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Review

From Cytoprotection to Tumor Suppression: The Multifactorial Role of Peroxiredoxins

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ABSTRACT

In the past decade, a new family of highly conserved antioxidant enzymes, Peroxiredoxins (Prxs), have been discovered and defined. There are two major Prx subfamilies: one subfamily uses two conserved cysteines (2-Cys) and the other uses 1-Cys to scavenge reactive oxygen species (ROS). This review focuses on the four mammalian 2-Cys members (Prx I–IV) that utilize thioredoxin as the electron donor for antioxidation. The array of biological activities of these proteins suggests that they may be evolutionarily important for cell function. For example, Prxs are capable of protecting cells from ROS insult and regulating the signal transduction pathways that utilize c-Abl, caspases, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) to influence cell growth and apoptosis. Prxs are also essential for red blood cell (RBC) differentiation and are capable of inhibiting human immunodeficiency virus (HIV) infection and organ transplant rejection. Distribution patterns indicate that Prxs are highly expressed in the tissues and cells at risk for diseases related to ROS toxicity, such as Alzheimer's and Parkinson's diseases and atherosclerosis. This interesting correlation suggests that Prxs are protective against ROS toxicity, yet overwhelmed by oxidative stress in some cells. Prxs tend to form large aggregates at high concentrations, a feature that may interfere with their normal protective function or may even render them cytotoxic. Imbalance in the expression of subtypes can also potentially increase their susceptibility to oxidative stress. Understanding the function and biological role of Prxs may lead to important discoveries about the cellular dysfunction of ROS-related diseases ranging from atherosclerosis to cancer to neurodegenerative diseases. Antiox. Redox Signal. 1, 385–402.

INTRODUCTION

ALL ORGANISMS THAT LIVE UNDER AEROBIC CONDITIONS have developed mechanisms to manage the toxic effects of reactive oxygen species (ROS). ROS, including $O_2^{-\bullet}$, hydrogen peroxide (H_2O_2), and $OH^{\bullet}$, are naturally generated from the incomplete reduction of oxygen during respiration for energy metabolism, or from external sources such as light, ionizing radiation, or certain drugs. Exposure of cells to such chemical or physical insults induces a "stress" response resulting in synthesis of heat shock proteins and many other proteins in the 12–110 kDa molecular mass range, including chaperones (proteins involved in protein folding and translocation) and antioxidant proteins (Stadtman, 1992; Ross, 1993; Sies, 1993; Halliwell, 1996; Berlett and Stadtman, 1997; Diaz *et al.*, 1997; Henle and Linn, 1997; Quillet-Mary *et al.*, 1997; Outinen *et al.*, 1998). Unchecked ROS can lead to oxidative damage in the cell, including lipid peroxidation, protein modification, DNA base modification, and strand breaks.

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ROS are not just toxic byproducts of metabolism, but have been shown to act as signal transduction agents involved in regulating normal functions including cell growth and differentiation, immune responses by phagocytic cells, and apoptosis (Sen and Packer, 1996; Nakamura *et al.*, 1997; Finkel, 1998, 1999; Karin, 1998; Sen, 1998). For example, the tumor suppressor protein p53, which helps maintain genomic stability by halting cell cycle progression under cellular stress conditions, is regulated by thiol oxidation state and thioredoxin reductase via Ref-1 (Jayaraman *et al.*, 1997). Another example is the signaling by ROS of the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) (Schreck *et al.*, 1991; Meyer *et al.*, 1993; Sen and Packer, 1996; Hirota et al., 1997; Quillet-Mary *et al.*, 1997; Karin, 1998; Li and Karin, 1999; Ouaaz *et al.*, 1999). On the other hand, imbalance between ROS and antioxidant defense mechanisms have been implicated in pathological situations like atherosclerosis, Alzheimer's disease, and human immunodeficiency virus (HIV) activation (Staal *et al.*, 1990; Schreck *et al.*, 1991; Ross, 1993; Diaz et al., 1997; Münch *et al.*, 1998; Pitchumoni and Doraiswamy, 1998).

Several different strategies are employed by cells to manage ROS. These include scavenger proteins such as superoxide dismutases that take superoxide anion and produce oxygen and peroxide, and catalase or peroxidases that destroy peroxide (like glutathione peroxidase) (Sies, 1993; Halliwell, 1996; Berlett and Stadtman, 1997; Diaz *et al.*, 1997; Nakamura *et al.*, 1997; Finkel, 1998). In addition, scavenger molecules such as vitamin C, vitamin E, β-carotene, and the mineral selenium perform related antioxidant functions.

Discovered just over a decade ago, peroxiredoxin (Prx) is a large antioxidant gene family that is well conserved from bacteria to humans. The Prx gene products relevant to this review were initially identified by some of the diverse functions they perform—for example, enhancement of natural killer (NK) cytotoxicity (Shau and Kim, 1994), cell proliferation (Prospaeri *et al.*, 1993), and heme binding (Iwahara *et al.*, 1995). However, computer analysis of DNA and protein sequences clearly demonstrated a close relationship between these proteins. The family name, Prx, was chosen to reflect the fact that this is a family of peroxidases that uses conserved cysteine (Cys) residues for the sites of antioxidation. Besides Prx, another term often used by investigators has been peroxidoxin (Chae *et al.*, 1994a; Rabilloud *et al.*, 1995; Frank *et al.*, 1997). The Prx family contains six known protein subtypes. Recently, several reviews were published that outline each of these six family members (Rhee *et al.*, 1994; Kang *et al.*, 1998a; McGonigle *et al.*, 1998; Chae *et al.*, 1999; Jin and Jeang, 1999; Matsumoto *et al.*, 1999). In addition to the four Prx family members with two conserved Cys residues (2-Cys), there are also two additional Prx families that contain only one conserved Cys residue (1-Cys). This review will address the four 2-Cys types of Prxs and look in greater detail at their diverse functions in mammalian cells.

PEROXIREDOXIN FAMILY

In 1988 the protein "TSA," or thiol-specific antioxidant, was purified from yeast and shown to function in a thiol-containing mixed-function oxidation system, yet not in an ascorbate-containing one (Kim *et al.*, 1988, 1989). At the same time, "AhpC," the alkylhydroperoxide reductase subunit C, from bacteria was isolated and shown to be coupled to NADPH via another protein, AhpF, for regeneration (Storz *et al.*, 1989; Tartaglia *et al.*, 1990). Later, when the genes were cloned, sequenced, analyzed and compared, it was clear that TSA and AhpC were related. The relationship to other genes subsequently cloned from a variety of different contexts was also revealed. Table 1 shows a list of the different Prx family members, their various original published names, chromosome assignment in the human genome, cellular localization, amino acid length, and available GenBank accession numbers.

