Recent Developments in Research of Reactive Sulfur Species
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Regulation of redox signaling by reactive sulfur species

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Reactive sulfur species, such as cysteine persulfide, are produced endogenously at significant levels in cells and have rapidly emerged as common biomolecules. By virtue of improved analytical methods for detecting reactive persulfides, it has been demonstrated that these reactive molecules exhibit unique chemical properties and are present in various forms in vivo. Accumulating evidence has suggested that persulfides may be involved in a variety of biological processes, such as antioxidative and anti-inflammatory responses, biosynthesis of sulfur-containing molecules, mitochondrial energy metabolism via sulfur respiration, and cytoprotection via regulation of redox signal transduction induced by endogenous and exogenous electrophiles. Elucidation of the persulfide-dependent metabolism of redox signals is expected to facilitate our understanding of the importance of persulfides in regulating redox signals.

Key Words: persulfide, reactive sulfur species, 8-nitro-cGMP, 8-SH-cGMP, electrophile

Recent developments in research of reactive sulfur species have indicated that cysteine persulfide (CysSSH) and glutathione persulfide (GSSH), which are generated endogenously in both eukaryotes and prokaryotes, are involved in a variety of biological processes. Since the endogenous generation of persulfides was reported, their reactive molecules have been attracting increasing attention. To date, various forms of persulfides/polysulfides, compounds containing a longer chain sulfur, have been identified not only as low molecular weight compounds, such as CysSSH and GSSH, but also as high molecular weight compounds, such as proteins. Because persulfides/polysulfides contain sulfur, which has six valence electrons and no charge, they exhibit unique chemical properties that differ from those of their corresponding thiol compounds. Accumulating evidence has suggested that persulfides/polysulfides may be involved in various biological processes to maintain reduction/oxidation (redox) homeostasis by regulating the production, elimination, and metabolism of electrophilic substances (electrophiles) under physiological and pathological conditions.

In fact, persulfides exhibit cytoprotective effects against electrophilic stresses by interacting with electrophiles to form sulfur adducts with little toxicity. In this review article, we discuss the regulatory mechanism of redox signaling by persulfides/polysulfides.

Biosynthesis of Persulfides and Polysulfides

To date, several enzymes that contribute to the biosynthesis of persulfides and polysulfides have been identified. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) produce CysSSH using cysteine as a substrate. Due to its sulfuric anion, CysSSH can react with other thiols, such as glutathione (GSH), to form GSSH. Therefore, the transfer of sulfur from persulfides and polysulfides to protein-bound cysteine residues has been thought to be a mechanism of protein polysulfidation (also known as protein persulfidation or protein S-sulfhydration). Indeed, an increase in intracellular GSSH levels, as well as protein polysulfidation, was observed in CBS/CSE-overexpressing cells. In addition, persulfides can be formed in proteins, such as ethylmalonic encephalopathy protein 1, 3-mercaptopropyvulate sulfurtransferase, sulfide:quinone oxidoreductase, and rhodanase, via enzymatic reactions.

Our recent study revealed that cysteinyl-tRNA synthetase (CARS) catalyzes the production of CysSSH from cysteine in a tRNA- and ATP-independent manner, and the CysSSH produced can be incorporated into nascent polypeptides. These findings indicate that protein polysulfidation occurs via both post- and co-translational pathways. Indeed, a significant decrease in the endogenous production of persulfides and polysulfides, including CysSSH, GSSH, and polysulfidated proteins, was observed in HEK293 cells lacking the mitochondrial isoform of CARS (CARS2), and in liver tissue obtained from heterozygous CARS2 knockout mice. These results suggest that CARS2 is a primary enzyme for the endogenous production of persulfides and polysulfides. However, the detailed mechanism underlying the endogenous production of persulfides/polysulfides is still not fully understood, and further studies are required.

Chemical Properties and Oxidant Scavenging Capability of Reactive Sulfur Species

Persulfides and polysulfides can either work as electrophiles when protonated (RSSH), or nucleophiles when deprotonated (RSS). The pKα values of persulfides have been reported previously to be within the range of 4.3–6.23, which is lower than that of the corresponding thiols. In fact, Li et al. recently reported that the pKα value of GSSH is 6.9, which is lower than that of GSH (pKα 8.9). According to these values,

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the majority of GSSH exists in the deprotonated form under physiological pH conditions, while GSH exists largely in the protonated form. These results imply that persulfides display much more potent nucleophilic properties at physiological pH than do thiol compounds.

