II antioxidant enzymes under a variety of physiological and pathophysiological conditions [218-224].

#### 5. Protein oxidative modifications and ischemic tolerance

Posttranslational protein oxidative modifications, in particular cysteine modifications, have been implicated in ischemic tolerance or preconditioning [168, 225-231]. Ischemic tolerance constitutes a positive stress that reprograms cellular defense systems to prevent subsequent lethal injuries [232-237]. The phenomenon of preconditioning seems to be universal as all tissues in mammalian systems as well as all organisms can be preconditioned. In particular, the heart and the brain can be preconditioned by a variety of mechanisms to prevent further injuries caused by ischemia reperfusion [232, 238]. Therefore, preconditioning has both prophylactic and therapeutic value. Despite intensive studies, the mechanisms of preconditioning has not been well understood. Nonetheless, ROS are known to be the key molecules involved in preconditioning development [239-243] as antioxidants administered during induction of preconditioning can block the preconditioning effect [28, 30]. Moreover, a moderately-elevated level of ROS, in particular, H<sub>2</sub>O<sub>2</sub>, has been shown to be neuroprotective [221, 244-246]. Nevertheless, how ROS work in preconditioning induction and tissue protection remains elusive. As ROS can impart their effects by modifying proteins, identification of endogenous protein targets of ROS may elucidate mechanisms of protection induced by ischemic tolerance. It is thus conceivable that identification of oxidatively modified protein targets, especially those that can undergo reversible oxidative modifications, may provide insights into novel therapeutic strategies for ischemic tolerance. It is also worth mentioning that a concept of postconditioning, whereby the reperfusion procedure can be disrupted and intervened to elicit protection against lethal injury, has been recently established [247-250]. We think that postconditioning can also be placed under the notion of ischemic tolerance. In fact, preconditioning and postconditioning may share similar pathways or mechanisms [250-254].

So why could protein oxidation, in particular, reversible oxidation-induced by ischemic tolerance be involved in protection against subsequent ischemic injury? As it is the reperfusion stage that often incurs the injury due to a sudden burst in ROS production concurrent with resupply of oxygen [255-259], oxidized proteins with altered protein function could slow down the rate of ROS production during reperfusion and hence could attenuate ischemic injury [230, 260]. In addition, as already pointed out earlier in this review, oxidized proteins induced by ischemic tolerance could also be involved in eliciting

cellular defense systems to protect against further severe ischemia reperfusion injury [261, 262].

## 6. Summary and Perspectives

While studies on the detrimental or deleterious effects of protein oxidative modifications are, and will still be, dominating the field of protein oxidation, investigation of the beneficial roles of protein oxidation appears to be gaining increasing interest [135, 263]. For beneficial purposes, efforts should be focused on proteomic identification of reversibly oxidized proteins that may exhibit protective effects. Further, studies on a comprehensive understanding of the mechanisms or pathways that regulate the reversible nature of the corresponding modifications should be undertaken. This should be particularly true for reversible cysteine oxidation, which not only reflects changes in cellular redox state, but can also protect the target proteins from further damage. Additionally, reversible cysteine oxidation is also involved in redox signaling cascades [264-267] that can elicit positive stress responses to prevent unpredicted disastrous events such as stroke and heart attack. Therefore, equal efforts will also be needed to identify those protein targets that undergo reversible cysteine modifications in preventative or protective approaches as such identified protein targets may provide therapeutic values in fighting diseases, in particular, ischemia associated cerebral and cardiovascular diseases.

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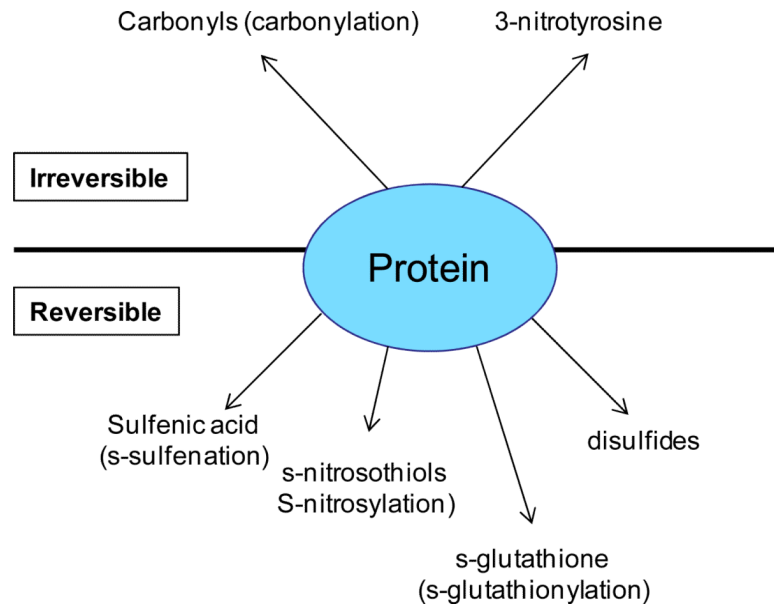
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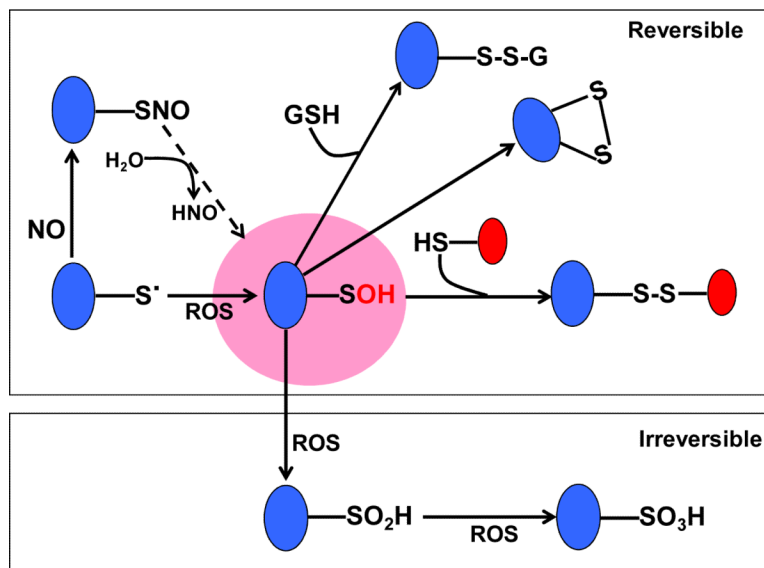
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**Fig. 1.** Irreversible and reversible protein oxidation products discussed in this review. Irreversible oxidation includes protein carbonyls and 3-nitrotyrosine while reversible oxidation includes cysteine modification products such as sulfenic acid, nitrosothiols, and s-glutathione.



**Fig. 2.** Chemistry of cysteine oxidative modifications. Sulfenic acid is truly an intermediate product during cysteine oxidation. Given appropriate conditions, s-nitrosothiols can also be decomposed to yield sulfenic acids with concurrent production of nitroxyl [137]. Sulfenic acid can be further oxidized to form disulfide bonds, s-glutathionylation. Irreversible oxidation products sulfenic and sulfonic acids are also shown.