In addition to the four 2-Cys Prx family members (Prx I–IV) (Prospaeri *et al.*, 1993; Shau *et al.*, 1994; Iwahara *et al.*, 1995; Pahl *et al.*, 1995; Jin *et al.*, 1997; Ichimiya *et al.*, 1997; Schreoder *et al.*, 1998; Araki *et al.*, 1999; Chae *et al.*, 1999; Matsumoto *et al.*, 1999), two additional 1-Cys Prx families have been described. Prx V remains unpublished to date (S.G. Rhee, personal communication). The Prx VI members have

TABLE 1. THE FOUR 2-CYSTEINE PEROXIREDOXIN FAMILIES

	PrxI	*PrxII*	*PrxIII*	*PrxIV*
Members (organism)[a]	PAG (human) NKEF A (human) MSP23 (murine) OSF-3 (murine) HBP23 (rat)	TSA (human) PRP (human) NKEF B (human) Calpromotin (human)	AOP-1 (human) MER5 (murine) SP22 (bovine)	AOE372 (human) TRANK (human)
Length[b]	199 amino acids	198 amino acids	256 amino acids	271 amino acids
Chromosome[c]	1q34.1	13q12	?	Xp21-22.1
Localization[d]	Cytosol/nucleus	Cytosol	Mitochondria	Cytosol/secreted
GenBank accession numbers[e]	L19184, x67951 (human), D16142 (murine), D30035 (rat)	L19185, z22548 (human)	D49396 (human), M28723 (murine), D82025 (bovine)	U25182 (human), U96746 (murine) AF106945 (rat)
Other names[f]	TxP-2, TPx-I, TDPX1	TxP-1, TPx-II		
Comments[g]	95% (murine) and 97% (rat) identical to human	93% (murine and rat) identical to human	85% (murine) and 88% (bovine) identical to human	89% (murine) identical to human

[a]Original names of different genes identified by function.
[b]Protein length in amino acids.
[c]Human chromosome assignment, PrxIII not yet identified.
[d]Subcellular localizations of family members described.
[e]GenBank accession numbers for different species are listed. PIR, SwissProt and other database identification numbers not listed.
[f]Previous "thioredoxin peroxidase" family names used in publications.
[g]Protein sequence percent identities for non-human members of each family are listed where known.

been listed under several names, including: hORF6 (human), keratinocyte growth factor-related protein, AOP-2 (murine), calcium-independent phospholipase A_2 (PLA_2) (human and rat), and non-selenium glutathione peroxidase (bovine and human) (Frank *et al.*, 1997; Kim *et al.*, 1997b; Munz *et al.*, 1997; Choi *et al.*, 1998; Peshenko *et al.*, 1998; Phelan *et al.*, 1998; Singh and Shichi, 1998; Syed and Hecht, 1998). Prx I, II, III, IV, and V all use thioredoxin as the electron donor, whereas the electron donor for Prx VI has yet to be identified. It should be noted that in a recent Prx review, PAG/NKEF A and other Prx I proteins were listed as "Prx II" whereas TSA/NKEF B was listed as "Prx I" (Jin and Jeang, 1999). The recently agreed upon, and therefore "correct" nomenclature, is specified in Table 1.

Figure 1 shows an amino acid sequence alignment among human Prx I–IV family members. Different species alignments within a given family type have been published several times and will not be shown here (Tartaglia *et al.*, 1990; Prospaeri *et al.*, 1993; Cha *et al.*, 1996; Chae *et al.*, 1994a, 1999; Lim et al., 1994a; Watabe *et al.*, 1994; Ishii *et al.*, 1995; Iwahara *et al.*, 1995; Poole *et al.*, 1997; Jin *et al.*, 1997; Haridas *et al.*, 1998; Jeong *et al.*, 1999). There are two well-conserved amino acid sequence regions, each containing a Cys residue, that define the Prx family. At the amino terminus of the protein the region is FFYPLDFTFV**C**PTEI, and the region at the carboxyl terminus of the protein is HGEV**C**PA. These regions are boxed in Fig. 1. There are additional conserved regions whose significance has yet to be identified. The conserved region SVDS(H/Q)F(x)HLAW(I/V) is homologous to a thioredoxin peroxidase family signature in the Prosite Protein Group Database. The divergent sequences at the amino terminus of Prx III and IV are the mitochondrial localization and signal sequence, respectively. Although there is little in the way of a consensus sequence for either endoplasmic reticulum or mitochondrial targeting, the Prx III amino terminus contains 29 hydrophobic and 24 polar residues in the first 60 amino acids. The hydrophobic residues are assumed to aid in transport across a membrane. Similarly, the Prx IV amino terminus has 6 polar residues and is largely hydrophobic (25 of the first 40

FIG. 1. Human Prx family protein sequence alignment. The full amino acid sequences are shown for the four 2-cysteine Prx family members. The two highly conserved regions containing the important Cys residues are boxed. The amino-terminal signal sequences are underlined, as is the ProSite thioredoxin peroxidase signature domain. The symbols beneath each set of sequences are as follows: (*) identical residue; (:) conserved residue change; (.) partially conserved amino acid change. A dash (-) in the sequence indicates no amino acid in a position where a different family member does have a residue.

amino acids, including a continuous 13-amino-acid region), which is a common structure for signal sequences.

