ROS

RESEARCH HIGHLIGHTS

Peroxiredoxins in Redox Relay

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ABSTRACT | Peroxyredoxin (Prx) is one of the three major defenses against hydrogen peroxide toxicity, with the other two being catalase and glutathione peroxidase. Prx represents a family of enzymes that currently include 6 members, namely, Prx 1-6. In addition to their classical function in hydrogen peroxide detoxification, some Prx isozyme may also function as signaling molecules. This ROS Research Highlights article summarizes some recent key research findings on Prx-mediated redox signaling, pinpointing certain Prx isozymes as signaling antioxidants.

KEYWORDS | Antioxidants; Cell signaling; Peroxyredoxin

ABBREVIATIONS | CuZnSOD, copper, zinc superoxide dismutase; Prx, peroxiredoxin; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3

CONTENTS

1. Overview
2. Biochemistry
3. Biological Functions
   3.1. Antioxidant Functions
   3.2. Redox Relay and H_2O_2 Oscillation
4. Conclusion and Perspectives

1. OVERVIEW

Peroxiredoxin (Prx) is a general term that refers to a family of small (22–27 kDa) nonseleno peroxidases currently known to possess six mammalian isozymes, namely, Prx1–6. These isozymes are able to reduce reactive oxygen species (ROS), including hydrogen peroxide, organic hydroperoxides, and possibly peroxynitrite, and thus represent a class of important antioxidants in mammals. The six Prxs expressed in mammalian cells are classified into three subgroups: (1) typical 2-Cys Prxs including Prx1–4; (2) atypical 2-Cys Prx (Prx5); and (3) 1-Cys Prx (Prx6). Prxs are widely distributed in mammalian tissues, and the subcellular localization varies with the isozymes. Prx1, 2 and 6 are mainly located in the cytosol. Prx3 is restricted to the mitochondrial compartment. Prx4 is present in the endoplasmic reticulum and also se-

TABLE 1. Basic characteristics of mammalian peroxiredoxin (Prx) isozymes

Isozyme	Subgroup	Cellular Location	Chromosomal Localization
Prx1	Typical 2-Cys	Cytosol	1p34.1
Prx2	Typical 2-Cys	Cytosol	19p13.2
Prx3	Typical 2-Cys	Mitochondria	10q25-q26
Prx4	Typical 2-Cys	Endoplasmic reticulum, extracellular space	Xp22.11
Prx5	Atypical 2-Cys	Cytosol, mitochondria, nuclei, peroxisomes	11q13
Prx6	1-Cys	Cytosol	1q25.1

Note: Prx3 is considered a mitochondrial enzyme as its presence is restricted to the mitochondrial compartment. Cys denotes cysteine residue.

creted into extracellular environment. Prx5 is localized intracellularly to the cytosol, mitochondria, nuclei, and peroxisomes. The ubiquitous presence in various cellular compartments suggests that Prx5 might function as a house keeping peroxide-detoxifier in mammalian cells. In humans, Prx1–6 are localized on chromosomes 1p34.1, 19p13.2, 10q25–q26, Xp22.11, 11q13, and 1q25.1, respectively. **Table 1** summarizes the basic characteristics of the six Prx isozymes in mammalian systems.

2. BIOCHEMISTRY

Prxs catalyze the reduction of hydrogen peroxide and various organic hydroperoxides to form water and alcohols, respectively through the reactive cysteine (Cys) residues of the enzymes (**Figure 1**). They may be able to also reduce peroxynitrite [1, 2]. The typical 2-Cys Prxs (Prx1–4) are homodimers and contain both the N- and C-terminal-conserved Cys residues and require both of them for catalytic function. Atypical 2-Cys Prx (Prx5) is a monomer and contains only the N-terminal Cys but requires one additional nonconserved Cys residue for catalytic activity. 1-Cys Prx (Prx6) is a homodimer and contains only the N-terminal Cys and requires only the N-terminal Cys for catalytic function. During the reduction of oxidative substrates, the Cys residues of Prxs are oxidized. Thioredoxin (Trx) provides the electron for reducing the oxidized Prx 1–5, whereas the reduced form of glutathione (GSH) is likely employed to reduce the oxidized Prx6 [3]. Hence, Trx and GSH act as integral components of the Prx-mediated antioxidant defense in mammalian systems.