Due to their sulfane sulfur, persulfides are more nucleophilic than the corresponding thiols.\(^{[2]}\) This can be explained by the alpha effect, which describes the increase in the nucleophilicity of an atom due to the presence of unshared pairs of electrons on an adjacent atom.\(^{[15,27]}\) Because persulfides, such as CysSSH and GSSG, exhibit higher nucleophilicity, they scavenge oxidants efficiently. In fact, hydrogen peroxide (H\(_2\)O\(_2\)) was remarkably decomposed in a reaction mixture containing glutathione reductase and oxidized glutathione trisulfide (GSSSG) to generate GSSH, whereas no measurable decomposition of H\(_2\)O\(_2\) was observed in a mixture containing glutathione reductase and glutathione disulfide to form GSH.\(^{[2]}\) A recent study by Li et al.\(^{[26]}\) reported that GSSH is 50-fold more reactive towards H\(_2\)O\(_2\); than hydrogen sulfide at pH 7.4. It has also been reported that persulfides possess enhanced radical scavenging capability compared to thiols and hydrogen sulfide.\(^{[24]}\) Taken together, these results suggest that persulfides/polysulfides represent more important antioxidant molecules than the corresponding thiols in vivo, and contribute to cytoprotection against oxidative stress.

**Fig. 1.** Structures of the various persulfide forms. CysS-SH, cysteine persulfide; GS-SH, glutathione persulfide; Protein-SSH, protein-bound cysteine persulfide; Cys-S-SCys, cystine persulfide; GS-S-SG, oxidized glutathione trisulfide.

**Formation of Electrophilic Redox Signaling Molecules and Their Metabolism by Persulfides**

As reactive oxygen species (ROS) and reactive nitrogen species (RNS) can react with biomolecules extensively, they are considered toxic molecules that impair cellular processes in earlier studies. However, accumulating evidence indicates that ROS and RNS mediate signal transduction under physiological and pathological conditions via a mechanism called ‘redox signaling’.\(^{[1,26–38]}\) Redox signaling is mediated by endogenous electrophilic byproducts of chemical reactions between ROS/RNS and various biomolecules, including nucleic acids, amino acids, lipids, and proteins.\(^{[31–39]}\) For instance, 8-nitroguanosine 3',5'-cyclic monophosphate (8-nitro-cGMP), a nitrated cyclic guanosine monophosphate derivative, is formed endogenously in a nitric oxide (NO)- and ROS-dependent manner under physiological and pathological conditions. 8-Nitro-cGMP is involved in a number of cellular phenomena including cardiac cell senescence, neuronal cell death, the antioxidant stress response, chondrocyte proliferation, bone growth, osteoclast differentiation, and stomatal closure.\(^{[10,14,32,34,40–43]}\) 8-Nitro-cGMP can activate cGMP-dependent protein kinase and stimulate vasorelaxation, similar to the well-known NO second messenger, cGMP.\(^{[32]}\) Moreover, 8-nitro-cGMP is active stronger than cGMP under physiological conditions because the nitrated nucleotide is resistant to phosphodiesterase-dependent degradation.\(^{[12]}\) 8-Nitro-cGMP possesses weak electrophilicity derived from the nitro group; hence, it can react with specific protein thiol residues to add the cGMP structure to proteins through S-guanylation. To date, this unique thiol modification has been identified in various proteins, such as Kelch-like ECH-associated protein 1 (Keap1) and H-Ras. S-guanylation of Keap1 activates nuclear factor erythroid 2-related factor 2, resulting in the expression of antioxidant enzymes such as heme oxygenase-1.\(^{[34]}\)

It has been documented that persulfides and polysulfides are involved in regulating redox signals.\(^{[1,10,13,46]}\) As mentioned earlier, these reactive species are present at significant levels in vivo and exhibit strong nucleophilicity, allowing them to easily react with electrophiles to form sulfur adducts. For example, 8-nitro-cGMP is converted to the sulfhydrated metabolite, 8-
mercaptopoguanosine 3',5'-cyclic monophosphate (8-SH-cGMP), via the reaction of reactive persulfides with the release of nitrite (Fig. 2). Because 8-SH-cGMP has nucleophilic rather than electrophilic properties, it does not react electrophilically with protein thiols (12,14). These results suggest that the nucleophilic substitution of the electrophilic 8-nitro group of 8-nitro-cGMP by reactive persulfide species contributes to the termination of electrophilic signaling. Honda et al. (45) however, reported that 8-SH-cGMP can prompt stroma closure via the activation of plant guard cell signaling and that this activity is higher than that of 8-nitro-cGMP. Therefore, the sulphydrylation of 8-nitro-cGMP by persulfides/poly sulfides is not only a terminating process of 8-nitro-cGMP signaling, but also a switching process from electrophilic to nucleophilic signaling.

