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Discoveries

FORUM REVIEW ARTICLE

The Multifaceted Impact of Peroxiredoxins on Aging and Disease

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Abstract

Significance: Peroxiredoxins (Prxs), a family of thiol-associated peroxidases, are purported to play a major role in sensing and managing hydrogen peroxide concentrations and transducing peroxide-derived signals.
Recent Advances: Prxs can act as detoxifying factors and impart effects to cells that can be either sparing or suicidal. Advances have been made to address the qualitative changes in Prx function in response to quantitative changes in the signal level and to understand how Prx activity could be affected by their own substrates. Here we rationalize the basis for both positive and negative effects on signaling pathways and cell physiology, summarizing data from model organisms, including invertebrates.
Critical Issues: Resolving the relationship between the promiscuous behavior of reactive oxygen species and the specificity of Prxs toward different targets in redox-sensitive signaling pathways is a key area of research. Attempts to understand Prx function and underlying mechanisms were conducted *in vitro* or *in vivo* under nonphysiological conditions, leaving the physiological relevance yet to be defined. Other issues: Why despite the high degree of homology and similarities in subcellular and tissue distribution between Prxs do they display differential effects on signaling? How is the specificity of post-translational protein modifications determined? Other than chaperone-like activity, how do hyperoxidized Prxs function?
Future Directions: Genetic models with mutated catalytic and resolving cysteines should be further exploited to dissect the functional significance of individual Prxs in their different states together with their alternative reducing partners. Such an analysis may then be extended to help identify Prx-specific targets. *Antioxid. Redox Signal.* 29, 1293–1311.

Keywords: peroxiredoxin, sulfiredoxin, redox signaling, reactive oxygen species

Introduction

PEROXIREDOXINS (Prxs) COMPRISE a family of thiol-based peroxidases, which possess antioxidant and cell signaling functions. The scope of their biological action is remarkably broad, ranging from regulation of cell proliferation and metabolism to cell death pathways and aging (72). This diverse array of functions may be ascribed in large part to the fate of a catalytic sulfenic acid (Cys-SOH) intermediate, which is formed upon reaction of thiolate ion Cys^- with peroxides, a first step common to the various Prx subtypes (131).

Typically the Cys-SOH intermediate reacts with other thiols, mostly with a resolving sulfhydryl–SH group to form a disulfide bond that is subsequently restored to its original state by a variety of reducing equivalents, including thioredoxins (Trxs), which have differential affinities to the individual Prxs. The Cys-SOH-reacting partners may also include Cys-SH groups associated with other protein species, forming heterodimers whereby transient oxidation states may be transmitted through Prxs to target regulatory proteins with attendant repercussions. The Cys-SOH may also react with glutathione, which can serve as a reducing equivalent in Prx recycling or as a resolving cysteine (Cys_R) (118). These types of reactions are typical for the 1-Cys Prx group [reviewed in Chae *et al.* (19)].

Alternatively the Cys-SOH may undergo further oxidation events to form the sulfinic ($Cys\text{-}SO_2H$) and sulfonic ($Cys\text{-}SO_3H$) acids or other modifications such as glutathionylation that

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result in reversible or irreversible inactivation of peroxidase activity [reviewed in Chae *et al.* (19)]. These reactions are dependent on molecular characteristics of the individual Prxs and occur when the resolving cysteine or other thiols are deficient while concentrations of hydrogen peroxide (H_2O_2) are high. It is noteworthy that such modifications may allow Prx to assume other functional roles, such as a multimeric complex with chaperone activity or transducers of reactive oxygen species (ROS) signals, both subject to regulation by reducing factors, such as sulfiredoxin (Srx), which is able to reduce sulfinic but not sulfonic acids (Fig. 1). In this review, we examine how the differential roles of the Prxs are affected by changes in conformation, degree of oxidation, and recycling, and how these changes impact function at the cellular and organismal levels.

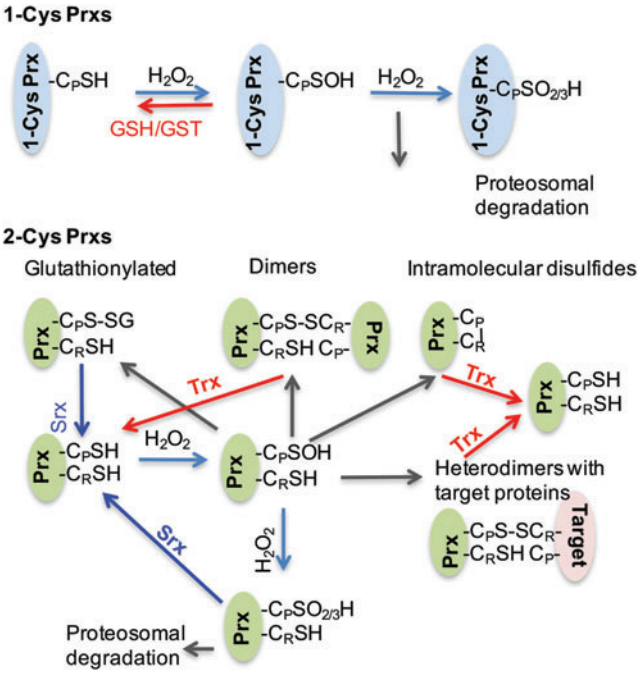

FIG. 1. Prx conversions and enzymatic cycles. The peroxidase activity of Prxs depends on the formation of disulfide bonds between a conserved cysteine in the Prx active site denoted as peroxidatic and a second less conserved cysteine denoted as resolving. The peroxidatic cysteine (C_PSH) is oxidized by hydrogen or other peroxides leading to the formation of sulfenic acid (C_PSOH). Upon proximity of the resolving cysteine (C_RSH) or an accessible cysteine of the target protein, the peroxidatic cysteine is condensed with another thiol group thus forming intermolecular (typical 2-Cys Prxs1–4) or intramolecular (atypical Prx5) disulfide bonds. Subsequently homo- and heterodimers are rapidly recycled by the Trx system with NADPH as an electron donor. In the case of 1-Cys Prx, recycling of sulfenic acid is mediated by glutathione with help of π glutathione transferase. At low Prx or Trx concentrations, and when peroxide levels are high, the longer lived Prx sulfenic acid can be further oxidized to a reversible sulfinic (C_PSO_2H) or irreversible sulfonic (C_PSO_3H) acid that are degraded by proteasomes or, in the case of C_PSO_2H, reduced by Srx in an ATP-dependent, slow reaction. Sulfenic acid may also be converted into an inactive state by glutathionylation, which is reverted by Srx or Grx. In this way, the catalytic Prx cycle competes with Prx arrested in its inactive state through hyperoxidation or glutathionylation. Recycling of Prxs by Trx/GSH systems (*red arrows*) is fast while the recycling loop mediated by Srx is slow (*blue arrows*) (6, 27, 31, 41, 43, 47, 119, 131, 132, 164, 165, 168–170, 175). Prx, peroxiredoxin; Srx, sulfiredoxin; Trx, thioredoxin. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

Differential Effects of Prxs on Physiology

First attempts to establish functional significance of the various members of the Prx family came from experiments with Prx mutants and overexpressors. Early reports revealed that enhanced Prx expression tended to have positive effects on cell function, physiology, and health, presumably, by limiting oxidative damages, whereas reduced Prx activity largely had a negative impact. In subsequent studies, this simple relationship did not always hold, and has given rise to a more nuanced appreciation of Prx function in different cellular contexts (Table 1).

Single Prx knockouts or knockdowns in a variety of model systems were often viable and displayed relatively minor effects under normal conditions. For instance, the Prx3 knockout mice as well as flies with severely depressed levels of Prx3 had no discernable phenotypes, although some age-associated markers such as oxidative stress/metabolic signatures and physical endurance deficits were more pronounced in older Prx-deficient animals than in controls (84, 127, 179). Similarly, the absence of Prx5 in *Drosophila*, other than a slight reduction in longevity, presented a normal phenotype (126). The Prx4 knockout in mice also displays a normal phenotype with the exception of a mild prostate atrophy (56), whereas Prx4 knockdown in flies had no strong phenotype but failed to transduce ROS-derived signals (71, 124) (Fig. 2).

The effects of deficits in Prx activity became more prominent when animals were subjected to stress conditions. Thus the Prx3 mouse knockout exhibited more prominent markers of lung inflammation in response to lipopolysaccharide (LPS) administration relative to controls. In the absence of Prx6, mice were more susceptible to oxidative stress (158), manifesting itself particularly in lung tissue (159), whereas transgenic mice overexpressing Prx6 survived longer during exposure to 100% O_2 (160). In insects, underexpression of Prx5 (126) or Jafrac1, an ortholog of mammalian Prxs1–2 (33), also increases sensitivity to oxidants, such as the insecticide paraquat (PQ), which is known to produce superoxide anion and impair mitochondrial function.

