ANTIOXIDANTS & REDOX SIGNALING
Volume 10, Number 9, 2008

DOI: 10.1089/ars.2008.2049

Forum Review

The Dual Functions of Thiol-Based Peroxidases in H_2O_2 Scavenging and Signaling

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Abstract

Thiol-based peroxidases consist of the peroxiredoxins (Prx) and the related glutathione peroxidase (GPx)-like enzymes. Their catalytic function is to reduce peroxides by using the reactivity of the cysteine residue, and their presumed primary physiologic role is to protect living organisms from peroxide toxicity. However, as peroxide-metabolizing enzymes, they also regulate hydrogen peroxide (H_2O_2) signaling. We review here enzymatic and biochemical attributes of thiol peroxidases that specify both distinctive peroxide-scavenging functions and the property of regulating H_2O_2 signaling. We then discuss possible thiol peroxidase physiologic functions, based on selected observations made in microorganisms and mammals. *Antioxid. Redox Signal*. 10, 1565–1575.

Introduction

THIOL-BASED peroxidases represent a major subgroup of nonheme peroxide-scavenging enzymes. They consist of the peroxiredoxins (Prxs) (107), which are conserved in all kingdoms, and of the related glutathione peroxidase (GPx)-like enzymes, also called CysGPxs (25, 60, 92), which are confined to bacteria, fungi, protozoa, insects, and plants. Prxs were initially discovered as peroxide-scavenging enzymes in yeast (11, 14, 85) and in bacteria (38). Their main characteristic is indeed to reduce hydrogen peroxide (H_2O_2) and organic peroxides catalytically, by using the peroxide reactivity of the cysteine sulfur atom and thioredoxin as the hydrogen-donor pathway (Fig. 1). Despite extensive characterization of their peroxide-reducing activity, the *in vivo* function(s) of thiol-peroxidases is unclear and certainly complex. Tangible demonstrations of their antioxidant protective function are available in prokaryotes and lower eukaryotes, but are missing in higher eukaryotes. Concurrently, a multitude of observations made in fungi, plants, and mammals have established both Prxs and CysGPxs as modulators as much as direct effectors of H_2O_2 signaling. This dialectic of the biologic functions of thiol-peroxidases as protective or regulatory enzymes closely mirrors the question of the biologic impact of H_2O_2 as a toxic or as a signaling molecule, which is still a debated matter (24, 68).

In this review, we discuss some of the enzymatic and biochemical attributes of thiol-peroxidases that suggest cellular functions other than protective ones. We then critically consider the *in vivo* cell biologic functions of thiol peroxidases, based on selected observations, made in microorganisms and mammals, that have addressed their roles as protective or signaling devices. We conclude that the mechanisms of antioxidant defenses and those used in ROS signaling are intertwined.

The Enzymology of Thiol Peroxidases Indicates Specific Functions

It is essential to consider briefly the enzymologic features that might distinguish Prxs from the other peroxide scavengers. Many Prxs (93) but only a few CysGPxs (60, 90) have been enzymatically well characterized. Most but not all of them have been shown to possess ping-pong kinetics that obey to the Michaelis–Menten saturation type (90, 93) and have been considered relatively weak peroxide scavengers compared with catalase and selenol-based GPxs (SeGPxs) (33). However, in most circumstances, the *in vitro* characterization of these enzymes by using the Michaelis–Menten parameter (k_{cat}/K_m) cannot be applied to the *in vivo* conditions of low substrate-to-enzyme ratio. Accordingly, *in vivo* enzyme efficiencies are best compared by using the rate con-

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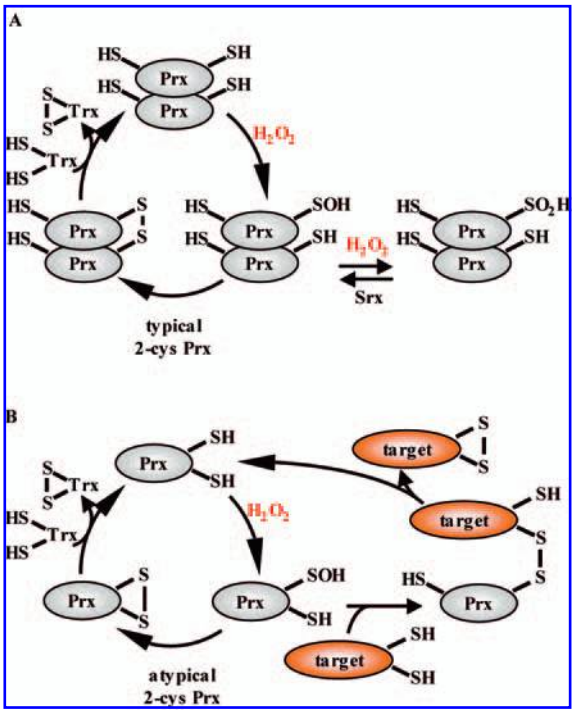