3. BIOLOGICAL FUNCTIONS

3.1. Antioxidant Functions

Prxs play an important role in the detoxification of hydrogen peroxide and various organic peroxides as well as peroxynitrite. This antioxidant function is the basis for this family of enzymes in protecting against oxidative stress and pathogenesis of various types of diseases and conditions that involve an oxidative stress mechanism, such as cardiovascular disorders, diabetes, neurodegeneration, cancer, and aging [4–12].

3.2. Redox Relay and H_2O_2 Oscillation

In addition to their well-known antioxidant function, Prxs are reported to participate in other cellular processes, such as regulation of the activities of transcription factors (e.g., NF-κB, AP-1, p53), and growth factor signaling [13], as well as ROS signaling [14]. With regard to ROS signaling, Prx1 has been shown to regulate the localized levels of hydrogen peroxide (H_2O_2) for redox signaling and mitotic progression [15, 16]. Notably, Prx2 and signal transducer and activator of transcription 3 (STAT3) form a redox relay for H_2O_2 signaling. In this regard, H_2O_2 oxidizes Prx2, which then interacts with the transcription factor STAT3, resulting in the flow of the

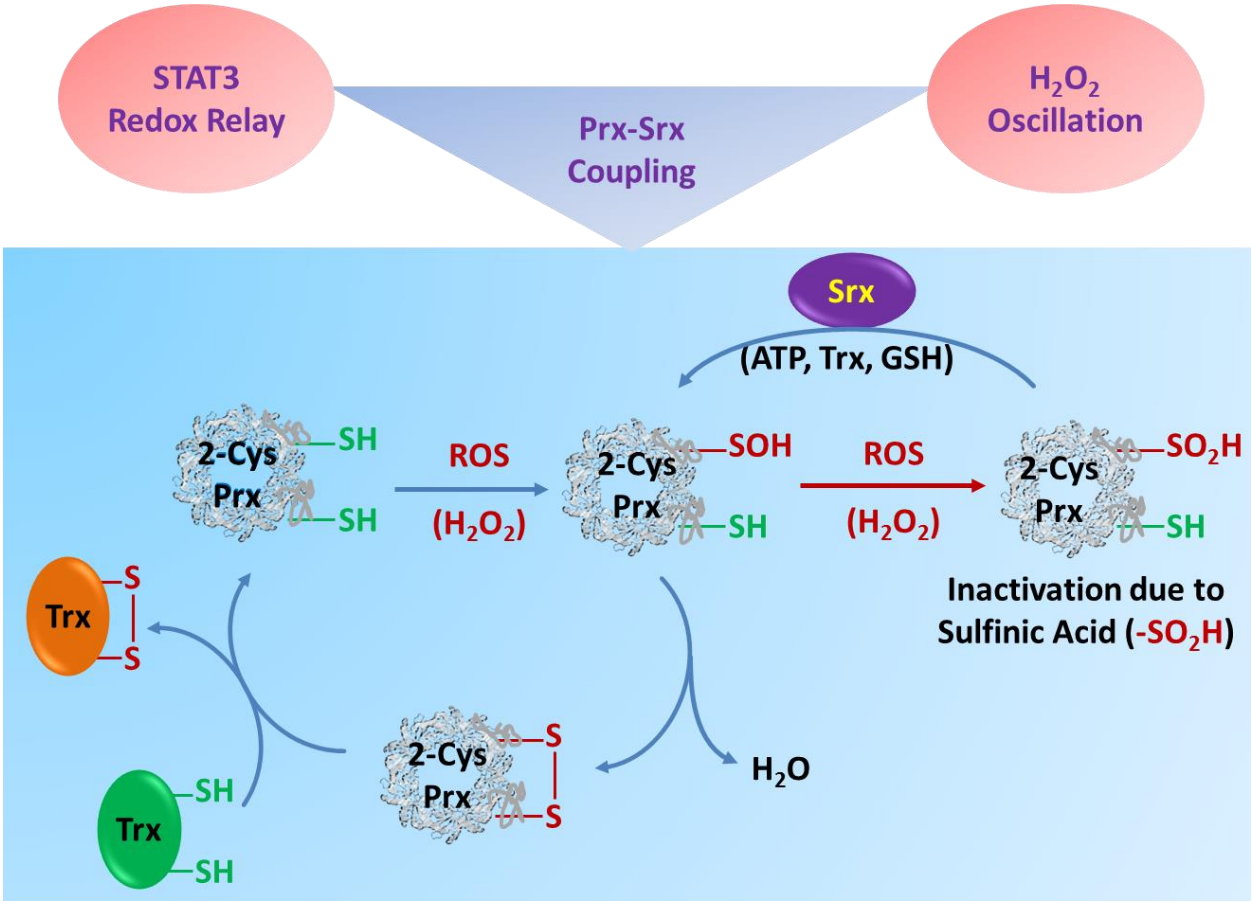

FIGURE 1. Peroxiredoxin (Prx) and sulfiredoxin (Srx) in H_2O_2 homeostasis, redox relay, and oscillation. During normal reduction of H_2O_2 (and organic hydroperoxides), the cysteine residue of Prx is oxidized to sulfenic acid (-SOH), leading to the formation of a disulfide bridge, which can be reduced by thioredoxin (Trx). However, under excessive oxidative conditions, the sulfenic acid can be further oxidized to sulfinic acid (-SO_2H), resulting in the inactivation of the enzyme. Srx catalyzes the reduction of sulfinic acid to sulfenic acid. This reaction is dependent on adenosine triphosphate (ATP) and utilizes Trx or reduced form of glutathione (GSH) as the electron donor. On the one hand, the Prx-Srx coupling ensures H_2O_2 homeostasis, oscillation, and redox signaling of circadian rhythm. On the other hand, Prx might relay the oxidative equivalents to transcription factors, such as STAT3, thereby modulating the expression of selective genes.