In yeast, the deficits in Prx activities clearly increased susceptibility to oxidative and nitrosative stress; however, even the quintuple mutant lacking all five Prxs was viable, although its growth rate was lower under normal aerobic conditions (166). In part, these mild effects can be ascribed to Prx antioxidant function redundancy or the impact of other species possessing peroxidase activity. Consistent with this notion is that when both Prxs that are expressed within the mitochondrial compartment (Prx3 and Prx5) are knocked down in flies that lack other peroxidases in mitochondria, the phenotype is quite dramatic, including extensive accumulation of oxidative damage and greatly reduced longevity compared with the mild effects observed when either Prx alone is knocked down (127) (Fig. 3).

Table 1. Effects of Peroxiredoxin Under- and Overexpression on Physiology

Peroxiredoxin	*Species (synonyms)*	*Phenotypes*		*References*
		Knockdowns/knockouts	*Overexpressors/transgenics*	
Prx1	Mouse	Cell-specific increase in ROS, increased oxidative damage; promoted development of age-dependent hemolytic anemias and cancers; shortened lifespan; increased apoptosis in precancerous lesions; increased susceptibility to *Mycobacterium tuberculosis* by lowering levels of cytokines and nitric oxide in the lungs; impaired T_H1 responses and antimicrobial activity of macrophages.	Promoted hepatic tumorigenesis	(13, 36, 48, 88, 178)
Prx2	*Drosophila* (*jafrac1*)	Reduction in adhesion between cells	Neuronal overexpression extended lifespan	(8, 33, 49, 75, 81, 82, 91, 107, 108, 116, 172, 174)
	Caenorhabditis elegans	Shortened life span; increased stress resistance by reducing insulin secretion	Reduced age-associated intestinal dysplasia; protected from oxidative stress	
	Mouse	Hemolytic anemia, altered erythropoiesis; increased sensitivity to LPS-induced inflammatory response; inhibition of immune cell responsiveness; accelerated cell senescence and premature aging of skin; decreased number and size of tumors	Aggravated the hepatic tumor phenotypes; promoted tumorigenesis	
Prx3	Mouse	Increased apoptosis; reduced physical strength, increased apoptosis in brains; accelerated oxidative stress and mitochondrial impairment, impaired function of skeletal muscles; increased oxidative damage and lung inflammation in response to LPS, reduced resistance of macrophages to oxidative stress, higher levels of TNF-alpha; metabolic dysregulation, accumulation of fat by adipocytes; increased insulin resistance	Improved glucose homeostasis; maintained insulin sensitivity	(23, 25, 55, 80, 83, 84, 109, 179)
Prx4	*Drosophila*	Increased oxidative damage and cell death of spermatogenic cells	Extended lifespan when overexpressed at moderate levels or in neurons, shortened life span when overexpressed globally at high levels	(34, 44, 56, 71, 98, 100, 124)
	Mouse		Suppressed atherosclerotic progression in apolipoprotein E-deficient mice; delayed progression of nonalcoholic fatty liver disease; protected from nonalcoholic steatohepatitis and ameliorated symptoms of type 2 diabetes; protected from progression of type 1 diabetes	
Prx5	*Drosophila*	Increased sensitivity to oxidative damages	Extended lifespan	(113, 125, 126)
	Mouse	Enhanced resistance to infection	Suppressed neuronal death in Alzheimer's disease model	
Prx6	Mouse	Increased lung injury under oxidative stress; increased susceptibility to ischemic reperfusion injury; enhanced mucin secretion in bronchial epithelia; increased sperm chromatin damage, reduced fertility; affected pH homeostasis, vacuolation in kidneys	Promoted the development of Alzheimer's disease; exacerbated the development of rheumatoid arthritis, increased proinflammatory response; lessened lung oxidative damage; protected keratinocytes from oxidative damage and cell death; attenuated LPS-induced acute kidney injury	(65, 74, 78, 85, 99, 110, 146, 159, 160, 173, 177)

LPS, lipopolysaccharide; Prx, peroxiredoxin; ROS, reactive oxygen species.

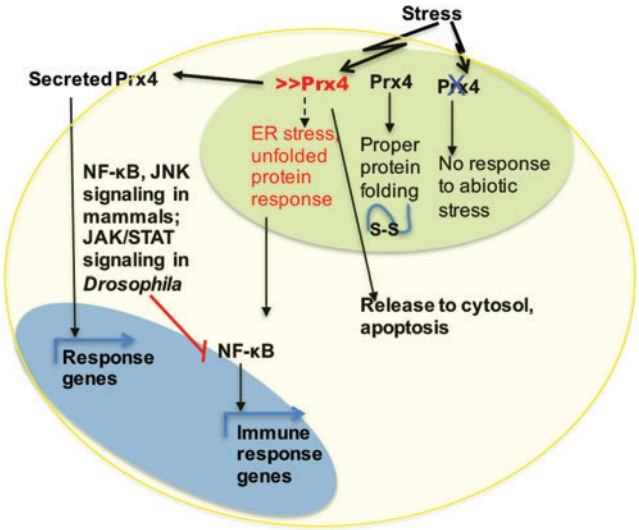

FIG. 2. Differential functions of Prx4. Under normal conditions, Prx4 resides in the ER, where it functions to eliminate peroxide and also essential for proper protein oxidative folding. High levels of the ER-residential Prx4 or certain stress conditions cause relocalization of Prx4 to another subcellular compartments, induction of apoptosis, ER stress, NF-κB-dependent activation of the immune response through a noncanonical immune pathway(s), and shortened longevity. Activity of Prx4 is absolutely required for transmission of the responses to abiotic stresses, stresses that are not elicited by microbial infection. The links indicated by *dotted lines* have yet to be established (71, 124, 150, 151, 180, 181). ER, endoplasmic reticulum. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

In a series of clinical and animal studies, deficits in Prx activity were shown to be associated with the development and progression of various pathologies, effects that have been largely attributed to increases in the production of ROS and consequent oxidative damage. In the case of Fanconi anemia, reduced Prx activity due to cleavage of the mitochondrial Prx3 contributed to the accumulation of oxidative DNA damage in bone marrow precursors, leading to apoptosis, bone marrow failure, and ultimately increased predisposition to blood cancer (95).

The absence of Prx1 activity in knockout mice led to oxidative damage in red blood cells (RBCs), a reduction in hemoglobin activity and an increase in hemolysis, culminating in the development of hemolytic anemia and shortened life span (102). The Prx1 knockout also exhibited increased tumor frequency promoted by a variety of effects on cell cycle and cell proliferation, including impaired lytic function of NK, and activation of the c-Myc oncogene that is normally sequestered through its interaction with Prx1 (36). Likewise, lack of Prx2 in Prx2 knockout mice enhanced oxidation of RBCs, leading to hemolytic anemia (82).

In *Caenorhabditis elegans* the lack of Prx2 elicited a progeric phenotype and a shortened lifespan (75, 107). Moreover, these Prx2-deficient animals were found to exhibit redox-sensitive modifications at oxidation-sensitive cysteines in 40 different proteins (75), 2 of which were more oxidized in the mutant than in wild type worms and whose potentially altered activities may contribute to the mutant phenotype; nevertheless the links between activities and redox-sensitive modifications have yet to be established.

In contrast, overexpression of Prxs tends to alleviate or prevent the progression of pathologies, associated with oxidative stress, such as Alzheimer's disease (AD), Parkinson's disease, fatty liver disease, and diabetes, and also extend longevity. Thus, overexpression of Prx3 in transgenic mice resulted in reduced levels of H_2O_2 in mitochondria, greater resistant to stress-induced cell death and apoptosis, and improved glucose homeostasis (25).

Likewise, enhanced Prx activity may play a protective role in other pathologies. More recently, such beneficial effects were confirmed in an extensive series of overexpression studies involving all six Prx subtypes. In general, enhanced peroxidatic activity of all Prx subtypes (Prxs1–6) conferred antiapoptotic effects and lessened the severity of pathological conditions, whereas these beneficial effects were lost in redox-negative mutants with the substituted catalytic cysteine residue and, consequently, lost peroxidatic activity (26, 29, 34, 44, 54, 67, 98, 100, 113, 125).

Studies in invertebrates have shown that global or tissue-specific overexpression of Prxs can lessen oxidative stress, restore mitochondrial function, reduce proapoptotic changes, and extend life span (81, 126). Importantly, tissue-specific distribution and the levels of expression played a determining role in the beneficial effects of Prxs on physiology.