FIG. 1. Thiol peroxidases enzymatic cycles. (**A, B**) On reaction with H_2O_2, the peroxidatic cysteine (Cys_P) of thiol peroxidases oxidizes to a sulfenic acid (R-SOH), which then condenses with the resolving cysteine (Cys_R) to form a disulfide bond. The peroxidatic cycle ends with the reduction of the disulfide bond by thioredoxin and regeneration of reduced enzyme. (**A**) In typical 2-Cys peroxiredoxins (Prxs), this disulfide forms between two monomers, whereas (**B**) in atypical 2-Cys Prxs and CysGPxs, it is intramolecular. (**A**) In typical 2-Cys, The Cys_P-SOH can be further oxidized by a second H_2O_2 molecule, which leads to the formation of a sulfinic (-SO_2H) acid and the inactivation of the enzyme. Such inactivation is reversed by the ATP-dependent reduction of the Cys_P-SO_2H catalyzed by sulfiredoxin (Srx). Inactivation is dependent on an additional C-terminal helix absent in inactivation-insensitive Prxs, which slows the rate of condensation of the Cys_P–SOH) with Cys_R, thereby allowing further oxidation of the Cys_P-SOH by H_2O_2 (106). (**B**) As described in the oxidation of Yap1 by Orp1 (see text), the Cys_P-SOH can form a disulfide with another protein-thiol target instead of condensing with the resolving cysteine. The intermolecular disulfide bond then isomerizes into an intramolecular disulfide, releasing the oxidized target and the reduced thiol peroxidase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

stants for the bimolecular reaction of reduced enzyme with H_2O_2 (k'_A) and the relative molarities of the enzymes under consideration. The k'_A parameter reflects the rate of oxidation of the catalytic cysteine (Cys_P) to the Cys_P sulfenic acid (R-SOH) form (see Fig. 1) and is at least in part dependent on the reactivity of the enzyme for its substrate.

Direct determination of k'_A values or competition kinetics by stopped-flow techniques revealed, for some Prxs, values up to 3.7×10^7 M/s (76), which are as fast as those of SeGPxs and catalase (see Table 1). Hence, a reactive Prx with a k'_A comparable with that of catalase becomes as efficient as the latter at low concentrations of H_2O_2, if it is at a higher level. However, catalase will become more efficient at higher H_2O_2 concentrations because of the saturation kinetic behavior of Prxs. Under high or sustained peroxide challenge, regeneration of the ground-state enzymes or turnover rate becomes important for ongoing catalysis, which, depending on the Prx system under consideration, may become limited by a low K_{mB} (the rate of reduction of the oxidized Prx by the thioredoxin system), low levels of Trx, or rapid consumption of reduced Trx. This situation is reflected in the very low apparent K_{mA} values (<20 μM) of mammalian Prxs, when measured at Trx concentrations near physiologic levels (see Table1). It therefore appears realistic to assume an activity threshold in the low micromolar range of H_2O_2, at which catalase takes over. Similarly, a Prx will not be able to compete with a SeGPx at high hydroperoxide fluxes. Although the overall Prxs rate constants for the reductive part of catalysis (k'_B) are quite high (5×10^4–10^7 M/s) and in fact often higher than those of SeGPxs ($k'_2 \sim 10^4$–10^5 M/s), the very high abundance of the SeGPx reductant glutathione (GSH) relative to the Prx reductant thioredoxin should give a clear advantage to SeGPxs, whenever the later are present in reasonable amounts. Most important, Prxs become disqualified under high or sustained H_2O_2 concentration by substrate-mediated inactivation (see later).

In summary, Prxs should efficiently compete with catalase and SeGPxs at low peroxide fluxes but likely become inefficient (or inactivated) at higher fluxes. Such a view is totally consistent with the *in vivo* evaluation of the respective contributions of the AhpC Prx and catalase to *Escherichia coli* H_2O_2 scavenging (88) and with the unique ability of the *Saccharomyces cerevisiae* Prx Tsa1 to protect DNA from the toxicity of low levels of endogenous peroxide (36) (see later). The very high reactivity of Prxs for hydroperoxide, as reflected by the generally fast k'_A, and their abundance should also allow these enzymes to efficiently degrade low peroxide levels as noncatalytic scavengers, as recently suggested for Prx2 in erythrocytes (57). The very high Prx Cys_P reactivity for H_2O_2 also makes these enzymes ideal for H_2O_2 sensing and signaling, which provides the specificity required for these processes. Hence, Prxs can react with H_2O_2 at low "signaling" concentrations before this molecule is intercepted and degraded by other systems, which fits the function of H_2O_2 receptor described for thiol peroxidases in lower eukaryotes (24).

Regulation of Thiol Peroxidase by Posttranslational Modifications

The very existence of a posttranslational regulation of an ROS scavenger is by itself a strong indication of the presence of a regulated function(s) other than protective. Many different posttranslational modifications of Prxs that alter their peroxidase function have been described, which strongly suggests an extended set of regulatory functions. Such modifications are not described for CysGPxs.