The Prx family members have several features in common. First of all, they have a wide tissue distribution. Northern blot indicates their presence in most tissues and cell types (although each family member is not equally represented in each tissue examined) (Yamamoto *et al.*, 1989; Lim *et al.*, 1994a; Prospaeri *et al.*, 1994; Shau *et al.*, 1994; Cha and Kim, 1995; Iwahara *et al.*, 1995; Pahl *et al.*, 1995; Ichimiya *et al.*, 1997; Immenschuh *et al.*, 1997; Lim *et al.*, 1998; Araki *et al.*, 1999; Chae *et al.*, 1999; Matsumoto *et al.*, 1999; Sarafian *et al.*, 1999). Each of the Prx proteins have been shown to be induced by cellular proliferation, differentiation, oxidative stress, and/or pro-inflammatory cytokines (Prospaeri *et al.*, 1993, 1998; Lim *et al.*, 1994a,b; Rhee *et al.*, 1994; Shau *et al.*, 1994; Yim *et al.*, 1994; Immenschuh *et al.*, 1995; Ishii *et al.*, 1995; Rabilloud *et al.*, 1995; Kim *et al.*, 1997a; Wen and Van Etten, 1997; Lim *et al.*, 1998; Outinen *et al.*, 1998; Sarafian *et al.*, 1998, 1999; Matsumoto *et al.*, 1999). In terms of their antioxidant function, they do not utilize transitional metals for their ROS savenging activity (Cha and Kim, 1995; Ishii *et al.*, 1995; Sauri *et al.*, 1995; Tsuji *et al.*, 1995; Jin *et al.*, 1997; Haridas *et al.*, 1998; Kang *et al.*, 1998b; Kowaltowski *et al.*, 1998; Syed and

Hecht, 1998). Unlike catalase, the Prx family can reduce alkylhydroperoxides. This ability to scavenge both organic and inorganic hydroperoxides is at least partially responsible for both mammalian and nonmammalian Prx protection of cellular components and therefore protection of cell viability from oxidant toxicity (Lim *et al.*, 1993; Netto *et al.*, 1996; Shau *et al.*, 1997; Watabe *et al.*, 1997; Zhang *et al.*, 1997; Bruchhaus *et al.*, 1997; Ellis and Poole, 1997; Jin *et al.*, 1997; Kang *et al.*, 1998b; Prospaeri *et al.*, 1998). Only the amino-terminal conserved Cys residue is required for peroxidase function (Chae *et al.*, 1994b, 1999; Rhee *et al.*, 1994; Yim *et al.*, 1994). Prx proteins can also block formation of thyl radicals. Although blocking thyl radical formation may be the mechanism for Prx protection, its *in vivo* significance has yet to be proved.

All of the 2-Cys Prxs form dimers, both homodimers and hetrodimers (Chae *et al.*, 1994b; Ellis and Poole, 1997; Jin *et al.*, 1997; Kim *et al.*, 1988; Schreoder *et al.*, 1998). These dimers are linked through head-to-tail disulfide bonds between the conserved amino-terminal and carboxy-terminal cysteines. Although both amino- and carboxyl terminal cysteines are required to form dimers, only the amino-terminal cysteine is absolutely required for the antioxidation function. By coupling with the redox cycle of thioredoxin, Prxs can transfer the reducing equivalents to scavenge ROS (Fig. 2).

Another interesting feature of Prxs is their tendency to form large, insoluble, noncovalent aggregates when present in high concentrations (Shau *et al.*, 1993; Kim *et al.*, 1988; Schreoder *et al.*, 1998). The formation of large aggregates occurs in spite of, or possibly because of, the presence of strong reducing reagents. The *in vivo* significance of the aggregates is not clear. However, for many well-conserved proteins like β-amyloid precursor peptides, huntingtin, and prions, aggregation can turn important proteins into toxic agents that kill the cells (Harrison *et al.*, 1997; Arawaka *et al.*, 1998; Prusiner *et al.*, 1998; Safar and Prusiner, 1998; Martin *et al.*, 1999; Scherzinger *et al.*, 1999; Yang *et al.*, 1999). (This point will be further discussed below in "Peroxiredoxin Aggregation and Cytotoxicity.")

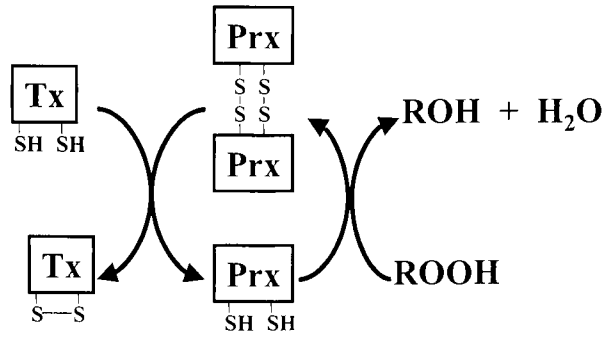

FIG. 2. Prx redox reaction cycle. Oxidized dimeric Prxs accept electrons from reduced thioredoxin (Tx) and become monomeric. The reduced monomeric Prxs scavenge hydroperoxides (ROOH) to produce water and alcohol, and become dimeric again. R represents hydrogen or a carbohydryl group.

Peroxiredoxin I

Prx I was originally purified by our group using a functional assay based on the enhancement of cytotoxicity mediated by NK lymphocytes (Shau *et al.*, 1993). The two highly homologous cDNAs for Prx I and Prx II were cloned and named NKEF A and B, repectively, for NK enhancing factor (Shau *et al.*, 1994). When the recombinant versions of these proteins were tested for their ability to increase the cytotoxicity of NK cells, only the reduced form of Prx I, but not Prx II, was shown to be an efficient enhancer of NK cytotoxicity (Sauri *et al.*, 1996). No increased cytotoxicity was detected with interleukin-2 (IL-2)-mediated lymphokine-activated killer (LAK) cell activity, demonstrating a selectivity in stimulatory capacity for native unstimulated NK cytotoxicity.

NKEF A and PAG (proliferation-associated gene) (Prospaeri *et al.*, 1993) may be the product of the same gene, although their GenBank sequences differ at two amino acid residues. High levels of Prx I/NKEF A/PAG in different cells had been shown previously to correlate with proliferation (Prospaeri *et al.*, 1993, 1998). However, the mechanisms by which Prx I may induce cell proliferation are still unclear. The association of Prx I with the tyrosine kinase c-Abl, a known cell cycle regulator, has shed new light in this area (Wen and Van Etten, 1997). This interaction is mediated via the Src-homology 3 (SH3) domain and kinase domain of c-Abl and inhibits its kinase activity *in vivo* (Fig. 3). Interestingly, the inability of Prx I