In flies, ectopic expression of the cytosol-localized homologue of mammalian Prx2, Jafrac1, in neurons, attenuated JNK/FOXO signaling, thereby reducing oxidative damage and restoring mitochondrial function in neurons, and resulted in life span extension (81). The endoplasmic reticulum (ER)-localized homologue of Prx4, expressed at moderate levels or in a neuron-specific manner, also had a longevity-extending effect, whereas higher levels of this Prx resulted in its subcellular redistribution, which triggered apoptosis and pro-inflammatory responses mediated *via* NF-κB-like pathways (71, 124).

In worms, expression of Prx2 in pharyngeal neurons restored a normal pumping response to light and light-generated H_2O_2, as well as normal feeding behavior to the *prx2* mutant (7), whereas the differential effects on stress resistance and longevity were determined when Prx2 was expressed in intestines. By acting through different signaling mechanisms, intestine-targeted Prx2 expression increased the resistance to H_2O_2 but did not influence resistance to the oxidative stress-causing agent, arsenite, and also failed to rescue the shortened longevity phenotype of the *prx2* mutant (107).

Surprisingly, with regard to carcinogenesis, it was shown that Prx overexpression could have a negative impact, promoting both tumor progression and metastasis (48, 116). Similarly, underexpression of Prx would have differential effects on carcinogenesis, ranging from procarcinogenic, as was documented in earlier studies with *prx1* mutant mice that displayed increase in oxidative DNA damage (102), to anti-carcinogenic, mainly *via* reducing the spread of tumors or increasing apoptosis (48). This phenomenon has been explained by the dual role of ROS in cancer, whereby ROS may enhance either DNA damage or cell proliferation contributing to procarcinogenic effects (13), or ROS may damage cancer cells and thus prevent promotion of growth and spread of tumors (89). From this perspective, Prx status may be

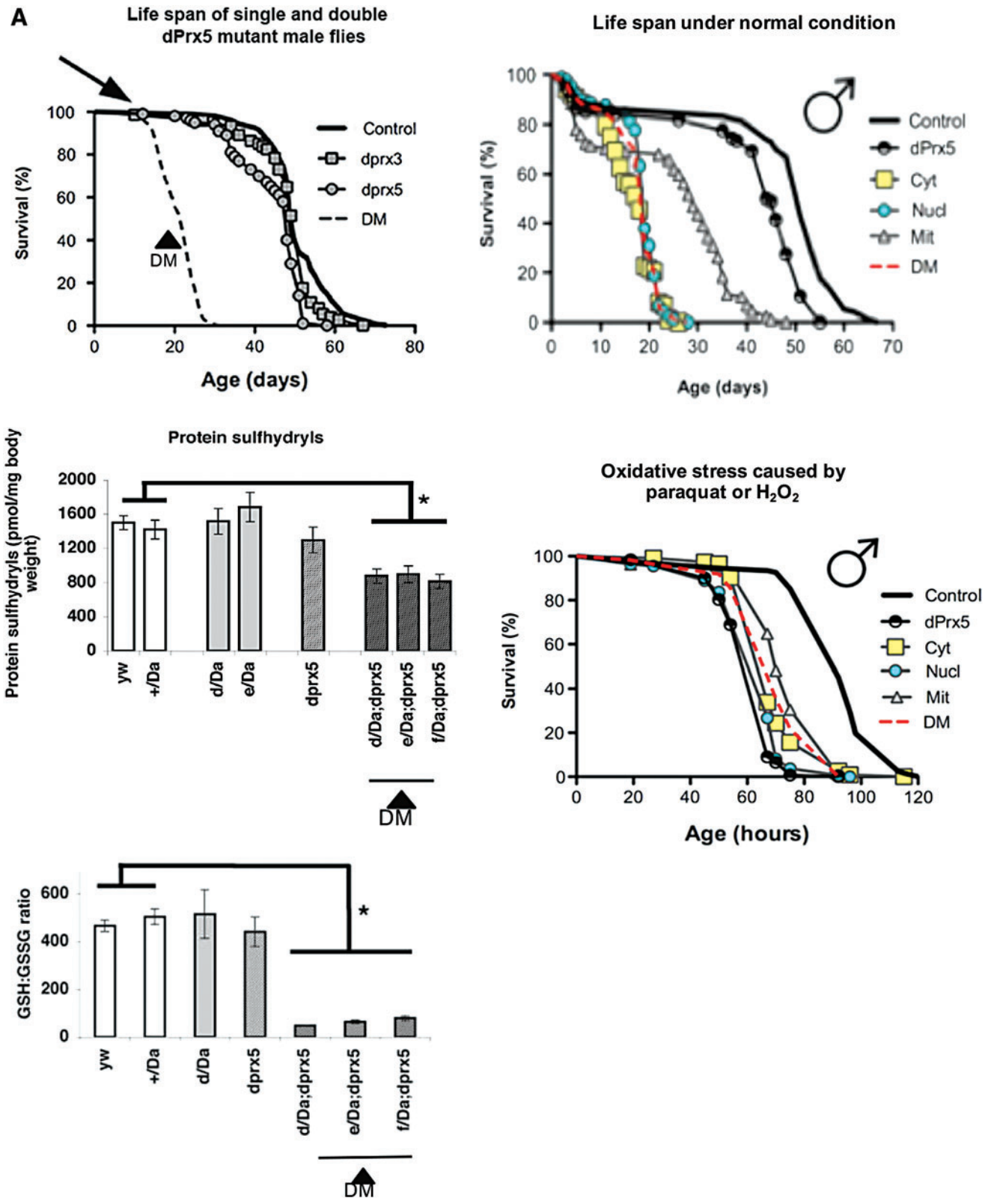

FIG. 3. Effects of Prx3 and Prx5 on longevity and stress resistance. *Drosophila* Prx3 is solely localized to the mitochondrion, whereas Prx5 is also found in cytosol and nucleus. Individual underexpression of either Prx3 or Prx5 (*dprx3*, *dprx5*) did not affect longevity, but lifespan was dramatically shortened in the *dprx3*, *dprx5* DM, accompanied by pro-oxidizing alterations in thiol homeostasis, as determined by measurements of sulfhydryls and GSH/GSSG ratios. Mitochondrial form of Prx5 (Mit) conferred partial rescue effects on longevity, whereas expression of Prx5 from the wild type transgene (dPrx5), which is distributed to all three compartments (mitochondrial, cytosolic, and nuclear), essentially restored life span, suggesting an interplay between functional redundancy of the Prxs and effects on yet-to-be-defined specific targets. At the same time, peroxidatic capacity of the transgene-expressed Prx5 was not sufficient to overcome exogenous oxidative stress caused by H_2O_2 or paraquat and protect the redox-sensitive targets (see third paragraph of Differential Effects of Prxs on Physiology). DM, double mutant. Figures are adapted from Radyuk *et al.* (127) and Odnokoz *et al.* (105). Statistically significant difference is denoted by an asterisk. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

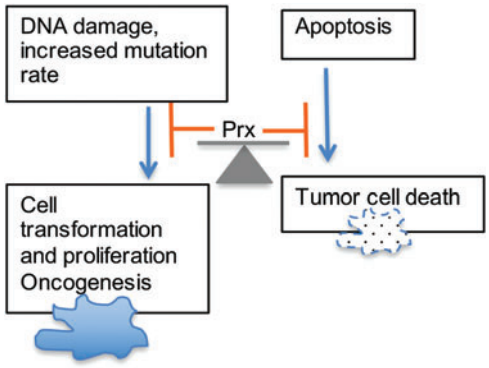

FIG. 4. Differential effects of Prxs on cancer development and progression. By helping to maintain the DNA damage response, Prxs counter the effects of mutagenesis leading to cell transformation and proliferation. In contrast, Prxs' antiapoptotic effects in cancer cells foster the promotion of carcinogenesis and spread of tumors. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

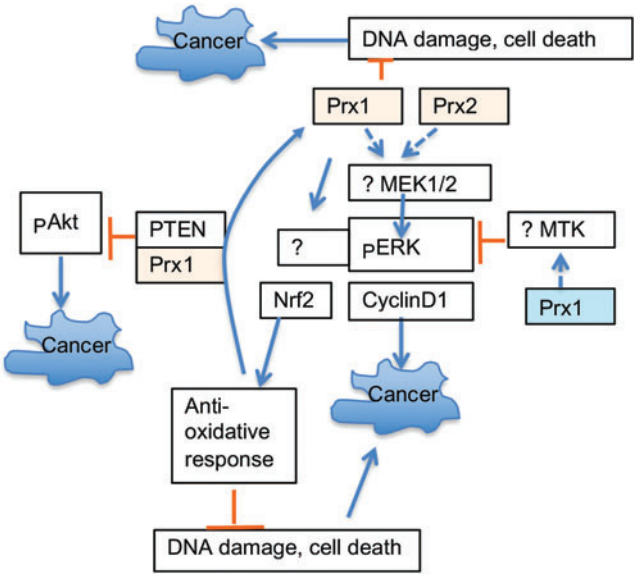

FIG. 5. Activating (*pink*) and inhibiting (*blue*) effects of Prxs on carcinogenesis depend on cell type and the interplay between different pathways. In breast cancer cells, Prx1 protects PTEN phosphatase from oxidation and thus inactivation; PTEN in turn controls Akt activation and suppresses tumor development (13). In lung cancer cells, Prx1 suppresses activation of extracellular signal-regulated kinase (ERK)/cyclin D1 pathway by inhibiting phosphorylation of ERK (117). In hepatocytes, both Prx1 and Prx2 induce activation of ERK, and Prx1 also increases Nrf2 signaling (48, 116). The activity of ERK is controlled through the status of specific tyrosine and threonine residues that can be phosphorylated by MEK1/2 kinases or dephosphorylated by MAP kinase phosphatases MKP1/DUSP1 (134). Prxs may affect different targets in different tissues, and thus have opposite effects on activation of the ERK/cyclin D1 or Nrf2 pathways, ultimately promoting either cell proliferation or cell death. Nrf2, nuclear erythroid 2-related factor 2. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

critical in determining prosurvival *versus* cell death responses in tumor cells (Fig. 4).