Reversible inactivation of Prxs by substrate-mediated inactivation

2-Cys Prxs undergo substrate-mediated inactivation by overoxidation of the Cys_P-SOH to the sulfinic acid form (R-SO_2H) (see Fig. 1). This feature being unique to eukaryotic enzymes has led Poole *et al*. (82) and others to suggest that it indicates an acquired gain of function (106). Discovery of

Table 1. Kinetic Parameters of Selected Peroxiredoxins (Prx), Selenothiol Glutathion Peroxidases (SeGPx), and Heme Catalases (HeCat)

		Oxidizing substrate	k'_A (M/s)	k'_B (M/s)	k_{cat} (per s)	K_m (ROOH) (μM)	K_m (Red) (μM)	References
Prx	PRX2 *H. sapiens*	H_2O_2	1.3×10^7[a]	9.0×10^5[b]	2[c]	<20[h]	2.7[d]	12, 79
	PRX1 *H. sapiens*	H_2O_2	$>2.2 \times 10^5$[b]	8.0×10^5[b]	4.4[c]	<20[h]	5.5[d]	12
	PRX3 *H. musculus*	H_2O_2	$>2.4 \times 10^5$[b]	1.1×10^6[b]	4.8[c]	<20[h]	4.3[d]	12
	AhpC *S. typhimurium*	H_2O_2	3.7×10^7[b]	8.9×10^6[b]	52.4	1.4	5.9[e]	76, 81
		t-BOOH	2.3×10^5[b]	1.3×10^7[b]	54.7	238	4.1[e]	
		CH	4.9×10^5[b]	1.3×10^7[b]	52.0	107	4.0[e]	
	Tpx *E. coli*	H_2O_2	4.4×10^4[b]	3.0×10^6[b]	76	1,730	22.5[f]	3
		CH	7.7×10^6[b]		70.1	9.1	22.5[f]	
	Tsa1 *S. cerevisiae*	H_2O_2	2.5×10^7[a]		0.31	12	—	67, 71
		t-BOOH			0.29	7.9	—	
		CH			0.26	17.1	—	
	Tsa2 *S. cerevisiae*	H_2O_2	1.3×10^7[a]		0.39	13.8	—	67, 71
		t-BOOH			0.29	5.1	—	
		CH			0.28	4.5	—	
SeGPx	GPX1 *H. sapiens*	H_2O_2	4.1×10^7[g]	2.3×10^5[g]				91
		t-BOOH	4.2×10^6[g]	2.3×10^5[g]				
	GPX3 *H. sapiens*	H_2O_2	4.0×10^7[g]	7.9×10^4[g]				91
		t-BOOH	2.3×10^6[g]	7.9×10^4[g]				
	GPX4 *Pig heart*	PCH	1.5×10^7[g]	5.7×10^4[g]				
HeCat	Catalase *Horse erythrocytes*	H_2O_2	0.6×10^7	1.8×10^7				15
	Catalase *Horse liver*	H_2O_2	1.7×10^7	2.9×10^7				15
	Catalase *M. lysodeikticus*	H_2O_2	1.1×10^7	1.7×10^7				15

k'_A and k'_B are the bimolecular second-order rate constants for the first (oxidizing) step and the second (reductive) step of the overall reaction.

[a]Obtained from competition with horseradish peroxidase. TBH, *tert*-butyl hydroperoxide; CH, cumene hydroperoxide; PCH, phosphatidylcholine hydroperoxide.

[b]k'_A and k'_B were calculated as k_{cat}/K_m for the oxidizing and reducing substrate, respectively.

[c]Calculated from specific activities and molecular weight of the enzymes. The reducing substrates used were [d]rat thioredoxin, [e]S128W N-terminal domain of AhpF, and

[f]*E. coli* thioredoxin 1.

[g]Calculated from Dalziel coefficients.

[h]Apparent K_m at highest experimentally possible Trx concentration.

the reversible nature of this inactivation and of sulfiredoxin (Srx) and sestrins (4, 7, 19, 104), the enzymes that catalyze ATP-dependent reduction of the Prx Cys_P-SO_2H, further supports this hypothesis. Overoxidation occurs only during enzymatic cycling and is proportional to the amount of substrate, even in "nonsaturating" conditions (111). Excess substrate further increases the rate of overoxidation by increasing the likelihood of collision of the Cys_P–SOH with H_2O_2. In *S. pombe*, Prx inactivation by Cys_P-SO_2H formation has been established as a redox switch regulating the H_2O_2-receptor function of the Prx Tpx1 (5, 98) (see later). In mammals, the biologic significance of this modification is not established. Inactivation could act as a "floodgate" that restricts the Prx scavenging function to the low levels of endogenous H_2O_2, while allowing unchecked signaling at higher levels (106). Prx inactivation might also play a pivotal role as a signaling crosstalk between H_2O_2 and other pathways. For instance, endogenously produced arachidonic acid lipid hydroperoxide metabolites of lipoxygenase and cyclooxygenase inactivate Prx1, Prx2, and Prx3 (23). Nitric oxide (NO) produced by lipopolysaccharide (LPS) and IFN-γ–stimulated macrophages induces Prx1, Prx6, and Srx, prevents H_2O_2-induced Prx1 inactivation, and accelerates Srx-dependent cysteine sulfinic acid reduction (26), suggesting a global positive effect of NO on Prx-dependent peroxide scavenging.

Oligomerization of Prxs

Another striking property of Prxs is their ability to assemble reversibly into ring-shaped decamers, dodecamers, and even higher-order ball-shaped oligomeric structures [for a review, see (107)]. Except a few exceptions (8), assembly into decamers and their stabilization are favored when Prxs are in the reduced or overoxidized forms, respectively (107), and disassembly is triggered when Prxs are oxidized into their disulfide-linked homodimeric form or on Cys-SO_2H reduction. Structural constraints within the decamer alter the enzyme active site, further increasing the Cys_P reactivity toward substrate (77). Thus, during catalysis, Prxs likely cyclically assemble as decamers and disassemble or form metastable decamers when trapped into the inactive Cys-

SO_2H form. This idea is consistent with the observation that on exposure to elevated H_2O_2 levels, the *S. cerevisiae* 2-Cys Prxs Tsa1 and Tsa2 multimerize, presumably as a result of overoxidation, eventually disassembling in a manner requiring Srx (40). Such cyclical assembly might also explain the changes of Prx1 and Prx2 observed by fluorescence microscopy within mouse cells exposed to H_2O_2, forming cytoplasmic filamentous structures that correlated with Prx overoxidation and cell-cycle arrest (80).