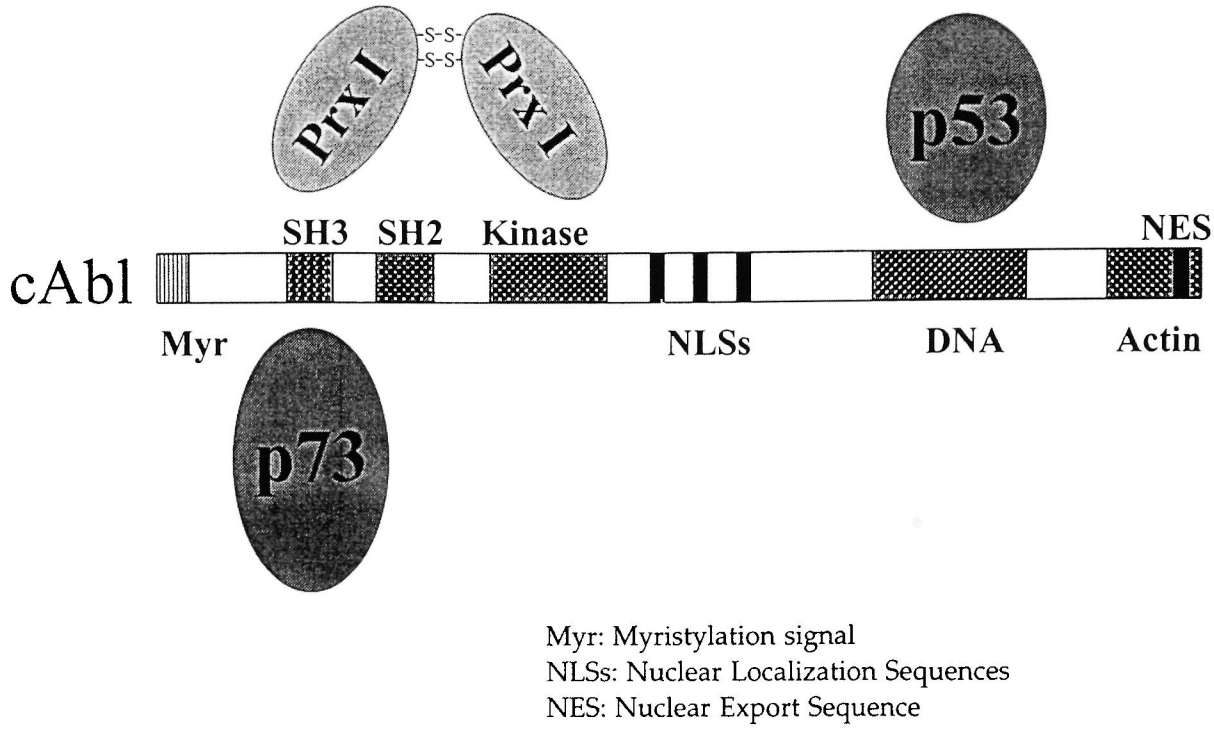

FIG. 3. c-Abl protein structure. Sites of interaction with tumor suppressors p53 and p73 are shown, as well as sites of Prx I interaction. Also shown are the following domains: Mys, Myristylation; NLS, nuclear localization sequence; SH2 and SH3, Src-homology domains; DNA binding and kinase domains; NES, nuclear export sequence: and actin binding domain.

to inhibit c-Abl kinase activity using purified recombinant proteins suggested that Prx I may need additional protein(s) to inhibit the c-Abl kinase activity efficiently *in vitro*. Nevertheless, exogenous Prx I has been shown to counteract the cytostatic effect of c-Abl overexpression in fibroblasts (Wen and Van Etten, 1997). On the basis of this information, it becomes clear that we need to understand more about c-Abl function to better understand Prx I function.

The cytostatic function of c-Abl overexpression has been mainly attributed to its ability to induce G_1 arrest in a p53-dependent fashion (Sawyers *et al.*, 1994; Goga *et al.*, 1995). Moreover, overexpression of a dominant negative kinase-deficient mutant of c-Abl, as well as antisense c-Abl, have been shown to accelerate the onset of S phase and shorten G_1 phase in fibroblasts. Further evidence supporting the potential role of c-Abl in regulating cell growth are the observations that oxidative stress and ionizing radiation have now been shown to lead to increased c-Abl kinase activity (Kharbanda *et al.*, 1998; Van Etten, 1999). Recently, c-Abl has also been implicated in the induction of apoptosis by different signals mediated at least in part by p73, a p53 tumor suppressor homolog (Agami *et al.*, 1999; Gong *et al.*, 1999; Yuan *et al.*, 1999). Prx I expression seems to increase in synchronized cells entering S phase, raising the possibility that elevated levels of Prx I counteract the cytostatic activity of cAbl (Prospaeri *et al.*, 1998). These observations not only may help to link higher expression levels of Prx I with induction of proliferation but also to the response to compounds inducing oxidative stress. Because p73 and Prx I can compete for the SH3 domain of c-Abl, an intriguing possibility is that Prx I may perform an anti-apopototic function via its ability to prevent p73–c-Abl complex formation, thereby diminishing the propagation of this specific apoptotic signal.

The mouse Prx I was identified as macrophage stress protein 23 (MSP23) because it was induced by oxidative stress in the peritoneal macrophages caused by heavy metals, oxidized low-density lipoproteins, heme, or sulfhydryl-reactive agents (Sato *et al.*, 1993; Ishii *et al.*, 1995). The same gene was cloned from (and

found to be highly expressed in) osteoblastic cells, and named osteoblastic specific factor-3 (OSF-3) (Kawai *et al.*, 1994). The name heme binding protein 23 (HBP23) indicates its strong affinity for heme in the rat hepatocytes (Immenschuh *et al.*, 1995, 1997; Iwahara *et al.*, 1995). Thioredoxin peroxidase (TPx)-I or thioredoxin-dependent peroxidase-1 (TDPX1) (Pahl *et al.*, 1995) has also been used for Prx I to indicate its usage of thioredoxin as reductant. However, in the GenBank database as well as in one of our own publications (Shau *et al.*, 1998), Prx I was referred to as thioredoxin peroxidase (TxP)-2. The most recent consensus terms are listed in Table 1.

Peroxiredoxin II

We cloned Prx II by homology with Prx I but found that Prx II did not have the same NK-enhancing activity. On the basis of homology of Prx II/NKEF B with TSA previously cloned (Kim *et al.*, 1988, 1989; Chae *et al.*, 1994; Yim *et al.*, 1994), we investigated the antioxidant function of Prx II and found that it could protect both DNA from nicking and protein from inactivation mediated by oxidative damage in a mixed-function oxidation system (Shau and Kim, 1994; Sauri *et al.*, 1995). Prx II expression is induced by H_2O_2, and the overexpression of Prx II in an endothelial line protects the cells from oxidative stress caused by the heavy metal mercury, the inorganic hydrogen peroxide as well as the organic *t*-butylhydroperoxide (Kim *et al.*, 1997a; Sarafian *et al.*, 1997; Shau *et al.*, 1997). It has also been shown to protect red blood cell (RBC) membranes from peroxidation (Cha and Kim, 1995; Lim *et al.*, 1993). These observations support the fact that Prx II has a wide variety of antioxidant functions throughout the cell.