It is interesting to note the appearance of higher levels of Prxs in some cancers (22, 101, 116, 117), suggesting an adaptive response to a pro-oxidant environment that may in turn favor tumor growth. For instance, Prx3 levels together with Ki67, a marker for cell proliferation, positively correlate with sectors of cervical cancer in tissue sections but not in adjacent normal epithelia (53, 76), and furthermore suppression of Prx activity limits tumor growth, which may be due in part to an increase in apoptosis (70). Similarly, Prx2 knockout mice exhibited a reduction in the number and size of tumors, whereas overexpression of this Prx aggravated the hepatic tumor phenotype by promoting ERK phosphorylation and subsequent activation of the downstream ERK target, cyclin D1, thereby enhancing cell proliferation (116).

The protumorigenic function of Prx2 was also reported in colorectal cancer cells (62). Mechanistically, Prx2 promoted tumors by interacting with and preventing oxidative inactivation of tankyrase, a polymerase that controls the pro-oncogenic β-catenin pathway *via* degradation of oncogenic β-catenin. Conversely, Prx2 deletion in mice reduced β-catenin levels and thereby promoted survival. Knockdown of Prx1 elicited a reduction in hepatic tumor formation due to ROS-mediated DNA damage and cell death, whereas overexpression had the opposite effect (48). Similar to Prx2, Prx1 overexpression enhanced phosphorylation of ERK with subsequent activation of cyclin D1. Surprisingly, activation of ROS-modulated ERK/cyclin D1 pathway and K-ras-mediated lung tumorigenesis was significantly promoted in Prx1 knockout mice (117).

In other words, the same post-translational modification, phosphorylation of ERK, was elicited by Prx1 overexpression in hepatic cancer cells and Prx1 knockout in lung cancer cells, suggesting interplay of other yet-to-be-defined pathways modulated by Prx1 (Fig. 5).

Prxs may also affect carcinogenesis *via* another mechanisms, for instance by influencing the spread of cancerous cells due to changes in E-Cadherin levels, as was suggested by DeGennaro *et al*., who showed that *Drosophila* Jafrac1, the ortholog of mammalian Prdx1, is required to maintain E-Cadherin levels (33, 79). Underexpression of Prx1 and decrease in E-Cadherin levels would lead to a reduction in adhesion between cells, thus promoting metastasis. This function of Prx1 has also been demonstrated with human lung adenocarcinoma cells (45). Similar results were obtained in mice underexpressing Prx2. The human melanoma cells injected into these mice invaded and colonized lungs more aggressively than the control animals, since the *prx2* mutants had a reduced E-Cadherin level and thus enhanced cell migration (79).

Apart from the differential effects of Prx activity in cancers, enhanced Prx activity may not only impose protective effects but also negative effects on cell physiology and functions *via* different mechanisms, such as reductive stress or aberrant redox-sensitive signaling, both of which may result in increased ROS production and cytotoxicity (2, 73). Prxs may also promote inflammatory responses. Prx1 overexpression enhances the LPS-induced release of proinflammatory cytokines, such as IL-6 and TNF-α, as well as

neutrophil-attracting chemokine IL-8, whereas Prx1 knockdown considerably reduces release of these interleukines (86). Mechanistically, Prx1 is postulated to impact nuclear translocation of NF-κB, which is a known target of redox regulation (112), although specific Prx1-NF-κB interactions were not demonstrated in the reported study (86).

LPS-induced proinflammatory responses were also observed in the blood of Prx6-overexpressing transgenic mice, including increases in HNE (marker of lipid peroxidation) and nitric oxide (NO) levels, as well as higher levels of proinflammatory TNF, IL-6, and IL-1β in the blood, contributing to the development of arthritis (65). These effects were attributed to interactions of Prx6 with redox-sensitive components of NF-κB and JNK signaling, resulting in activation of these oxidative stress-mediated signal pathways. Specifically, Prx6 affected NF-κB signaling by enhancing the DNA binding activity of NF-κB, nuclear translocation of p50 and p65, and degradation of IκBα protein, as well as phosphorylation of IKKα and IKKβ. Prx6 also increased DNA binding activity of AP-1, translocation of pJun and pFos into the nucleus, and phosphorylation of JNK, ERK, and p38.

Although there were connections between Prx6 levels and levels of ROS, such as H_2O_2 and NO, that were elevated due to activation of JNK signaling and expression of the downstream oxidases, the exact mechanisms of the proinflammatory effects of Prx6 are not clear. In part, this paradoxical effect of the antioxidant enzyme may be ascribed to the bifunctional nature of Prx6, which unlike other Prxs possesses phospholipase (PLA) activity that could enhance an inflammatory response (39).

Such interplay between peroxidatic and PLA activity with a net negative effect on physiology has been reported in the AD model, wherein progression of the disease has been accelerated in the Prx6 overexpressor (177). Similarly, Parkinson's disease was exacerbated in the Prx6 transgenic mice model (176), although experimental evidence as to which activity, peroxidatic or PLA, contributes to disease progression, and how, is yet to be provided.

In addition, Prxs can affect H_2O_2-mediated signaling in different ways, either by silencing ROS-activated signaling *via* removal of peroxides with subsequent post-translational modifications of the target proteins, as was the case for platelet-derived growth factor signaling regulated by Prx2 (28) or by transducing H_2O_2 signals and thus promoting the induction of the redox-sensitive pathways. These differential effects were documented for MAPK-mediated signaling, as reviewed in Latimer and Veal (77), wherein Prxs regulated signal transduction by affecting post-translational modifications, such as phosphorylation of various targets, or *via* H_2O_2-dependent inhibition of Trxs. In this way, Prxs could have different effects on cell physiology.

For instance, Prx1 promoted invasiveness of cancer cells by contributing to the formation of membrane protrusions by increasing p38 MAPK phosphorylation (149). Alternatively, Prx1 affected p38 MAPK signaling through modulating activity of the p38 MAPK-coupled phosphatases MKP-1 and MKP-5 (156). Although having a protective role under normal conditions, Prx1 conferred differential effects on the activities of two phosphatases under conditions of oxidative stress, which was dependent on the state of oxidation and inactivation of its peroxidatic cysteine (Cys_P). Although overoxidized Prx1 failed to protect MKP-1 from inactivation, it was able to bind and protect MKP-5, thus having differential effects on p38 MAPK signaling and physiological outcomes.

Another remarkable example of the dual function of Prx1 is its impact on lipid-laden macrophages, responsible for development of atherosclerosis. These effects are mediated *via* both Prx antioxidant activity (cytoprotective) and modulation of p38 MAPK signaling (potentially proapoptotic) (30).

The differential effects of Prxs can also be governed by other factors. For instance, higher Prx levels or exposure to stressors, such as LPS, may cause relocalization of Prxs to other subcellular compartments, thus initiating different interactions and events. In such circumstances, these proteins may function as ligands for cell receptors and trigger proinflammatory and cytotoxic responses, as was observed when Prx1, Prx2, or Prx4 were released into extracellular space (21, 96, 124, 140), although it was not always clear whether this function is linked to their peroxidase activity.

Thus, Prx4, which is normally localized to the ER, may be secreted into the extracellular milieu, where it may function as a cytokine to promote inflammatory responses and cell proliferation by triggering NF-κB and JNK signaling and the expression of inducible nitric oxide synthase and ICAM-1 molecules (51). In *Drosophila*, Prx4 relocalizes to extracellular environment or cytosol under certain stress conditions and modulates the immune response or induces apoptosis (71, 124) (Fig. 2). Thus, depending on specific conditions, Prx activity may have both positive and deleterious effects on cell function and survival, which has to be taken into account when developing strategies for prevention or treatment of various disorders.

