



Review

Protein *S*-nitrosation: Biochemistry and characterization of protein thiol–NO interactions as cellular signals

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Abstract

The interaction of nitric oxide with thiols is complex and still an active area of research. Herein, we provide an overview of the ways in which nitric oxide can be biologically transformed into species capable of adding an $\cdot\text{NO}$ moiety to protein sulfhydryls, emphasizing how protein *S*-nitrosation differs from nitrosation of low molecular weight thiols. Protein *S*-nitrosation is being revealed as a post-translational means of chemically modifying and functionally altering proteins. Changes in protein function, which persist on a physiologically relevant time scale, effectively transmit biological signals and thus provide a framework for elucidating signaling networks. A description of recently developed methodology facilitating inquiry into this area is provided, along with a sketch of various proteins reported to be targets for nitrosation and the functional consequences therein. Protein denitrosation appears to be an active and perhaps enzymatically catalyzed process. Here, we summarize the evidence that suggests this and proffer a précis of proteins possessing denitrosation activity.

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Keywords: Protein *S*-nitrosation; Denitrosation; Nitric oxide; Redox congeners; Post-translational modification; Biotin switch method; Reactive nitrogen species; Signal transduction

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Introduction

The intense investigation of the biochemistry of nitric oxide (\cdot NO) over the last 20 years has yielded a wealth of both physiological and pathophysiological functions for this small free radical species. It has been implicated in diverse roles, including respiration, nerve transmission, apoptosis, host defense, DNA replication, transcription, modulation of vascular tone and hemostasis. These functions can be attributed to the transient interaction of the gaseous diatom or its redox congeners with transition metal centers, protein and non-protein sulfhydryls, tyrosine and tryptophan residues, reactive oxygen species or perhaps to the formation of lipid-NO or *O*- and *N*-nitrosated adducts. However, given the dynamic nature of nitric oxide and the labile nature of nitrosated and nitrosylated species, characterization of the NO-based signals transduced transiently within the cell remains incomplete. Literature to date focuses largely on NO signals via the interaction of \cdot NO and reactive nitrogen species (RNS) with protein-bound metal centers, protein thiols or reactive oxygen species. The paradigm of protein thiol *S*-nitrosation is generally thought to be in relative infancy with only a handful of reviews published [8,20,24,54,66]. Inquiry into this area has only recently benefited from technical advances in detection and characterization, based largely upon variations in methodology referred to as the biotin switch method [38]. This methodology facilitates study of the process of reversible nitrosation as a post-translational means of transmitting signals within the cell, oft likened to phosphorylation. In contrast, regulatory mechanisms that govern *S*-nitrosation and denitrosation of proteins are to date largely non-enzymatic, thus distinguishing the two forms of signal transduction. Several investigators have made inroads to delineating the functional significance of NO-based signals transduced through protein nitrosation [29,41,39,60]. However, suggestion that the nitrosoproteome may be comprised of greater than 100 proteins [21] indicates that a thorough characterization of

the network of signals transmitted by active \cdot NO species remains to be delineated.

This review will include relevant nitric oxide and thiol chemistries, the role of cellular environment in regulating the various paths of reaction to yield the resultant *S*-nitrosated (SNO) species and proteomic methodology for isolating and identifying *S*-nitrosated proteins. It will conclude with an overview of SNO proteins detected thus far and a discussion of protein thiol nitrosation as a signaling framework.

Chemistry of nitric oxide, oxygen and *S*-nitrosothiols

S-nitrosothiols represent a pool of nitric oxide donors that effectively stabilize the relatively short-lived free radical, extending the lifetime of the active NO species. Any protein that bears a free thiol moiety can, in principle, be *S*-nitrosated. However, as has been demonstrated, endogenous nitrosation of protein thiols appears more often selective. Formation and degradation of *S*-nitrosothiols is a dynamic process that is influenced largely by the prevailing redox environment, oxygen and metal ion availability and thiol reactivity.

Considering the limited direct reaction between \cdot NO and thiols [104], nitrosothiol formation is generally preceded by reaction with other species. Thus, an understanding of protein *S*-nitrosation is predicated upon knowledge of the chemistry of nitric oxide and its redox congeners with oxygen, metal ions and reactive oxygen species.

Reaction of \cdot NO with oxygen

An interesting aspect of nitric oxide chemistry is the relative unreactive nature of \cdot NO to most biological molecules, excluding other free radicals and metal centers. It has been demonstrated that \cdot NO will not nitrosate low molecular weight thiols, such as cysteine and glutathione, in the absence

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