Of potential clinical importance is the finding that Prx II can block the adhesion of monocytes to endothelial cells that is activated by minimally oxidized low-density lipoprotein (LDL) (Shau *et al.*, 1997), a key early step in the progression of atherosclerosis (Ross, 1993; Diaz *et al.*, 1997). In addition, Prx II can also inhibit the monocyte-endothelial cell binding induced by LPS (Shau *et al.*, 1997). It is not yet known whether Prx II is involved in signal transduction from adhesion molecules on the cell surface or at another step in the process. Besides these functions, Prx II also regulates at least three signal transduction pathways that directly relate to apoptotic cell death: AP-1, caspases, and NF-κB. Heterodimers of members of the Jun and Fos transcription factor families constitute the transcription factor AP-1 (Karin *et al.*, 1997). Phosphorylation of c-Jun by Jun N-terminus kinase (JNK) increases the AP-1 transactivation function to transcribe a wide range of genes. In many different types of culture systems, ROS and inflammatory cytokines are known to activate the JNK/AP-1 signal transduction pathway (Meyer *et al.*, 1993; Singh *et al.*, 1995; Sen and Packer, 1996; Hirota *et al.*, 1997) and that, in turn, triggers programmed cell death (Singh *et al.*, 1995; Hirota *et al.*, 1997; Quillet-Mary *et al.*, 1997; Faris *et al.*, 1998; Le-Niculescu *et al.*, 1999). We have documented that overexpression of Prx II blocks tumor necrosis factor-α (TNF-α) activation of AP-1 in ECV304 cells (Shau *et al.*, 1998). Because activation of AP-1 initiates apoptosis in many different types of cells, by blocking AP-1 function Prxs would be predicted to inhibit programmed cell death. So far, no investigations have directly addressed this possibility.

Another signal transduction pathway in which Prx II has recently been shown to play an important role is the activation of caspases. Prx II was found to block apoptosis by scavenging H_2O_2 which would have otherwise led to cytochrome *c* release from mitochondria and caspase activation in cells induced to apoptosis after serum deprivation, ceramide exposure, or treatment with the chemotherapeutic drug etoposide (Zhang *et al.*, 1997; Shau *et al.*, 1998). It is believed that Prx II acts upstream of bcl-2, which blocks apoptosis by inhibiting cytochrome *c* release from mitochondria.

NK-κB, a member of the *rel* family of transcription factors, exists in an inactive form in the cytoplasm bound to an inhibitor protein I-κB. When cells are stimulated by TNF-α, phorbol esters, lipopolysaccharide (LPS), or double-stranded RNA, many respond by phosphorylating I-κB at the conserved serine residues. Serine phosphorylation is immediately followed by conjugation of ubiquitins to and proteosome degradation of I-κB, allowing

NF-κB to migrate to the nucleus for initiating transcription of a wide range of genes. Interestingly, ROS are known to activate and antioxidants to block NF-κB function in cytoplasm (Schreck *et al.*, 1991; Sen and Packer, 1996; Shono *et al.*, 1996; Karin, 1998; Kikumori *et al.*, 1998; Li and Karin, 1999), hence it is not surprising that increased expression of the cytoplasmic peroxidase Prx II correlates with a decrease in NF-κB signal transduction (Kang *et al.*, 1998b). Paradoxically, NF-κB initiates protective mechanisms in many cell types against apoptotic death (Chu *et al.*, 1997; Van Antwerp *et al.*, 1998; Yamit-Hezi and Dikstein, 1998; Reuther and Baldwin, 1999). By blocking the activation of NF-κB, Prx II could theoretically enhance cellular susceptibility to apoptosis, while simultaneously inhibiting apoptosis via the mechanisms discussed above. These paradoxical effects suggest that the balance of these contradictory activities may be a determinant of the fate of the affected cells.

One other Prx II homolog has been named Calpromotin, a RBC protein that has been shown to form dimers and oligomers as well as bind various RBC membrane components (Moore *et al.*, 1997). It is involved in the activation of a calcium-dependent potassium channel. Although originally identified as a MER5/Prx III homolog, its sequence clearly indicates that calpromotin is a human Prx II (Kristensen *et al.*, 1999; Schreoder *et al.*, 1998). Prx II is important in erythroid cell differentiation (Rabilloud *et al.*, 1995; Ichimiya *et al.*, 1997), and is probably the most abundant protein in the mature RBC cytosol after hemoglobin (Lim *et al.*, 1994b; Shau and Kim, 1994). A more recent study found a correlation between dense cells in sickle cell disease and localization of Prx II in increased amounts at the RBC membrane, possibly in an oligomeric form (Moore *et al.*, 1997). The formation of dense cells by repeated deoxygenation/reoxygenation (which leads to increases in calpromotin/Prx II) is a possible link to its antioxidant function.

Peroxiredoxin III

Due to the membrane localization sequence at its amino terminus, Prx III is the only family member that is localized to the mitochondria. This localization supports an important antioxidation function for Prx III given that the mitochondria consume 85% of the oxygen in the cell and generate ROS as byproducts. Prx III could play a general protective role in these organelles. The murine gene MER5 was the first family member described by a group of investigators studying genes regulated during *in vitro* differentiation of murine erythroleukemia cells to RBC (Yamamoto *et al.*, 1989). Prx III was found to be highly expressed in erythroid lineage cells. Induction of cellular differentiation led to increased globin and Prx III/MER5 expression. Later, antisense MER5 was shown to inhibit the differentiation of murine erythroleukemia cells (Nemoto *et al.*, 1990).

The bovine Prx III homologue has been described as SP22, which is expressed in adrenal cortex mitochondria and is a major substrate of an ATP-dependent protease. After being identified as a Prx family member, the antioxidant function of Prx III/SP22 was demonstrated by upregulation of the protein by various oxidative stressors (Tsuji *et al.*, 1995; Watabe *et al.*, 1995, 1997). When Prx III/SP22 was inhibited by antisense oligonucleotides, ROS-mediated damage to endothelial cells was increased.