Functions of Catalytically Inactive Prxs

Apart from the positive (antioxidant activity, ''proper'' regulation of redox-sensitive signaling, and sensor function) and negative (reductive stress, impaired, or silenced redox signaling) effects of Prxs on cell function and physiology that are mediated *via* peroxidatic activity, the catalytically inactive forms have also been shown to possess functional aspects. These functional aspects become apparent when post-translational modifications such as overoxidation or glutathionylation of the catalytic/Cys_P disrupt peroxidase activity (123, 169).

Overoxidized Prxs are formed during catalysis as an ''escaper'' product instead of the disulfide formation that occurs between the oxidized intermediate (sulfenic acid) of the Cys_P and the resolving cysteine in the normal catalytic Prx reaction (Fig. 1). Efficiency of the peroxide-degrading catalytic cycle depends on Prx concentrations and the availability of reducing agents, such as Trx (18) and GSH+π isoform of glutathione transferase (GST) (128) that delivers reducing equivalents (GS^-) to the catalytic domain of 1-Cys Prx6 *via* formation of heterodimer complexes (153). In the case of Prx deficiency or in the presence of excessive levels of H_2O_2, the sulfenic intermediate of Cys_P can easily undergo further oxidation to Cys-SO_2H or even Cys-SO_3H, resulting in the transient or permanent loss of peroxidase activity (157) (Fig. 1).

In vitro studies [reviewed in Chae *et al.* (19) and Peskin *et al.* (120)] have also revealed that, under conditions of oxidative stress, the sulfenic acid intermediate may undergo a mixed disulfide reaction involving glutathione, which results

in glutathionylation of Cys_P and attendant functional ramifications.

Under normal physiological conditions, changes in H_2O_2 production follow a circadian rhythm and occur in concert with fluctuations in levels of the over-oxidized Prx forms (35, 104). Similarly, the increase in H_2O_2 levels that accompanies aging correlates with greater Prx hyperoxidation, as was documented in yeast (90) and in the rat model, wherein the mitochondrial Prx3 in older animals was found to possess higher levels of cysteinyl sulfonic acid, an effect that was partially reversed by treatment with the antioxidant acetyl-L-carnitine (97). Consistent with these observations, in tissue and organismal studies involving the application of exogenous oxidative stress, the accumulation of Prx-$SO_{2/3}$ forms was found to be dependent on the level and duration of stressor administration (175).

Prx overoxidation has also been observed in pathological conditions or disease states normally associated with oxidative stress. For instance, overoxidized Prx forms were detected after ischemia/reperfusion occurring during human liver transplantation (17). 2-Cys Prxs1–3, particularly Prx type II, are heavily overoxidized in injured arterial vessels of rodents and in human atherosclerotic lesions (61). An increase in the levels of Prx-$SO_{2/3}$ forms was detected in the erythrocytes of type 2 diabetic men in response to endurance exercise, but not in nondiabetic men (12). In the condition known as obstructive sleep apnea characterized by severe sleep fragmentation, it has been suggested that periods of hypoxia induce oxidative stress.

Interestingly when protein oxidation patterns were studied in the morning in the RBCs of patients suffering from this condition, significantly higher oxidation of Prx2 was observed, to the extent that it is now considered a viable candidate biomarker for monitoring the severity and treatment of this pathological condition (37). This correlation does not hold true in invertebrates, though. For instance, no alterations in the oxidation status of cytosolic Prx2 were detected in worms at any time point during *C. elegans* lifespan, suggesting that overoxidation of Prx2 in worms is physiologically irrelevant (154). Also, it remains to be proven whether the variations in Prx overoxidation play a functional role in mammals, or simply reflect changes in H_2O_2 fluxes.

Although hyperoxidation of 2-Cys Prxs seems to be a good marker for changes in peroxide levels, there is some controversy regarding oxidation of the catalytic cysteine of the 1-Cys Prx subtype. In yeast, 1-Cys Prxs localized to mitochondria seem well protected from overoxidation by glutathione and the Trx system, wherein the former provides its cysteine as a resolving thiol (118). In contrast, 1-Cys Prxs in other eukaryotes can be susceptible to hyperoxidation, particularly under conditions of oxidative stress, and these modifications correlate with the accumulation of oxidative damage, such as lipid peroxidation (69).

Interestingly in certain tissues, such as lungs, Prx6 seems to be present mostly in its overoxidized form under normal conditions (155). Unexpectedly, upon exposure to exogenous oxidants, such as PQ, the proportion of the fully active reduced form of Prx6 increases, thus limiting Prx overoxidation and consequently helping to maintain antioxidant activity under a severe oxidative burden (155).

Unlike Prx overoxidation, the *in vivo* conditions that lead to Prx glutathionylation and its physiological significance remain relatively underexplored. In the experiments *in vitro*, Peskin *et al.* (120) demonstrated that Prx2 can be glutathionylated under conditions of oxidative stress (treatment with H_2O_2) and recycled back to its active form by glutaredoxin 1, an enzyme involved in protein deglutathionylation. However, this event could be physiologically relevant, as they also found that glutathionylated Prx2 accumulates and becomes detectable in mutant mice deficient for glutaredoxin 1 activity.

Recently it was reported that when glutathionylated in response to stimulation of macrophages by LPS, Prx2 relocalizes to the extracellular space where it acts as a cytokine in inflammatory signaling by inducing TNF-α production (138). It was not clear, however, which of the cysteines, peroxidatic or otherwise, represent targets for glutathionylation. The detection of glutathionylated Prx2 dimers would suggest that the Cys_P may not be the principle target, although it remains plausible that an alternative cysteine residue may participate in dimer formation whereas a second peroxidative cysteine is susceptible to glutathionylation (115). The glutathionylation of Prx causes dissociation of oligomers into dimers and monomers, thus greatly reducing the chaperone function, whereas deglutathionylation restores the ability of Prx to assemble into decameric structures.

These glutathionylation/deglutathionylation transitions of Prx and thus switches between dimer and chaperone function-possessing oligomer forms may also be transmitted into signals that regulate cellular pathways. For instance, activities of phosphatase PTEN or kinase MST1, involved in regulation of cell cycle and apoptosis, were modulated by Prx1 and strongly depended on monomeric/dimeric/oligomeric structural changes, suggesting the possibility of regulation *via* Prx glutathionylation (13, 94).

Hyperoxidation and Chaperone Function

Overoxidized Prxs may not only reflect changes in H_2O_2 concentrations but also play a functional role in regulating many cellular processes. There are two potential outcomes resulting from inactivation of Prxs: (i) a transient build up of peroxides that may foster increased oxidative damage or participate in selective redox-sensitive signaling and (ii) a gain of chaperone function.

This first scenario is supported by studies in mice, such as those of Kang *et al.* (61) who showed a correlation between atherosclerotic lesions and the levels of overoxidized Prx2. Moreover, experimental injury to blood vessels, which mimicks atherosclerosis, was aggravated in animals underexpressing Prx2 (61). Since the vascular function was restored using drugs, possessing the Trx-dependent H_2O_2-reducing activities that mimic 2-Cys Prx peroxidase activity, it might be inferred that overoxidation of Prx2 is a causal factor in vascular injury (61).

In contrast, the damage observed in cells that lack Prx was frequently more severe than damage observed when Prx protein was present but inactivated by hyperoxidation. This partial rescue activity was first observed in mutants in which the catalytic cysteine of Prx2 was replaced with serine (57, 92). Although these mutants no longer possessed peroxidase activity, they exhibited partial resistance to a variety of stressors, including heat shock (57). Further analysis revealed that overoxidized Prxs could adopt oligomeric conformational structures that exhibited molecular chaperone function