oxidative equivalents from Prx2 to STAT3. The redox relay generates disulfide-linked STAT3 oligomers with attenuated transcriptional activity [17]. STAT3, a member of the signal transducer and activator of transcription (STAT) protein family, mediates the expression of a variety of genes in response to cell stimuli, and plays a key role in many cellular processes, such as cell growth and apoptosis. Prxs may not only regulate redox signaling, but also fine tune redox rhythm. In this regard, hydrogen peroxide released from mitochondria regulates various cell metabolic signaling pathways and Prx3 is a major antioxidant enzyme in controlling the levels of mitochondrial H_2O_2. Notably, sulfiredoxin (a recently identified enzyme for reactivating oxidized Prxs; **Figure 1**) is found to undergo translocation to mitochondria and reactivate mitochondrial Prx3, and this interaction results in an oscillatory hydrogen perox-

ide release from the organelle for possibly fine tuning of cell metabolic signaling [18, 19].

4. CONCLUSION AND PERSPECTIVES

Multiple studies published in highly influential journals suggest prx isozymes, especially Prx1 and Prx2, may act as signaling antioxidants. Although many antioxidants, including Prxs have well-established ability to scavenge ROS, inhibit their formation, or repair the oxidative damage, it is important to bear in mind that in addition to their effects on ROS, some antioxidants, including both protein and non-protein antioxidants may also exert other biological effects. In line with this notion, a recent study shows copper, zinc superoxide dismutase (CuZnSOD) as a transcription factor to regulate oxidative stress resistance. In response to elevated endogenous and exogenous reactive oxygen species, including H_2O_2, CuZnSOD rapidly relocates into the nucleus, and in the nucleus, CuZnSOD binds to promoters and regulates the expression of oxidative resistance and repair genes [20].

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