The human Prx III was the recently cloned anti-oxidant protein (AOP)-1 and it has been shown to bind the cyclophilin CyP18, which increases its antioxidant function (Jeaschke *et al.*, 1998). Cyclophilins are peptidyl-prolyl *cis-trans* isomerases, which are major cytoplasmic targets of the immunosuppressive drug cyclosporin A. Similar to cyclosporin A (Dallaporta *et al.*, 1998), the mouse Prx III/MER5 as well as the yeast Prx II/TSA (Kowaltowski *et al.*, 1998) block an essential step for apoptosis, the mitochondrial permeability transition (Hirsch *et al.*, 1998). Because cyclosporin A does not inhibit the binding to and activation of CyP18 to Prx III, the significance of the connection between these molecules in not clear.

Peroxiredoxin IV

Prx IV is a recently described 2-Cys Prx family member, and many of its described properties are contradictory. Prx IV has been described as both cytoplasmic and secreted with

a long 79 amino acid signal peptide at the amino terminus (Jin *et al.*, 1997; Haridas *et al.*, 1998). It has been found to form a heterodimer with Prx I, as well as Prx IV homodimers. AOE372/PrxIV was found to inhibit NF-κB (like Prx II) while TRANK/Prx IV induces NF-κB activity.

AOE372/Prx IV was found by a Prx I-binding protein search (Jin *et al.*, 1997). It performs the customary Prx family member antioxidant functions, using thioredoxin as the electron donor for H_2O_2 scavenging. It has a fairly ubiquitous tissue distribution. Of potential importance is the observation that Prx IV can block function of the HIV promoter and HIV viral proliferation in human T cell lines as assayed by p24 levels and reverse transcriptase activity (Jin *et al.*, 1997). Conversely, HIV reduces Prx IV levels in infected T cell lines.

TRANK/Prx IV was found by searching an expressed sequence tag database for a secreted form of Prx II (Haridas *et al.*, 1998). It has been found to increase NF-κB, JNK, ICAM-1, and iNOS expression as well as fibroblast proliferation. Although an increased level of Prx IV might be expected to correlate with increased cellular proliferation (as has been shown with other family members), the NF-κB data are surprising. The conflicting aspects of this report will have to await further repetition and analysis. Because the NF-κB results from studies with Prx II are also counterintuitive compared with the AP-1 and caspase data, the cell systems and different assays employed by different investigators may play an important role.

TISSUE EXPRESSION AND POTENTIAL BIOLOGICAL IMPLICATIONS

A wide variety of therapeutic interventions involving the Prx family can be envisioned given the importance of ROS and antioxidant activity in disease. The differential activities, subcellular localizations, and tissue expression patterns of the different members in the Prx family provide a diverse set of prospects for the use of up- or down-regulation of individual Prxs for manipulating cell growth and death. Although a generalized increase in antioxidant levels is often mentioned as having a potential for overall health improvement (Stadtman, 1992; Sies, 1993; Sen, 1995, 1998; Berlett and Stadtman, 1997; Halliwell, 1996), it is now clear that ROS and antioxidants exist in a careful balance, where cell survival requires many molecules interacting in complex pathways. The recently reported toxicity of β-carotene in a clinical trial involving cigarette smokers only highlighted the need to understand better the interconnections between different antioxidant molecules in order to maintain a balance of ROS and nontoxic end products (Mayne *et al.*, 1996; Handelman, 1997; Paolini *et al.*, 1999).

Cell-type-specific expression

When present, Prx usually is a major protein component of the cell. This occurs not only in the mammals (Kim *et al.*, 1988; Prospaeri *et al.*, 1993; Sato *et al.*, 1993; Kawai *et al.*, 1994; Lim *et al.*, 1994b; Shau and Kim, 1994; Cha and Kim, 1995; Iwahara *et al.*, 1995; Siow *et al.*, 1995; Ichimiya *et al.*, 1997; Moore *et al.*, 1997; Kang *et al.*, 1998a, 1998b; Phelan *et al.*, 1998; Chae *et al.*, 1999; Matsumoto *et al.*, 1999), but also in other species (Kim *et al.*, 1989; Storz *et al.*, 1989; Tartaglia *et al.*, 1990; Torian *et al.*, 1990; O'Toole *et al.*, 1991; Chae *et al.*, 1994a; Poole *et al.*, 1997; Chen *et al.*, 1998; Jeong *et al.*, 1999). Considering their abundance, it is surprising that Prxs were not discovered earlier. The amount of protein and the high degree of conservation are consistent with the importance of Prxs in differentiation and cell survival.

The analysis of tissue distribution and differential expression of Prx I and Prx II has led to interesting observations. Although the expression of Prx I and Prx II genes is fairly ubiquitous, the highest mRNA levels occur in bone marrow, liver, testis, ovary, and heart, followed by brain and spleen (with greater expression levels in anemic spleen vs. control spleen cells) (Ichimiya *et al.*, 1997; Kim *et al.*, 1997a; Lim *et al.*, 1998; Matsumoto *et al.*, 1999). Studies on human brain tissue have revealed higher levels of Prx II in large neurons (hippocampal pyramidal and Purkinje neurons), whereas Prx I was found to be more abundant in astrocytes (Sarafian *et al.*, 1998, 1999). This follows a general pattern of greater expression of antioxidants like glutathione in glial cells when com-

pared to neurons. The induction of Prx I in macrophages under stress (Sato *et al.*, 1993) is also consistent with the hypothesis that this protein is expressed when and where the host defense system needs it for protection of tissues against oxidant damage. Prx I is obviously important for cell proliferation because it is hyperexpressed only in proliferating cells (Prospaeri *et al.*, 1993, 1998) and can reverse the cell growth arrest by c-Abl (Wen and Van Etten, 1997). Similarly, we found that transduction of human Prx I gene results in greater growth in murine fibroblast cells (Shau *et al.*, manuscript submitted). However, the role Prx I in the nonproliferating RBC is less clear. Although we can easily detect Prx I in human RBC (Shau and Kim, 1994), Lim and colleagues did not detect the protein there (Lim *et al.*, 1994b).