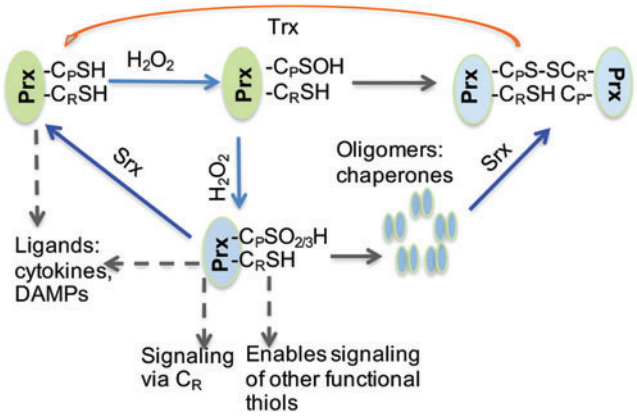

FIG. 6. Functions of peroxidatically inactive Prxs. Prxs can form oligomers, which are more stable when Prxs are hyperoxidized. Oligomers may acquire chaperone activity, antagonized by Srx. Prxs may also interact with their targets by acting as ligands to various cell receptors, and the domains responsible for such interactions are distinct from consensus sequences that form the peroxidase active sites. However, it is not clear which forms of Prxs, reduced or hyperoxidized, permit ligand–receptor interactions. Prx hyperoxidation may also facilitate interactions of the resolving cysteine with potential targets, although the putatively disulfide bridge is yet to be captured. Hyperoxidized Prxs may also enable functions of Trxs. Srx reduces sulfinylated Prx forms, Prx-SO_2, but not sulfonylated Prx-SO_3 forms. *Dotted arrows* indicate reactions whose mechanisms are yet to be clarified. Shaded by *blue* are the least reactive Prx forms. When Prxs are glutathionylated, reversibly hyperoxidized, or exist as disulfide dimers, they are in a nonfunctional state and protected from further oxidation and thus inactivation. Unlike the 2-Cys Prx2, Prxs1, 3, and 4 are mainly detected as dimers due to differences in the rate of disulfide formation, thus ensuring higher protection from hyperoxidation, being quickly reduced by Trx when needed for catalysis (6, 27, 31, 32, 41, 43, 47, 111, 119, 131, 132, 164, 165, 168–170, 175). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

(57) (Fig. 6). This transition protects proteins from denaturation and confers resistance to heat stress (57, 92, 107). Interestingly, hyperoxidized Prxs can also provide protection against oxidative stress by acting as chaperones, whereas simultaneous protection is mediated through the reduction of H_2O_2 by peroxidatically active reduced forms of Prxs.

Oligomers of Prxs, acting as chaperones, protect cells from protein misfolding and formation of H_2O_2-induced protein aggregates. By switching to chaperonic function, hyperoxidized Prxs are able to recruit heat shock proteins, which facilitate the destruction of misfolded proteins formed by H_2O_2 stress, as was demonstrated with Tsa1, a yeast homologue of mammalian 2-Cys Prxs (50). Thus, chaperonic forms of Prxs can confer protection from both heat and oxidative stresses.

There remains some controversy regarding the role that Prx overoxidation plays in this gain of chaperone function. Prx oligomers can exist in both reduced and overoxidized forms (6), and Prx2 oligomers, predominantly composed of monomers in the reduced form, were found to exert a chaperone activity equal to that of overoxidized Prx2 polymers (106), although the latter tended to be more stable. Hyperoxidation is also not necessary for oligomers formation in some species, such as *Schistosoma mansoni* (1). The propensity of different Prxs to become hyperoxidized varies, as does their ability to assume chaperone function.

For instance, mitochondrial Prx3 is the most resistant to inactivation, but is still able to form oligomers, presumably acquiring chaperone function (14, 52). Although unpublished data from the Wei and colleagues laboratory (89) indicate that ER-localized Prx4 is highly susceptible to overoxidation, which was found to promote chaperone function, other reports indicate that Prx4 is mostly detected as a dimer that is resistant to overoxidation, presumably because of the lack of a reducing Trx system in the ER (15), although the reducing power could be provided by protein disulfide isomerases (151). Altogether, the connection between Prx overoxidation and chaperone activity remains unresolved.

Hyperoxidation and Signaling

The identification of mixed disulfide intermediates involving Prxs and specific interacting partners has led to mechanistic insights on how Prxs may modulate redox sensitive signaling (143). Less evident are the mechanisms by which signaling is mediated by overoxidized Prxs. As has been proposed by the ''floodgate'' model (169), inactivation of Prx activity by overoxidation of the catalytic cysteine would elicit a local accumulation of H_2O_2, which could then serve to propagate signaling cascades [discussed in Hall *et al.* (46)]. For instance, an increase in SIR2 activity in breast cancer cells was found to restrict the antioxidant activity of Prx1 *via* deacetylation, presumably leading to transient increase in H_2O_2 concentrations and further inactivation of Prx1 due to hyperoxidation (40).

In turn, hyperoxidation of Prx1 could promote further production of H_2O_2 and cytotoxic effects, including DNA damage and cell death. Increased ROS also caused translocation of transcription factor Foxo3A to the nucleus, resulting in induction of the proapoptotic BH3 domain-only (BIM) protein. Both events, DNA damage and activation of proapoptotic BIM, collectively culminated in cell death (40). In yeast, exposure to H_2O_2 and inactivation of Tpx1, the only 2-Cys Prx in *Schizosaccharomyces pombe*, *via* hyperoxidation, allowed its catalytic partner, Trx, to remain reduced and thus active. This resulted in redirection of Trx reducing power toward other antioxidant enzymes, such as methionine sulfoxide reductase and thus inhibition rather than promotion of H_2O_2-mediated effects (32) (Fig. 6).

As detailed earlier, Prx overoxidation appears to target specific factors/pathways despite the promiscuous nature of hydroperoxides produced as a result of Prx inactivation. Furthermore, kinetically preferred targets of H_2O_2, including other peroxidases and Prxs themselves and their relative abundance, would impede the reactions of H_2O_2 with less favorable thiol-containing targets, whose reaction kinetics are several orders slower (42, 129, 163). In other words, the ''floodgate'' theory does not provide a satisfactory explanation for the complexity of signaling *via* inactivation of Prxs. In eukaryotes, and especially higher eukaryotes, Prxs are differentially prone to oxidative dimerization or sulfinic acid formation (147).

This is particularly evident in case of highly homologous Prx1 and Prx2 species that colocalize in the cytoplasm. These Prxs were found to be affected by hyperoxidation to a

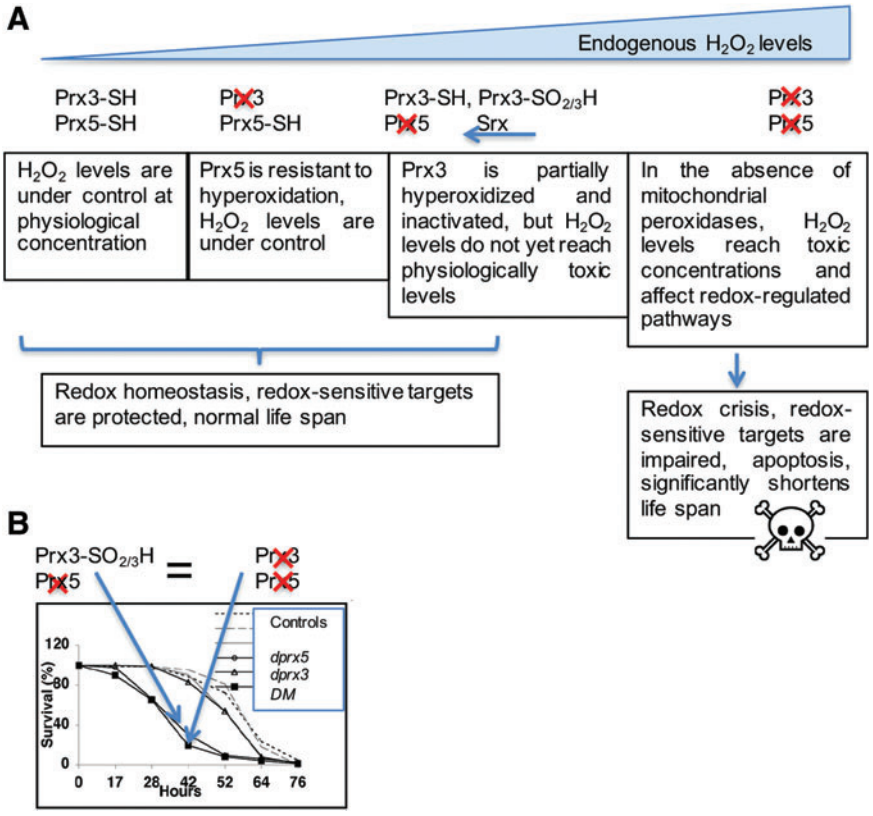

FIG. 7. Speculative model of the effects of Prx5 and Prx3 on cell function and physiology. Prx3 and Prx5 were underexpressed individually or together (DM). **(A)** Under physiological conditions, Prx3 and Prx5 are able to cope with H_2O_2 and maintain normal cell function. The accumulation of hyperoxidized Prx3-$SO_{2/3}$H forms is controlled by Srx (4) and is insufficient to cause an adverse effect on physiology. **(B)** Exogenous oxidative stress may lead to significant hyperoxidation of Prx3 and thus inactivation, resulting in the *prx5* mutant exhibiting a similar susceptibility to oxidative stress as the DM. As Prx 5 is relatively resistant to hyperoxidation, the *prx3* mutant is more resistant than the DM. We suggest that the observed phenotype of the DM was similar to that of the *prx5* single mutant because of hyperoxidation and thus inactivation of Prx3. Figure is adapted from Radyuk *et al.* (127). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

different degree, although being expressed in the same cells/tissues and with the same oxidative stress burden (3), and were also shown to display variability in the rate of dimer formation (139). Thus Prx2 is easily oxidized and forms covalent dimers due to noncatalytic removal of H_2O_2 (87), whereas Prx1 is mainly present in a reduced form indicative of high catalytic activity but more vulnerable to hyperoxidation during catalytic turnover (31). Similar to Prx2, the mitochondrial Prx3 is mostly found as a dimer due to a higher rate of dimerization, and is consequently more resistant to hyperoxidation (119).