Disruption of the Persulfide-dependent Regulation of Redox Signaling by Exogenous Electrophiles

A concept of exposome has recently emerged. This concept is defined as a “conceptual grid of cumulative lifelong exposures to compliment the genome in understanding human disease”. (46,47) Redox mechanisms serve as an important interface between the genome, including the epigenome, transcriptome, (epi) proteome, and metabolome, and the associated biological responses to the environment. (46) It has been reported that exogenous electrophiles, such as naphthalquinone (NQ) in cigarette smoke, methyl mercury (MeHg) and cadmium in foods, can activate cellular redox signaling. (14,48-52) Reactive persulfides can mediate the metabolism and detoxification of exogenous electrophiles via reactions with diverse endogenous and exogenous electrophiles including MeHg, cadmium, 1,2-NQ, 1,4-NQ, 15-deoxy-Δ12,14-prostaglandin J2, 4-hydroxy-2-nonenal, and 8-nitro-cGMP. (10,14,48-52)

There is increasing consensus among researchers that both acute and long-term exposure to environmental heavy metals, such as MeHg and cadmium, can significantly affect human health and may be indirectly involved in the pathogenesis of various diseases including cardiac dysfunction and neurodegeneration. Long-term exposure to low doses of environmental electrophilic species, such as MeHg, is now a global concern and considered a risk to human health. For instance, we recently demonstrated that MeHg disrupted the persulfide-dependent regulation of redox signaling (i.e., the conversion of 8-nitro-cGMP to 8-SH-cGMP) by forming bismethylmercury sulfide, resulting in neuronal cell death via the excessive accumulation of endogenous 8-nitro-cGMP followed by S-guanylation, and simultaneous activation of the H-Ras/extracellular signal-regulated kinase signaling pathway in rat cerebellar granule neurons. (10) Pretreatment with sodium tetrasulfide, a polysulfide donor, significantly inhibited the MeHg-induced accumulation of endogenous 8-nitro-cGMP and attenuated the neuronal cell death caused by MeHg exposure. (10)

In addition, Nishimura et al. (53) demonstrated that exposure to a sub-neurotoxic dose of MeHg (10 ppm), which reportedly does not affect neuronal functions in mice over the course of one year (54) induced depoly sulfidation of dynamin-related protein 1 (Drp1), resulting in an increased cardiac fragility to mechanical load through filament-dependent mitochondrial hyperperfusion after pressure overload in mouse hearts. (53) Treatment with sodium hydrosulfide, a donor for reactive polysulfides, reversed the MeHg-mediated Drp1 depoly sulfidation and the associated vulnerability to mechanical load in rodent and human cardiomyocytes, and mouse hearts. (53) Thus, exposure to harsh exogenous electrophiles, such as MeHg, disrupts endogenous persulfide-dependent redox signal regulation, which may be a critical event in the pathogenesis of neurodegenerative diseases and cardiac dysfunction (Fig. 3). In this regard, it is essential to elucidate the molecular mechanisms underlying the regulation of redox homeostasis by exogenous/endogenous electrophiles and nucleophiles (i.e., reactive persulfide species) in order to predict and reduce the risk of neurodegenerative diseases and cardiac dysfunction.

Conclusions

Various forms of reactive persulfide compounds (both low and high molecular weight fractions) are abundantly present in vivo and play vital roles in multiple physiological functions, such as the antioxidant stress response, regulation of redox signals, maintenance of protein structure/function, and mitochondrial biogenesis/bioenergetics. Collapse of intravital persulfide homeostasis could contribute to the pathogenesis and development of various diseases, such as MeHg-induced neurodegeneration and cardiac dysfunction. Therefore, elucidation of the molecular mechanisms underlying the regulation of redox homeostasis between electrophiles and nucleophiles is essential to predict and reduce the risk of neurodegenerative disorder and cardiovascular disease.

Author Contributions

SK and HI wrote and edited the manuscript.

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Fig. 3. Exogenous electrophile-induced redox signaling via disruption of persulfide-dependent endogenous electrophilic signaling. Exogenous electrophiles, such as methylmercury (MeHg), interact with endogenous persulfides resulting in disrupting the persulfide-dependent electrophilic redox signal (i.e., conversion of 8-nitro-cGMP to 8-SH-cGMP by persulfides). In addition, MeHg causes oxidative stress in cells, followed by the excessive production of endogenous electrophiles, such as 8-nitro-cGMP, resulting in cellular stress via activation of downstream redox signaling pathways.

Abbreviations

CARS: cysteinyl-tRNA synthetase
CBS: cystathionine 8-lv-synthase
CSE: cystathionine 7-lyase
CysSSH: cysteine persulfide
Drp1: dynamin-related protein 1
GSH: glutathione
GSSH: glutathione persulfide
GSSG: oxidized glutathione trisulfide
Keap1: Kelch-like ECH-associated protein 1

MeHg: methylmercury
8-Nitro-cGMP: 8-nitroguanosine 3',5'-cyclic monophosphate
NO: nitric oxide
NQ: naphthoquinone
RNS: reactive nitrogen species
ROS: reactive oxygen species
8-SH-cGMP: 8-mercaptopguanosine 3',5'-cyclic monophosphate

Conflict of Interest

No potential conflicts of interest were disclosed.

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