Prx multimerization is associated with the acquisition of the new function of a chaperone that prevents heat shock–induced protein aggregation and contributes to heat-shock tolerance (40). Similar observations have been made with human Prx1 and Prx2 (54, 63), also showing that Prx1 is more efficient as a molecular chaperone, and Prx2, as a peroxidase (54). Such a difference is explained by a cysteine residue (Cys83) uniquely present in Prx1 at the dimer–dimer interface that stabilizes the enzyme decameric form by disulfide bond formation. Oligomerization might also be important for the interaction of Prxs with regulatory proteins.

Phosphorylation of Prxs

Prx1 is reversibly inactivated during mitosis by phosphorylation by the cyclin-dependent kinase Cdc2 (18). Phosphorylation also shifts Prx1 into high-molecular-weight structures with chaperone activity (39). Prx2 specifically interacts with, and becomes phosphorylated by Cdk5, which also leads to inactivation of peroxidase activity (83). Such phosphorylation of Prx2 was identified as the downstream event of a complex signaling cascade leading to the accumulation of peroxide and ultimately to neuronal cell death, in the methyl phenyl tetrahydropyridine model of Parkinson disease. In these two cases, phosphorylation occurred on the same threonine residues of Prx1 and Prx2.

Other posttranslational modifications of Prxs

Prxs can be inhibited by NO-mediated nitrosylation of both catalytic cysteines, as shown for Prx2 in primary rat cortical neurons exposed to *S*-nitrosocysteine (SNOC) or to *N*-methyl-D-aspartic acid (NMDA), which activates neuronal NO synthase–induced NO production (28). Cellular treatment by SNOC or NMDA also exacerbates H_2O_2-induced neuronal cell death, presumably as a result of Prx2 inactivation, a situation that is possibly relevant to the pathogenesis of Parkinson disease, which implicates both nitrosative and oxidative stresses. This study, thus concluding that NO promotes oxidative stress by nitrosative inactivation of Prx2, conflicts with the study of Diet (26) (see earlier) that rather showed NO promoting a global enhancement of Prx peroxidase function. Such a discrepancy underscores the complexity of the functions of Prxs and of the biologic impact of both NO and H_2O_2 on signaling and cell toxicity.

Prx3 is inactivated within mitochondria by cleavage by a calpain-like cysteine protease in response to peroxide (66). Further, interaction with FANCG—a protein of unknown function encoded by one of the Fanconi anemia complementation groups—protects Prx3 from calpain-induced proteolytic cleavage. Interestingly, the FANCG mutation G546R abrogates this interaction, promoting Prx3 cleavage and mislocalization, distortion of mitochondrial structures, and susceptibility to H_2O_2, which is possibly relevant to the pathogenesis of Fanconi anemia.

Genetic Insights Into Functions of Thiol Peroxidases

Genetics is a straightforward approach to decipher protein functions *in vivo*. However, for thiol-peroxidases this statement holds true in single-celled but not in multicellular organisms. As single-celled organisms, bacteria and fungi are directly exposed to exogenous peroxide. They are therefore tractable to a direct evaluation of the effects of exogenous peroxide, and hence of the protective functions of thiol peroxidases. In mammals, one important limit to these studies is the lack of a good experimental model to test the effects of exogenous peroxide on cells within their host habitat.

Genetics of thiol peroxidases in prokaryotes

Escherichia coli has three highly divergent Prxs that have been uniquely ascribed protective functions. The bacterial 2-Cys Prx AhpC is the most abundant and the primary endogenous H_2O_2 scavenger (88). The Hpx^- mutant that lacks all major peroxide-scavenging enzymes [*i.e.*, catalase G (KatG) and E (KatE) and AhpCF], grows well under anaerobiosis but very poorly under aerobiosis (73), which indicates some functional overlap between these enzymes. This mutant has also a dramatic increase in mutation frequency under aerobiosis. Despite their genetic overlap, an *in vivo* functional specialization exists, with AhpC being important for scavenging trace levels of endogenous H_2O_2, and catalase, elevated levels of this oxidant (88). Such specialization fits these enzyme kinetic differences (see earlier). The two other *E. coli* Prxs are periplasmic thiol peroxidase (Tpx), an atypical 2-Cys Prx with substrate specificity toward alkyl hydroperoxides (9), and bacterioferritin-comigratory protein (BCP), a weak 1-Cys peroxiredoxin with substrate preference toward linoleic acid hydroperoxides (43).

Genetics of thiol peroxidases in fungi

Yeast *S. cerevisiae* carries five Prxs (typical 2-Cys Tsa1 and Tsa2, atypical 2-Cys Ahp1/cTpxIII and nTpx, and thioredoxin-dependent 1-Cys mTpx) (85), of which Tsa1, Tsa2, and Ahp1 are cytoplasmic and also peroxisomal for the latter, nTpx is nuclear and mTpx is mitochondrial (74). *S. cerevisiae* also carries three CysGPxs: Gpx1, Gpx2, and Gpx3, also known as Orp1 and as Hyr1 (1, 25, 37, 92).

