S-Glutathionylation: A Redox-Sensitive Switch Participating in Nitroso-Redox Balance

Raul A. Dulce, Ivonne Hernandez Schulman, Joshua M. Hare

S-Glutathionylation Uncouples eNOS and Regulates Its Cellular and Vascular Function
Chen et al
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Cysteine side chains of proteins are being increasingly appreciated as the site of major posttranslational modifications that exert profound degrees of protein regulation.1–3 One of the consequences of tissue nitroso-redox imbalance is a process by which regulatory thiols switch from a state of physiologic regulation by S-nitrosylation to a state of dysregulated function because of oxidation.4–5 A key example of this is well described for regulation of the ryanodine receptor/Ca2⁺ release channels 1 and 2.6–13

The interaction between reactive oxygen species (ROS) and reactive nitrogen species can lead to the inactivation of nitric oxide (NO), formation of further highly reactive nitrogen species, such as peroxynitrite, or the dysregulation of biological signaling processes via irreversible oxidative modification of protein thiol moieties.5 It is increasingly recognized that an important posttranslational modification of thiols within this spectrum of biochemical reactions is that of S-glutathionylation.14–16 In a recent report in Nature, Chen and colleagues17 describe a fascinating feed forward system, in which a redox shift enhances S-glutathionylation of endothelial NO synthase (eNOS or NOS3) (Figure). This modification, in turn, shifts eNOS from an NO-generating enzyme to a producer of ROS.

One of the key principles of posttranslational modification of cysteine moieties is specificity; that is to say, there are specific cysteine sites that undergo posttranslational modification by S-nitrosylation, oxidation, or S-glutathionylation. In this regard, Chen et al use site-directed mutagenesis to identify Cys 689 and 908 as the key sites of regulation and, therefore, maladaptive to the extent that they block the more reversible and physiologic regulation mediated by S-nitrosylation.1 Although oxidation of thiols is nonspecific and irreversible, particularly when the cysteine is oxidized to sulfenic, sulfinic, or sulfonic acid, recent work demonstrated that oxidation of thiols (to sulfenic acid) could be specific, reversible, and controlled.21 Thus, as has been described by Irani et al,22 ROS can under certain circumstances serve as signaling molecules. There is also some evidence that S-glutathionylation may be a reversible modification, following restoration of a reducing GSH/GSSG ratio, and a protective mechanism against irreversible oxidation of regulatory thiols. However, it remains to be determined whether this modification is protective or detrimental in pathologic conditions associated with whole-body oxidative stress. For example, there is growing evidence that S-glutathionylated hemoglobin may be a useful biomarker of blood oxidative stress in humans,23 shown to be increased in patients with diabetes, hyperlipidemia, and renal failure.24,25 Whether this modification alters protein function in a way that impacts on

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From the Interdisciplinary Stem Cell Institute (R.A.D., I.H.S., J.M.H.), University of Miami Miller School of Medicine; and Nephrology-Hypertension Section (I.H.S.), Miami Veterans Affairs Healthcare System, Miami, FL.

Correspondence to Joshua M Hare, MD, Interdisciplinary Stem Cell Institute, Miami, FL 33101. E-mail: jhare@med.miami.edu


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tissue injury and disease progression or is simply a biomarker for the presence of oxidative stress is, at present, not known.20

Pathophysiologic Relevance

The work by Chen et al includes a highly important description in an in vivo model of hypertension, the spontaneously hypertensive rat.17 In these studies they show increased S-glutathionylation in immunoprecipitated eNOS, which was consistent with the immunohistology of aortae demonstrating that eNOS highly colocalizes with glutathionylated protein. Importantly, the authors show that dithiothreitol reduces S-glutathionylation in this animal model concomitantly with restoration of acetylcholine-induced aortic relaxation.

The findings in this study can be considered to represent a feed forward checkpoint, whereby oxidative stress promotes S-glutathionylation of eNOS, which in turn further enhances cellular nitroso-redox imbalance by shifting eNOS production of NO toward further ROS. This would be expected to continue to promote nitroso-redox imbalance and continue to stimulate a milieu in which susceptible thiols undergo oxidative or S-glutathionylated modifications. Findings such as these lead to exciting future questions and add further motivation toward the quest for developing new therapies targeting nitroso-redox balance.

In summary, the findings in this study add to the substantial amount of evidence pointing to a critical regulatory role of posttranslational thiol modification in pathophysiologic states, such as hypertension, atherosclerosis, and heart failure. In addition, they further contribute to the development of new therapeutic drugs with thiol-reducing properties, which may improve endothelial dysfunction, restore vascular tone, enhance excitation-contraction coupling, and improve left ventricular function in patients suffering from cardiovascular diseases.

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