Prx II was also found in mouse brain areas that are more susceptible to oxidative stress due to hypoxic and ischemic injury (Ichimiya *et al.*, 1997). ROS are thought to play an important role in the destructive aspects of neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, stroke, and other brain traumas (Hastings and Zigmond, 1997; Ichimiya *et al.*, 1997; Takeda *et al.*, 1998; Yang *et al.*, 1998). The differential expression of Prx I and II in both tissue culture and intact human brain samples suggests an important difference in function of these two antioxidants. An interesting possibility is that the selective expression of Prx members in different tissues could be indicative of specialized antioxidant functions for the individual cell types involved. Alternatively, it could reflect a lack of balance that causes susceptibility to ROS-mediated damage in tissues without equivalent expression of some other family members (Jin *et al.*, 1997).

Both Prx II and Prx III are highly expressed in the early phase of erythroid cell differentiation (Yamamoto *et al.*, 1989; Rabilloud *et al.*, 1995), indicating their importance in RBC development. Inhibition of Prx III expression, in particular, blocks the differentiation of the erythroid lineage (Nemoto *et al.*, 1990). Prx II exists in large quantities in the nonproliferating, terminally differentiated RBC compared to less mature erythroid cells (Shau *et al.*, 1993; Lim *et al.*, 1994b), suggesting that it is involved in later phase of RBC development. However, to unravel the time sequence and the cross talk between Prx I and Prx II in RBC development, one has to wait for the simultaneous study of these two genes.

The tissue expression of Prx IV mRNA follows a similar pattern to Prx I and Prx II, *i.e.*, generally high in muscles, liver, and the reproductive organs of testis and ovary (Prospaeri *et al.*, 1993; Jin *et al.*, 1997; Kim *et al.*, 1997a; Haridas *et al.*, 1998). The expression of all three subtypes in general is moderate to low in lung, leukocytes, and brain. The distribution of Prx III is least known. The available data indicate that, in contrast to the other three subtypes (Prx I, Prx II, and Prx IV), Prx III message level is high in the brain, moderate in kidney and low in testis (Yamamoto *et al.*, 1989).

Peroxiredoxin aggregation and cytotoxicity

One unique characteristic noted by many investigators of Prxs is that both mammalian and nonmammalian Prxs tend to form large (>200 kDa in size), insoluble, noncovalent aggregates upon storage (Kim *et al.*, 1988; Torian *et al.*, 1990; O'Toole *et al.*, 1991; Shau *et al.*, 1993; Chae *et al.*, 1994a; Schreoder *et al.*, 1998). Self-aggregation may affect the original biological functions of Prxs, making them less efficient in carrying out antioxidation activity, reducing their regulation of molecules that are their usual targets, increasing their resistance to proteolytic recycling processes, and even turning Prxs into toxic reagents. There are many situations where aggregation can transform important and well-conserved proteins into cytotoxic reagents. Prions can form insoluble aggregates without changing their sequence or altering the involvement of covalent bonds (Harrison *et al.*, 1997; Prusiner *et al.*, 1998; Safar and Prusiner, 1998). Dramatic conformational changes from α-helices to β-sheets induce plaque formation in brain tissue. Similar associations and theories also exist in many other proteins that are equally well conserved—β-amyloid peptides in Alzheimer's disease (Yang *et al.*, 1999), α-synuclein in the Lewy body of Parkinson's disease (Arawaka *et al.*, 1998; Takeda *et al.*, 1998), and huntingtin in Huntington's disease (Mar-

tin *et al.*, 1999; Scherzinger *et al.*, 1999) are just a few of the better-known examples. Thus, an abundance of Prx does not necessarily indicate more protection against ROS toxicity. Under many situations, too much Prx may lead to self-aggregation or aggregation with other proteins or even intracellular structures resulting in cell death. At present there is no evidence for this, but future studies should evaluate this hypothesis.

Regulation of apoptosis

Direct scavenging of ROS to block oxidant toxicity is assumed to be the basic biological function of Prxs throughout evolution. That is presumably why the domains responsible for the antioxidation activity are so well conserved. The exact role of Prxs in regulating programmed cell death (apoptosis), however, is more complicated. Zhang and colleagues showed that Prx II inhibits cytochrome *c* release from mitochondria, an essential step for activating caspase 3 in cytosol (Zhang *et al.*, 1997). Because caspase 3 is an effector enzyme for carrying out many of the manifestations of apoptosis, Prx II could serve as a potent inhibitor of programmed cell death. It is known that not all the oxidant-induced apoptosis depends on caspase 3 or involves cytochrome *c* release (Kolenko *et al.*, 1999; Reuther and Baldwin, 1999; Wolf and Green, 1999). This leads us to hypothesize that the balance between the other two pathways, NF-κB and AP-1, is also essential for controlling apoptosis.

NF-κB is the first eukaryotic transcription factor shown to respond directly to oxidative stress (Schreck *et al.*, 1991). NF-κB activation induces transcription of many proteins that are responsible for cellular resistance to apoptosis. Kang and colleagues reported that NF-κB activation is blocked by Prx II (Kang *et al.*, 1998b). Similarly we have observed that Prx II inhibits NF-κB activation in tumor necrosis factor (TNF)-treated endothelial ECV304 cells (data not shown). The effect of Prx IV on NF-κB activity is less clear. Jin and colleagues reported that Prx IV blocks basal as well as cytokine-activated NF-κB function in HeLa and HepG2 cells (Jin *et al.*, 1997). In contrast, Haridas and colleagues showed that Prx IV alone is an activator of NF-κB function in U937 cells (Haridas *et al.*, 1998). Again, these seemingly contradictory results could be due to differences in the cell systems used.

JNK/AP-1 is another signal transduction pathway that is inhibited by Prx II (Shau *et al.*, 1998). Interestingly, AP-1 is mainly involved in induction of apoptosis (Meyer *et al.*, 1993; Singh *et al.*, 1995; Quillet-Mary *et al.*, 1997; Faris *et al.*, 1998; Le-Niculescu *et al.*, 1999). The spectrum of Prx influences on different signal transduction pathways involved in apoptosis highlights the complexity of Prx regulation of programmed cell death. The overall outcome of cell survival depends on the balance between the influences on caspases, AP-1 and NF-κB pathways, as well as the basic ability of Prx to scavenge the toxic oxidants.