S. cerevisiae Prxs have only known stress-protective functions, in contrast to the unique *S. pombe* Prx Tpx1, which also carries H_2O_2 signaling functions. Tsa1 and Ahp1 are abundant, stress-inducible, and the predominant Prx isoforms. Tsa1 is more specific toward H_2O_2 (13, 52), and Ahp1, toward *tert*-butyl hydroperoxide (t-BOOH) (42, 52). Tsa1 is the primary scavenger of endogenous H_2O_2, as shown by its significant contribution to genome stability; its absence leads to a broad spectrum of spontaneous mutations (36). Other Prx genes have only a minor role in this function, but their deletion increases the spontaneous mutation frequency of the *tsa1* mutant (102). Importantly, mutations affecting recombinational repair or postreplication repair cause *tsa1* cells to die rapidly (35), emphasizing the importance of Tsa1 for genome protection. Tsa1 and Tsa2 also carry peroxynitrite reductase activity (71, 103). Tsa2, a structural and functional duplicate of Tsa1, is not abundant but is stress inducible (32,

51, 67, 103). Its *in vivo* peroxide-protective function is controversial (67, 103). Both Tsa1 and Tsa2 also have heat shock–protective functions because of their chaperone activity (see earlier). mTPx has a specific protective role toward peroxides produced during respiration, consistent with its localization (78), and nTPx does not have a demonstrated function. A Prx quintuple mutant with deletion of *TSA1*, *TSA2*, *AHP1*, *nTPX*, and *mTPX* is viable (102), which contrasts with the aerobic inviability of the *E. coli* Hpx^- mutant and of the *S. pombe* mutant lacking Tpx1 (41, 73).

All *S. cerevisiae* CysGPxs have peroxidase activity *in vitro*, but only the inactivation of Orp1/Gpx3 leads to defective tolerance to H_2O_2 and t-BOOH (1, 37), which is related to defective peroxide-induced antioxidant gene activation (25) (see later). Still, Orp1 is also active toward linolenic acid hydroperoxide, independent of its gene-regulatory function (2).

Genetic insights into the functions of mouse Prxs

Mammals carry six Prx isoforms that include four typical 2-Cys Prxs, which are the cytoplasmic Prx1 and Prx2, mitochondrial Prx3, and endoplasmic reticulum and secreted Prx4, an atypical 2-Cys enzyme Prx5, and a 1-Cys enzyme Prx6. Phenotypes that explicitly suggest a role of Prxs in peroxide protection were obtained with Prx6 knockout (KO) mice that have increased toxicity from the superoxide-generating herbicide paraquat (100). Further, Prx6 KO mouse lens epithelial cells are particularly prone to oxidative stress (29).

Mice with inactivation of either Prx1 (69) or Prx2 (53) have anemia and splenomegaly that are the consequence of a compensated regenerative hemolysis, possibly caused by increased red blood cell (RBC) oxidative-stress vulnerability. Prx2 expression during erythroid differentiation before hemoglobin accumulation, its high abundance in RBCs (87), and its suggested function of a noncatalytic scavenger of low levels of peroxide (57) are features compatible with a peroxide-protective function. However, the RBC plasma membrane localization of Prx2 (10) also suggests a role in membrane-associated processes. The role of Prx1 in the protection of RBCs against oxidative stress is less probable, given its much lower abundance, thus questioning the cause of the Prx2 KO mice hemolytic anemia.

Prx1 but not Prx2 KO mice are also prone to cancer, depending on the mouse genetic background (27, 69). Analysis of the tumors arising in Prx1 heterozygote mice showed that they carry a loss of the remaining Prx1 allele, which led to the suggestion that PRX1 is a tumor-suppressor gene. Such tumor-suppressing activity could be a consequence of the role of Prx1 as protecting the genome from endogenous peroxide, or inhibiting an oncogene such as *Myc* or c-*Abl* (27, 69, 101). Cancer occurrence could also be a consequence of defective tumor immunosurveillance, as Prx1 KO mice have abnormal NK cells, or could be also due to other uncharacterized signaling defects.

Another remarkable phenotype associated with the invalidation of Prx2 and also of Prx3 is the high hypersensitivity to LPS-induced endotoxic shock (55, 110). LPS hypersensitivity does not seem to be a result of defective oxidative-stress tolerance. Rather, it has been linked to LPS-induced hyperactivation of the Toll-like receptor 4 (TLR4) signaling pathway, which controls innate immunity and inflammation and involves an ROS signaling component (110). The abnormal LPS/TLR4 signaling of Prx2-deficient mice appears highly specific to this pathway, as signaling by agonists of the TLR2, TLR3, and TLR9 receptors was not altered in Prx2 KO mice.