Given the redundancy of Prxs toward H_2O_2, differential susceptibility to hyperoxidation and relatively small proportion of hyperoxidized forms, the actual mechanisms by which hyperoxidized Prxs may participate in signaling are yet to be delineated (Fig. 7). It is likely that selectivity of hyperoxidized Prxs toward the downstream targets depends on their structural characteristics as well as the involvement of coupled reducing agents (122).

Prxs Hyperoxidation and Srxs

Hyperoxidation of Prxs leads to deactivation of peroxidatic activity and thus accumulation of hydroperoxides and may also elicit chaperone function by favoring oligomeric formation. Both events may be in part reversible due to the action of Srx, which can convert the oxidized cysteine sulfinic acid form back to the catalytically active thiol form (9, 24, 167), whereas further oxidation of the catalytic cysteine to the sulfonic form appears to be irreversible (157) (Figs. 1 and 6). In this context, Srx may serve as a switch to affect the equilibrium between reduced and hyperoxidized Prx forms. Reduced forms would favor peroxidatic function, whereas hyperoxidized forms would promote chaperone function or signaling *via* redox signal buildup (Figs. 1 and 6). Although Srx is known to repair the sulfinic form of Prx, the role of Srx in the reversal of Prx oligomerization remains to be fully elucidated.

It has been demonstrated that Srx dissociates the H_2O_2-induced high molecular weight Prx1 complex in yeast, and that the Srx Cys84 residue, essential for its activity, is also critical for this dissociation (93). Srx is also involved in the reduction of glutathionylated Prxs (114) with a preference to deglutathionylate Prxs resolving and structural cysteines. Srx has a lesser preference toward Cys_P, whose deglutathionylation is more effectively catalyzed by glutaredoxin (114).

In addition, unlike sulfinic acid reduction that is exclusive to Prx, the deglutathionylation mediated by Srx is not as substrate specific (11, 38). Still, in this way, Srx functions as an antioxidant by restoring a pool of catalytically active Prxs that ultimately leads to reduction of oxidized macromolecules, such as the reduction of mitochondrial lipid peroxides upon translocation of Srx into mitochondria when other antioxidant enzymes, present in this organelle, were ineffective (103).

Owing to the ability of Srx to restore the peroxidatic activity of Prxs either *via* sulfinic acid reduction or *via* glutathionylation, this enzyme has been classified as an antioxidant. There is evidence that the action of Srx on oxidized Prx may take on functional significance under certain stress or pathological states, as was demonstrated in studies on mammalian cells depleted for Srx or Srx knockouts that lack obvious defects but become sensitive to exogenous stressors and demonstrate higher mortality rate under pathological conditions. The levels

of Prx-$SO_{2/3}$ were found to increase rapidly in response to oxidative stress and were constitutively high when Srx was deficient (59, 130).

The antioxidant and redox-maintaining function of Srx appeared to be critical for cell survivorship under low-level chronic H_2O_2 exposure, as was observed in *srx*$^{-/-}$ cells that become prone to apoptosis due to activation of mitochondrial cell death pathways (5). In a separate study, exposure to H_2O_2 caused Srx translocation to mitochondria, wherein it helps to counteract Prx3 hyperoxidation and reduce apoptosis (103). Similarly, Srx together with Prx3 mitigated oxidative damage and hepatotoxicity (4). Mice *srx*$^{-/-}$ knockouts were significantly more sensitive to ROS-mediated proinflammatory reactions, such as endotoxic shock (121). In yeast, an increase in Srx levels, provided either genetically or through cAMP-PKA signaling modulated by caloric restriction, extends the replicative lifespan of yeast cells by reactivating the hyperoxidized forms of Prx Tsa1, which otherwise accumulate in aging cells (90).

Under normal conditions, Srx does not seem to play a significant role in physiological processes, as loss of Srx does not produce any overt phenotype. Expression of this enzyme in cells is very low, as are the levels of hyperoxidized Prxs, with the exception of mitochondrial Prx3, and detected only in certain tissues (63, 64). Similar to hyperoxidized species of Prxs, Srx oscillates in a circadian manner under normal conditions, thus sustaining rhythmic release of H_2O_2, an input clock signal (64).

In wild type animals, Srx is quickly induced upon exposure to H_2O_2, suggesting the existence of a feedback loop in regulating peroxide levels *via* replenishing the pool of catalytically active Prx cysteines, inactivated by oxidation (58). Srx expression has also been found to be regulated by stress response pathways that are sensitive to redox, including JNK/AP-1 and nuclear erythroid 2-related factor 2 (Nrf2) (66, 144, 145, 152, 161), wherein the induction of Srx imparts a protective effect against oxidative damages (142).

The reduction of hyperoxidized Prx by Srx is energy demanding and proceeds through the transfer of the γ-phosphate of ATP to the sulfinic acid to form a Prx-SO-S-Srx thiosulfinate intermediate that is subsequently resolved by hydrolysis with the help of Trx or GSH (10, 136, 137).

The oxidation status of Prxs may be more sensitive to the availability of Trx-related electron donors, rather than Srx levels, at least under normal conditions (16). Indeed, the catalytic recycling of Prxs *via* the Trx system or degradation and *de novo* synthesis are significantly more energy efficient than the slow and energy-demanding reduction catalyzed by Srx (24) (Figs. 1 and 6). The rate constant for the reduction of Prx by Trx has been measured as 10^6 M^{-1} s^{-1}, considerably faster than the rate of Prx reduction determined for Srx (~ 2 $M^{-1} \cdot s^{-1}$) (135, 148). In addition to these kinetic considerations, genetic ablation of Srx in plant mutants does not result in increased 2-Cys Prx hyperoxidation in any of the tissues examined (16).

Although it appears that the impact of Srx on the Prx oxidation state and physiology is minimal, at least under normal conditions, its impact on pathologies, particularly cancer, has been amply demonstrated. In the context of carcinogenesis, the Srx–Prx system has been found to have both beneficial and deleterious effects (Fig. 8). The protective role is demonstrated by the finding that in Srx knockouts, the spread of tumors is enhanced by the promotion of colony formation and cell invasion (89). In contrast, the levels of Srx are preferentially increased in some cancer cells, where they presumably help protect against oxidative damage or affect sensitivity to oxidative stress, thus influencing tumorigenesis *via* effects on cell transformation, for instance (161).

Jiang *et al.* (60) determined that Srx was not detected in normal colon epithelial cells or well-differentiated carcinomas, but is highly expressed in poorly differentiated, aggressive colorectal cancer cells. In these cells exhibiting high Srx expression, the levels of 2-Cys Prxs remained stable and the level of hyperoxidized Prxs was clearly attenuated (60). Mechanistically, it seems that Srx prevents accumulation of sulfinylated Prxs by reducing them to catalytically active forms and thus counteracting oxidative stress arising from Prx inactivation.

Genetic or chemical inhibition of Srx induces oxidative stress, mainly *via* increase in H_2O_2, and induces the oxidation of mitochondrial membrane lipids leading to mitochondrial damage and apoptosis (68). Since the effects of Srx inhibition are reversed by supplementation with the antioxidant N-acetylcysteine, it may be inferred that Srx protects cancer cells by the antioxidant function of the Prxs spared by Srx activity. In contrast, Srx may affect specific redox signaling cascades mediated by Prxs. Thus, Wei *et al.* (162) showed that Srx and Prx4 work synergistically to promote the spread of tumors *via* oncogenic AP-1/MMP9 activation and MAPK signaling, whereas knocking out both components led to a significant reduction in metastasis.

The development of skin cancer has also been stimulated by Srx by lowering the level of hyperoxidized Prx, thus helping cancer cells survive under oxidative stress and avoid apoptosis (171). In contrast, Srx itself has been transcriptionally induced in a redox-independent manner *via* MAPK and JNK signaling.

Despite the established correlation between Srx activity, levels of hyperoxidized Prxs, and effects on cell function, it remains unclear whether Srx functions solely in conjunction with Prxs with respect to its effects on cancer or *via* different mechanisms.