Leukemogenesis and cancer biology

Prx I is not only capable of interacting with c-Abl kinase, but also has been shown to interact with other abl oncogenes such as the largely cytoplasmic Philadelphia chromosome gene product BCR-ABL (Wen and Van Etten, 1997). BCR-ABL is the hallmark of chronic myeloid leukemia (CML) where it is found in up to 95% of the patients, and in 5% of children and 15–30% of adults with acute lymphoblastic leukemia (ALL) (Faderl *et al.*, 1999). Prx I also seems to partially inhibit the tyrosine kinase activity of BCR-ABL *in vivo*, although less effectively than c-Abl. Prx I has been found in both the cytoplasm and nucleus; however, its ability to inhibit Abl kinases may depend on unidentified cellular co-factors. These interactions lead to speculation that Prx I may have a negative effect on BCR-ABL transforming potency. Analysis of the levels of Prx I during blast crisis may be useful if there is an inverse correlation with the aggressiveness of BCR-ABL-induced leukemias.

In another area of potential utility, Prx IV/AOE372 and HIV-1 are known to counterbalance each other's expression (Jin *et al.*, 1997). By blocking HIV-1 infection and proliferation, Prx IV could prove to be useful in preventing the development of Kaposi's sarcoma. Hematopoietic cells are well known by their fine balance between proliferation, differentia-

tion, and apoptosis. Disturbance of any of these processes could lead to immunodeficiencies, autoimmune diseases, or leukemias. Because the Prx proteins have been shown to be associated with proliferation and apoptosis (Prospaeri *et al.*, 1993, 1998), it is possible that deregulation of these proteins may lead to hematopoietic instability. Further research will be required to support or reject these possibilities. Unraveling the role of these proteins in other tissues with regard to cancer development or apoptosis is an interesting challenge that will be the subject of active investigation in the next several years.

Transplantation biology

Depending on the processes they affect, Prxs can be both beneficial and detrimental to the success of organ transplantation. Their antioxidation activity protects organs from stress incurred during the transplantation. However, the NK-promoting function could lead to failure of the transplanted organs. Organ transplantation from donor to recipient involves ischemia and reperfusion (I/R) due to the cutting off and later reconnecting of the blood supply. I/R of liver causes enhanced mitochondrial production of ROS. Among many diverse effects, cytokine release, neutrophil adhesion, sinusoid endothelial cell death, and hepatocyte injury are the most likely means to manifest these events (Serizawa *et al.*, 1996; Bzeizi *et al.*, 1997). The release of TNF-α appears predominant in I/R injury, contributing directly to ROS production as well as downstream effects, namely activation of NF-κB and AP-1 (Meyer *et al.*, 1993; Singh *et al.*, 1995; Jin *et al.*, 1997; Haridas *et al.*, 1998; Kang *et al.*, 1998b; Shau *et al.*, 1998).

Recently, we observed that the levels of Prx I and Prx II are increased by I/R during the liver transplantation process (Shau *et al.*, submitted). We hypothesize that the oxidative stress from I/R induces Prxs to protect the liver cells from ROS toxicity. To test this hypothesis, we transduced murine NIH-3T3 fibroblasts with human Prx I or Prx II genes and showed that the Prx-overexpressing cells are more resistant to the organic oxidant *t*-butylhydroperoxide. Thus, induction of Prxs in the transplanted organs could be beneficial in protecting the cells from oxidative damage.

Besides cytoprotection, Prxs can also affect the survival of transplanted organs by other mechanisms. Prx I enhances NK cytotoxicity (Sauri *et al.*, 1996) that is widely believed to be a major mechanism in rejecting transplanted organs (Katznelson *et al.*, 1998; Trinchieri, 1989). Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, has become a popular drug in recent years for prolonging the survival of transplanted organs (Katznelsosn *et al.*, 1996). We documented that in the rat liver transplantation model, a combination of Pravastatin and cyclosporin A, is much more effective than cyclosporin A alone in preventing organ rejection (Kakkis *et al.*, 1997). Although the mechanism of Pravastatin immunosuppression is not clear, it is suspected that inhibition of NK cell activity is of major significance. This hypothesis is especially attractive because the decrease of NK activity is correlated with Pravastatin-mediated decrease in Prx I and Prx II expression in the same liver recipients. If this hypothesis holds true, then Prx I and Prx II offer great potential for genetic and biochemical intervention of liver function in transplantation biology. By blocking Prx I-mediated enhancement of NK activity, one would reduce the risk of transplant rejection by the recipients. On the other hand, Prx antioxidation activity can be preserved or increased to protect cells from undergoing apoptosis. This strategy would afford protection of transplanted organs from I/R damage, thus preventing many of the incidents where donor organs need to be discarded due to delay by time or distance.

CONCLUSIONS

The Prx family of proteins are widely expressed, and localized in multiple cellular compartments. They have important functions not only in ROS scavenging but also in such basic cell processes as signal transduction, proliferation, and apoptosis. Although much has been learned in the last 5 years about some of their functions and interactions, we are now just beginning to unravel the mechanisms by which

these proteins cross react with each other as well as discovering new functions associated with normal or anomalous physiology. The questions are increasing exponentially and the field is expanding rapidly. The development of new molecular tools and assays in the coming years will help elucidate the intricacy of interplay between Prxs and other cellular components to regulate cell growth and death.

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ABBREVIATIONS

Ahp, Alkylhydroperoxide reductase; ALL, acute lymphoblastic leukemia; AOE372, antioxidant enzyme 372; AOP, anti-oxidant protein; AP-1, activator protein-1; CML, chronic myeloid leukemia; Cys, cysteine; H_2O_2, hydrogen peroxide; HBP23, heme binding protein 23; HIV, human immunodeficiency virus; I/R, ischemia and reperfusion; JNK, Jun N-terminus kinase; LAK, lymphokine-activated killer; LDL, low-density lipoprotein; LPS, lipopolysaccharide; MER5, murine erythroleukemia RNA 5; MSP23, macrophage stress protein 23; Mys, myristylation domain; NES, nuclear export sequence; NF-κB, nuclear factor-κB; NK, natural killer; NKEF, NK enhancing factor; NLS, nuclear localization sequence; ORF6, open reading frame 6; OSF-3, osteoblast specific factor-3; PAG, proliferation-associated gene; PLA_2, calcium-independent phospholipase A_2; PRP, protector protein; Prx, peroxiredoxin; RBC, red blood cell; ROS, reactive oxygen species; SH2 and SH3, Src-homology domains; SP22, substrate protein 22 for mitochondria ATP-dependent protease; TDPX1, thioredoxin-dependent peroxidase-1; TNF-α, tumor necrosis factor-α; TPx, thioredoxin peroxidase; TRANK, thioredoxin peroxidase-related activator of NF-κB and JNK; TSA, thiol-specific antioxidant; Tx, thioredoxin; TxP, thioredoxin peroxidase.

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