Another, and one of the best genetic proofs of very specific roles in signaling of both H_2O_2 and a Prx, comes from the abnormally high PDGF-R response of the Prx2 KO mouse line to artery restenosis, leading to local neointimal thickening with increased cellular proliferation and accumulation of vascular smooth muscle cells (20). In the absence of Prx2, PDGF stimulation led to a higher cellular production of H_2O_2, site-selective hyperphosphorylation of the PDGF-R, and a specific enhancement of the activation of phospholipase Cγ, without any alteration in AKT and ERK kinase signaling. The observation of a PDGF-induced recruitment of Prx2 to the PDGF-R suggests that Prx2 locally scavenges H_2O_2, thereby indirectly altering the redox state and hence the activity of a putative PDGF-R–cognate protein tyrosine phosphatase. H_2O_2 thus mediates the site-selective amplification of PDGF-R phosphorylation, and Prx2 appears as a physiologic regulator of this endogenous signal.

Mechanistic Insights Into Thiol Peroxidase Regulatory Functions

Thiol-peroxidases that propagate an H_2O_2 signal

Model fungi have revealed unique functionalities of thiol peroxidases, enabling them to operate as "peroxide receptors" and redox transducers in the regulation of peroxide-induced gene activation (24). As stated earlier, because of their high H_2O_2 reactivity, thiol peroxidases are ideally fitted to signal H_2O_2. The ability of thiol peroxidases to oxidize proteins-thiols other than their physiologic reductant thioredoxin also enables them to propagate the H_2O_2 signal. The further unique feature of 2-Cys Prxs to undergo reversible substrate-mediated inactivation provides a redox-switch mechanism regulating these signaling functions relative to the levels of H_2O_2.

The peroxide receptor and redox-transducing function of yeast thiol peroxidases

The *S. cerevisiae* CysGPx Orp1, also known as *Sc*Gpx3, constitutes the receptor of a major peroxide homeostatic pathway (25). On reaction with H_2O_2, the Orp1 Cys_P oxidizes to a Cys-SOH (58) and initiates a thiol-based redox relay that leads to the activation of the bZip transcription factor Yap1, which controls antioxidant gene expression. Orp1 activates Yap1 by catalyzing formation of at least two intramolecular disulfide bonds within this regulator (25, 72, 105). Orp1 reduces H_2O_2 with its Cys_P that oxidizes to an R-SOH. The Orp1 Cys_P-SOH then condenses with a specific Yap1 cysteine residue (Cys598) to form an intermolecular disulfide bond that is subsequently transposed into an intramolecular disulfide by nucleophilic attack by another Yap1 Cys residue (25). The second Yap1 disulfide bond presumably involves a second Orp1-oxidized molecule. Thus, Orp1 acts as a Yap1-specific thiol oxidase, and Yap1, as an Orp1 reductase, substituting for the Orp1 physiologically reductant thioredoxin. Orp1 might oxidize other proteins in addition to Yap1 and thioredoxin, as suggested by the identification of Orp1 in a disulfide linkage with the methionine sulfoxide reductase Mxr1, although surprisingly, this linkage was established with Orp1 Cys_R (47) and not with Orp1 Cys_P.

Orp1 and its close yeast homologue Gpx2 also operate as catalytic thiol peroxidases with a cycle involving an intramolecular disulfide that forms between the Cys_P and Cys_R and that is subsequently reduced by thioredoxin (25, 92) (see Fig. 1). Hence, the Orp1 Cys_P-SOH has two alternative cysteine-residue partners, Yap1 Cys598 or Orp1 Cys_R, the latter being preferred, based on its more-efficient molarity in the vicinity of Cys_P. A mechanism that brings the Orp1 Cys_P-SOH close to Yap1 Cys598 or away from Orp1 Cys_R (or both) is needed to favor Yap1 activation, which might be provided by Ybp1, a protein critically required for Orp1-Yap1 disulfide-bond formation (97). A mutant of Orp1 with an Ala substitution of Cys_R that abrogates the peroxidase but not the regulatory Orp1 function did not result in any observable H_2O_2 tolerance defects, suggesting that the Orp1 peroxidase function is of minor importance for direct H_2O_2 scavenging *in vivo* (25).

S. pombe has two parallel peroxide homeostatic pathways, each responding to quite different levels of H_2O_2 (84). Pap1, the homologue of Yap1, quickly responds to H_2O_2 at low concentration, but its activation is delayed at higher H_2O_2 concentration (84, 99). In contrast, the MAP kinase Sty1 responds to high concentrations of H_2O_2. The Pap1 restricted response to low H_2O_2 levels is the consequence of the use of the unique *S. pombe* Prx Tpx1 as the Pap1 peroxide receptor (5, 98). High H_2O_2 levels inactivate Tpx1 by Cys_P-SO_2H formation, thus inhibiting Tpx1-mediated redox transduction. Sty1-induced Srx1 eventually reduces the Tpx1 Cys-SO_2H and reactivates the redox relay. Both catalytic Tpx1 cysteine residues are required for Pap1 oxidation by a mechanism that seems to differ from the one used by the Orp1-Yap1 relay. Interestingly, Tpx1 is also required for H_2O_2-induced Sty1 activation by engaging the Cys_P into an H_2O_2-inducible disulfide linkage with a cysteine residue of the kinase (96). Tpx1 catalytic peroxidase activity is essential for aerobic viability (41), which contrasts with the viability of the *S. cerevisiae* quintuple Prxs mutant.

Is the H_2O_2 signaling function of yeast thiol peroxidases universal?