Unresolved Problems

A major area of investigation going forward will be to determine the potential impact of hyperoxidized Prxs on signal transmission. One possibility is that hyperoxidized Prxs may activate immune signaling. There is evidence that, in response to cell necrosis, Prxs are released into the extracellular environment where they act as DAMPs to initiate a cascade of immune responses. Specifically, it was determined that Prx5, Prx6, and, to a lesser extent, Prx1/2, interact with toll-like receptor (TLR), to induce the proinflammatory process (141). Although the specific regions in Prx structure responsible for these interactions with TLR were distinct from those encompassing the Cys_P, it was not clear whether the effects on signaling were mediated through the oxidized or reduced forms (Fig. 6).

Indeed, the interaction of Prx1 with TLR was determined by the ability of Prx to form a decamer, but did not depend on peroxidatic activity, since Cys_PSer mutation did not affect the Prx–TLR interaction (133). It does not preclude the possibility that the oxidation state of Cys_P could influence

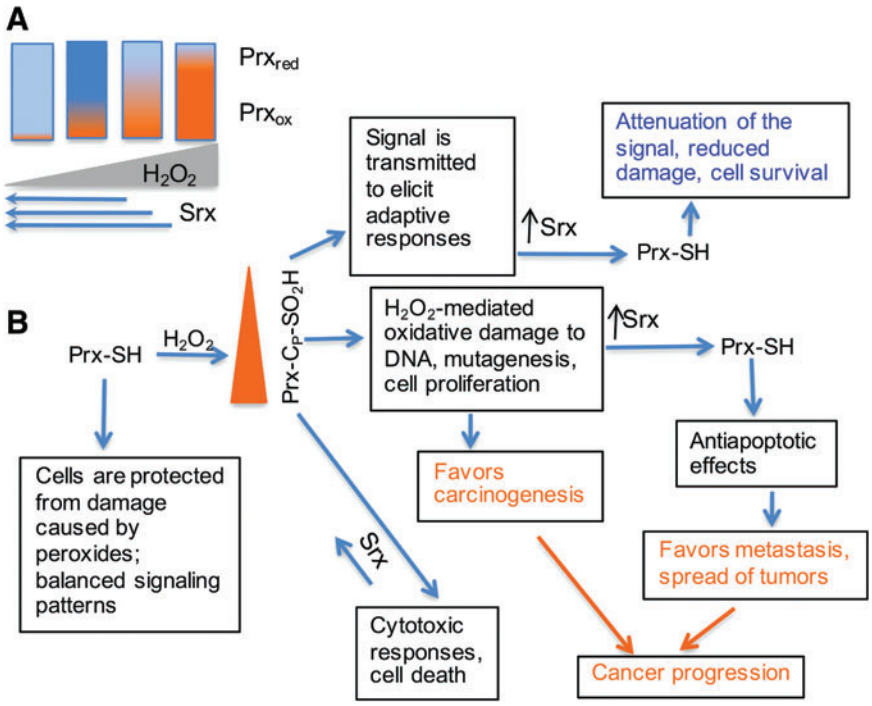

FIG. 8. Model for the role of Prxs coupled to the activity of Srx. (A) The increase in the levels of H_2O_2 is further promoted by the increase in proportion of hyperoxidized Prxs. Srx is induced in response to the higher H_2O_2 burden but is relatively slow in restoring the catalytically active pool of Prxs. **(B)** Moderate increase in H_2O_2 elicits adaptive responses, leading to upregulation of Srx, mediated *via* Nrf2 and JNK signaling (66), and as a result increased survivorship and resistance to stress. Higher levels of hyperoxidized Prx and concomitant increase in H_2O_2 can result in damage beyond repair, outstripping the sparing effects of Srx, and trigger cell death pathways. Higher levels of Prx hyperoxidation can also lead to further increase in H_2O_2 levels and exacerbate damage to cells, leading to DNA oxidation, increase in mutation rate, and cell proliferation. Altogether, these events can be responsible for the transformation of cells into an oncogenic state. In this case, sequential increases in Srx activity can protect tumor cells favoring cancer progression. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

the interactions with TLR through changes in Prx protein structure.

Although the effects of extracellular Prx4 on the inflammatory response have been established, it was not established whether these cytokine effects were mediated through the oxidized or reduced forms, as experiments were conducted *in vitro* with cells coincubated with Prx4 (51). In *Drosophila*, it was shown that Prx4 could be secreted extracellularly in response to stress conditions, such as bacterial infection, and trigger the JAK/STAT pathway (124) (Fig. 2). It has yet to be determined whether this activation is dependent on peroxidase activity or whether other mechanisms are involved. Since the secretable form of dPrx4 was mostly detected as a monomer, in contrast to the covalent dimers that are abundant in the ER, it would suggest that Cys_P is hyperoxidized and thus unable to form disulfide bonds.

In humans, Prx4 was detected in both ER and extracellularly in the blood serum, and these serum levels were found to be higher in individuals with pathologies than in healthy individuals (140). Furthermore, extracellular Prx4 was mostly detected as a decamer, which is formed through noncovalent linkages between reduced or hyperoxidized Prx molecules. The complex is more stable if formed by hyperoxidized species (6), suggesting that upon hyperoxidation, Prx4 is expelled from the ER where it accumulates in the extracellular space, perhaps for signaling purposes.

Another question that needs to be answered is whether hyperoxidized Prxs can signal through their resolving cysteine (Figs. 1 and 6). Can the resolving cysteine form disulfide bridges with target proteins, thus transmitting the redox signal? Can the interactions between Prxs and cysteine-containing targets occur under pro-oxidative conditions, when the Cys_P is hyperoxidized and inactive? There is at least one piece of evidence pointing to such an interaction involving Prx2 and the disulfide isomerase ERp46. This interaction involves the formation of a noncovalent complex. This complex requires the presence of the resolving cysteine, based on cysteine to serine replacement studies (111) as well as hyperoxidation of the catalytic cysteine.

However, the interactions were noncovalent and no evidence for formation of disulfides between ERp46 and Prx2 was found. Nonetheless, it is possible that the interaction was initiated by formation of a transient bridge permitting transition of Prx2 to its oligomeric form that would facilitate further conformational changes. Similarly, there were interactions between ERp46 and the noncatalytic cysteines of Prx4, suggesting that such interactions are possible when Cys_P is hyperoxidized, although the state of Prx4 oxidation has not been experimentally demonstrated (151). However, the functional significance of interaction of ERp46 with the resolving cysteines of both Prxs2 and 4 is yet to be determined in *in vivo* experiments.

Concluding Remarks

Here, we review the differential effects of Prxs on cell function and physiology and discuss the molecular mechanisms underlying these effects. Despite significant advances in understanding Prx functions, there are many questions that remain to be addressed, such as the relationship between the promiscuous behavior of ROS, including H_2O_2 and other peroxides, the apparent specificity of Prxs toward different targets in redox-sensitive signaling pathways, and how hyperoxidized Prxs contribute to signaling. Prxs share a significant degree of redundancy toward their substrates, but differ in their sensitivity to hyperoxidation and thus peroxidatic inactivation. Some members of the family, such as Prx5, are virtually resistant to hyperoxidation. Others are more sensitive but their effects, local H_2O_2 fluxes, may be modulated by spatially colocalized Prxs.

Although the Prx–Trx system provides an effective means to maintain redox state, Srx, with its capacity to reduce the sulfinyl group, has been invoked as a potential back-up system to help restore the pool of active Prxs. Given that only a minuscule proportion of hyperoxidized Prxs is present *in vivo* under physiological conditions and that the reduction of sulfinyl is both slow and ATP-dependent, this assumption needs to be carefully examined.

Recent attempts to understand the scavenging and signaling functions of Prxs and the underlying mechanisms have been largely correlative or rely on *in vitro* studies. Even the *in vivo* experiments, wherein specific chemical interactions between Prxs and their targets were determined, were conducted under nonphysiological conditions, leaving the physiological relevance in question. Experiments with mutants and transgenics under- and overexpressing Prxs or redox-negative mutants have helped to make advances in understanding Prx function but have not yet addressed the impact of Prx transitions between catalytically active and inactive forms.

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Abbreviations Used

AD = Alzheimer's disease
BIM = BH3 domain-only
Cys_P = peroxidatic cysteine
Cys-SOH = cysteine sulfenic acid
Cys-SO_2H = cysteine sulfinic acid
Cys-SO_3H = cysteine sulfonic acid
DM = double mutant
ER = endoplasmic reticulum
H_2O_2 = hydrogen peroxide
LPS = lipopolysaccharide
NO = nitric oxide
Nrf2 = nuclear erythroid 2-related factor 2
PLA = phospholipase
PQ = paraquat
Prx = peroxiredoxin
RBCs = red blood cells
ROS = reactive oxygen species
Srx = sulfiredoxin
TLR = toll-like receptor
Trx = thioredoxin