It is not known whether mammalian Prxs operate as their yeast counterparts, although an H_2O_2 signal-transducing function is suggested for Prx1 by its requirement for the activation of the p38 MAPK by H_2O_2 and oxidized lipids (22). The selenol phospholipid hydroperoxide GPx GPx4, also known as PHGPx, can function as a protein-thiol oxidase not to signal H_2O_2 but instead to polymerize the protective sperm mitochondrial capsule. The monomeric structure of Gpx4, which carries gaps at positions that correspond to dimerization and tetramerization interfaces in other GPxs (94), probably enables its interaction with and oxidation of protein-thiols other than GSH. Yeast CysGPxs also are monomeric, also lacking multimerization interfaces and are therefore more homologous to GPx4 than to other GPxs (1). Gpx4 promotes the polymerization of the sperm mitochondrial capsule by catalyzing disulfide bond formation between structural keratin-like and other proteins (59). GPx4 also contributes to the condensation of the sperm chromatin by oxidation of protamines, which replace histones during maturation (21). GPx4-catalyzed disulfide bond formation is presumably triggered by oxidation of GPx4 by peroxide, which might require the decrease in the concentration of the GPx4–physiologic reducing system GSH that occurs during sperm maturation.

In plants, genetic data also indicate the function of a transducer that relays an H_2O_2 signal for the *Arabidopsis thaliana* CysGPx *At*Gpx3, an enzyme very similar to *S. cerevisiae* Orp1. According to these data, *At*Gpx3 signals H_2O_2 in the abscisic acid (ABA) pathway of guard cells that controls drought stress tolerance (62). In these cells, *At*Gpx3 is required to inhibit the *ABA insensitive2* (ABI2)-encoded protein phosphatase 2C-type, presumably by oxidation.

Other possible signaling mechanisms for mammalian Prxs

Mammalian Prxs may also affect H_2O_2 signaling by controlling the fluxes and concentration of this molecule, and their reversible inactivation may add another control level (24, 82, 86, 106). This hypothesis is supported by the effects of Prxs in modulating H_2O_2 signaling downstream of growth-factor tyrosine kinases and cytokine receptors. For instance, when overexpressed in HeLa cells, Prx1 and Prx2 can inhibit EGF-R and PDGF-R signaling by eliminating the H_2O_2 produced on stimulation (46). In the same study, Prx2 overexpression was also shown to block H_2O_2 and TNF-α–induced NF-κB activation. Ectopic expression of Prx4 in HeLa cells also inhibits TNF-α or TPA-induced NF-κB activation (44). Such observations clearly demonstrate the importance of H_2O_2 as a signaling molecule. However, they cannot be taken as proof of a specific role of Prxs in regulating H_2O_2 signaling, only indicating that because of their peroxide-scavenging activity, Prxs, can when overexpressed, dampen H_2O_2-dependent signaling. Similar observations were also made on overexpression of SeGPxs (6), which underscores the lack of specificity of any observation made on overexpressing a peroxide scavenger. Gene KO approaches, which are much more reliable, have provided very strong evidences of a role of Prx2 in regulating H_2O_2 signaling. As already discussed, the use of the artery-restenosis experimental model in the Prx2 KO mouse has led to conclusions about the role of Prx2 in regulating PDGF-R activation, also revealing a mechanism imparting specificity to the messenger function of H_2O_2 (20). The LPS-hypersensitive phenotype of the Prx2 KO mouse line also strongly suggests a role of Prx2 in regulating H_2O_2 signaling, as it correlates with hyperactivation of NF-κB and of the JNK, ERK, and p38 MAPK on engagement of TLR4 by LPS (110). This latter study also indicated that Prx2 not only regulates H_2O_2 signaling levels, but can also, through a yet-unknown mechanism, modulate the strength of the activation of NADPH oxidase on LPS stimulation and the amount of H_2O_2 it produces.

A role of Prxs in regulating or interfering with cellular H_2O_2 fluxes is also suggested by the antiapoptotic effect of these enzymes, when considering the apoptotic effect of H_2O_2, whether it occurs from exogenous sources or is endogenously produced by apoptotic stimuli. For instance, the siRNA-mediated knockdown of Prx3 renders HeLa cells highly sensitized to TNF-α–induced or staurosporin-induced apoptosis (17). Such sensitization correlated with an increase in mitochondrial ROS and was reversed by ectopic expression of catalase in mitochondria, indicating a causative role for ROS in the execution of apoptosis and a regulatory effect of ROS elimination by Prx3 in this response. Similarly, oligonucleotide-mediated inactivation of Prx3 was shown to enhance mitomycin C–induced apoptosis of HeLa cells (66). In

addition, a multitude of studies have shown that overexpressed Prxs, as much as SeGPxs, can interfere with cell death (48, 70, 112, 114), which is at least another demonstration of the important signaling role of H_2O_2 in these death pathways.

Prxs can also affect cell signaling by virtue of an interaction with and modulation of regulatory proteins in a manner independent of their peroxidase function. Individual Prxs have indeed been shown to interact specifically with a multitude of regulatory proteins (listed in Table 2), and, in some instances, to alter their regulatory functions, as in the interaction of Prx1 with the c-*Abl* protooncogene (101), the c-*MYC* protooncogene (65), the JNK-GSTπ protein complex (49), and with the androgen receptor (75). Establishing the *in vivo* biologic relevance of these interactions will require further studies.

Summary and Perspectives

The thiol peroxidases, Prxs and CysGPxs, are fascinating peroxide-metabolizing enzymes that clearly carry biologic functions beyond those of simple peroxide-protective enzymes. Their biochemical and enzymatic attributes specify both distinctive peroxide-scavenging functions and the ability to signal H_2O_2. Their high reactivity for peroxide together with their relative overall catalytic inefficiency and their property to undergo reversible substrate-mediated inactivation provide the unique ability to scavenge the low levels of endogenously produced peroxide, also restricting scavenging to these low concentrations. Such an enzymatic characteristic confers the quasi-exclusive function of protecting the genome against mutations that would otherwise arise during normal cell metabolism, as shown in *E. coli* and in *S. cerevisiae* (36, 88). Regarding this function, selenothiol-based GPxs, which do not exist in prokaryotes and fungi, also must be considered as important in mammals.

Reactivity and reversible inactivation are also attributes exploited by Prxs for operating H_2O_2 signaling, which generally occurs under low to very low concentrations of the oxidant. Whereas prokaryotic thiol peroxidases primarily operate as peroxide-protective enzymes, eukaryotic ones are also used in the regulation of H_2O_2 signaling. Model fungi have revealed, for both Prxs and CysGPxs, the unique regulatory function of detecting and propagating H_2O_2 signals. This function is again dependent on the unique peroxide reactivity of these enzymes

Table 2. Protein-protein Interactions Involving Mammalian Peroxiredoxins

Peroxiredoxin	*Interaction partner*	*Significance*	*Cys_P*	*Reference*
Prx1	JNK-GSTπ complex	Prevents JNK activation by IR	Not necessary	49
	c-*Abl*	Abl tyrosine kinase activity inhibition		101
	eEF1A-2	Co-transfection of both proteins protects cells from H_2O_2-induced apoptosis		16
	Omi/HtrA2 mature form	*In vitro* activation of serine protease activity	Not necessary	34
	Androgen receptor, on hypoxia/reoxygenation	Prx1 increases AR activation by H/R and synthetic androgen R1881	Not necessary	75
	c-*Myc* (Myc Box II domain)	Prx1 inhibits tumorigenicity induced by myc		65
	MIF	Decreased D-dopachrome tautomerase activity of MIF	Not necessary	45
	Presenilin-1	PS-1 overexpression prevents Prx1 overexpression-induced cell death in SCG primary neurons culture		115
	Syk	Not assessed		113
Prx2	PDGFRβ, on PDGF	Prevents PDGFRβ Tyr857 phosphorylation and		20
	Cdk5	Prx2 phosphorylation		83
	PLD1 on PMA	Inhibits H_2O_2-induced PLD1 activity		109
	Stomatin (7.2b)	Could be linked to a role of Prx2 in Ca^{2+}-dependent K^+ transport		64
Prx3	LZK	Enhances IKK and NF-κB activation	Not necessary for interaction	61
	Abrin A chain	Prx3 blocks Abrin-induced apoptosis		89
	RPK118	RPK118 could be a transporter of Prx3 to mitochondria		56
	FANCG	Protection against Prx3 cleavage and mitochondrial oxidative stress		66
Prx4	Thromboxane A_2 receptor, isoform β	TPβ relocalization to ER and TPβ degradation on H_2O_2		31
Prx6	$p67^{phox}$	Linked to Prx6 phospholipase A_2 activity		50
	Surfactant protein A	Inhibition of Prx6 PLA2 activity		108
	Saitohin	Possible link to Pick disease		30

and on their ability to oxidize protein-thiols other than their physiologic reductant. These enzymes thus couple a highly reactive thiol with other protein-thiols, allowing the oxidation of regulatory proteins that are otherwise nonreactive to peroxide. Such unique H_2O_2 signal function has been hinted in plants (62) and, although highly suspected from the behavior of GPx4 in sperm cells, is not yet known to exist in mammals, in which it should be sought. In mammals, genetic and cell biologic investigations indicate complex and intertwined H_2O_2 protective and regulatory functions that can be for a large part rationalized by the H_2O_2-metabolizing function of Prx. Nevertheless, their physiologic role is far from clear. In this regard, the values of mouse genetic models should be further exploited, which will necessarily discover the functional Prxs isozymes redundancy.

Conclusions

Thiol peroxidases have complex physiologic functions that probably mirror the complex biologic regulatory and toxic impact of H_2O_2. Their study clearly indicates intricate relations between the mechanisms of H_2O_2 scavenging and those used in H_2O_2 signaling. Further studies of these systems should benefit the understanding of the biology of H_2O_2, which is at the crux of aging and its associated diseases.

Acknowledgments

This work was supported by grants from Agence Nationale pour la Recherche and from Association de Recherche sur le Cancer to MBT. Many thanks to Leopold Flohé for his expert scientific and editorial assistance.

Abbreviations

Cys_P, peroxidatic cysteine; Cys_R, resolving cysteine; GPx, glutathione peroxidase; GSH, glutathione; NO, nitric oxide; PHGPx, phospholipid hydroperoxide glutathione peroxidase; Prx, peroxiredoxin; RBC, red blood cell; ROS, reactive oxygen species; SeGPx, selenol glutathione peroxidase; Srx, sulfiredoxin; t-BOOH, *tert*-butylhydroperoxide.

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Date of first submission to ARS Central, February 19, 2008; date of final revised manuscript, February 26, 2008; date of acceptance, March 6, 2008.

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