ANTIOXIDANTS & REDOX SIGNALING
Volume 7, Numbers 5 & 6, 2005
© Mary Ann Liebert, Inc.

Forum Review

Peroxiredoxins, Oxidative Stress, and Cell Proliferation

STEPHAN IMMENSCHUH[1] and EVELINE BAUMGART-VOGT[2]

ABSTRACT

Peroxiredoxins (Prxs) are a family of multifunctional antioxidant thioredoxin-dependent peroxidases that have been identified in a large variety of organisms. The major functions of Prxs comprise cellular protection against oxidative stress, modulation of intracellular signaling cascades that apply hydrogen peroxide as a second messenger molecule, and regulation of cell proliferation. In the present review, we discuss pertinent findings on the protein structure, the cell- and tissue-specific distribution, as well as the subcellular localization of Prxs. A particular emphasis is put on Prx I, which is the most abundant and ubiquitously distributed member of the mammalian Prxs. Major transcriptional and posttranslational regulatory mechanisms and signaling pathways that control Prx gene expression and activity are summarized. The interaction of Prx I with the oncogene products c-Abl and c-Myc and the regulatory role of Prx I for cell proliferation and apoptosis are highlighted. Recent findings on phenotypical alterations of mouse models with targeted disruptions of Prx genes are discussed, confirming the physiological functions of Prxs for antioxidant cell and tissue protection along with an important role as tumor suppressors. *Antioxid. Redox Signal.* 7, 768–777.

INTRODUCTION

Peroxiredoxins (Prxs), synonymous with thioredoxin peroxidases, are a protein family whose members were initially identified as thiol-specific antioxidant enzymes (5–7). Prxs are involved in the enzymatic degradation of hydrogen peroxide, organic hydroperoxides, and peroxynitrite (20, 61, 83). They are found in a wide range of organisms, such as bacteria, plants, and mammals, and are divided into three major subclasses: typical 2-cysteine Prxs (Prx I–IV), atypical 2-cysteine Prxs (Prx V), and 1-cysteine Prxs (Prx VI). In the following, we discuss the physiological functions of Prxs, the mechanisms and signaling pathways that govern mammalian Prx gene expression, and the role of Prxs in the regulation of the cell cycle with a focus on Prx I. Gene expression of Prx I is not only up-regulated by oxidative stress, but appears to be also closely interrelated with the regulation of cell proliferation and differentiation. In detail, Prx I was independently identified in a Ras-transformed human epithelial cell line after serum stimulation [proliferation-associated gene (pag) (58)], in stress-stimulated mouse peritoneal macrophages [mouse stress protein 23 (MSP23) (26)], and in the erythroleukemic cell line K562 in which it enhanced the activity of natural killer cells [natural killer cell enhancing factor A (NKEF A) (68, 69)]. Moreover, Prx I was purified from rat liver cytosol as a protein with high binding affinity for the prooxidant tetrapyrrole heme [heme-binding protein 23 (HBP23) (31)].

STRUCTURE AND PHYSIOLOGICAL FUNCTIONS OF Prxs

Prxs are characterized by their content of conserved redox-active cysteine residues in the catalytic center that is involved in the enzymatic peroxidase activity of this protein. Redox-active cysteines of Prxs are oxidized to sulfenic acids by peroxide substrates, thereby inactivating their peroxidase enzyme activity. Formerly, this oxidation was assumed to be irreversible (20, 83), but, more recently, it was demonstrated that the oxidized sulfenic

[1]Institut für Klinische Immunologie und Transfusionsmedizin, Justus-Liebig-Universität Giessen, Giessen, Germany.
[2]Institut für Anatomie und Zellbiologie, AG Medizinische Zellbiologie, Justus-Liebig-Universität Giessen, Giessen, Germany.

acid can be converted back into a thiol in a second reduction step (80). An unusual dimer formation of recombinant Prx I with C-terminal domain swapping was demonstrated by crystal structure analysis. It was also shown that the oxidized N-terminal active cysteine residue formed a disulfide bond with the conserved C-terminal cysteine of the partner Prx I dimer subunit. Moreover, a potential heme-binding domain of Prx I was identified in this study (19). An overview on important structural aspects of Prxs and their potential functional consequences was recently published by Wood and colleagues (83).

A major common function of Prxs is the enzymatic degradation of hydrogen peroxide. As hydrogen peroxide can be rapidly converted into highly toxic reactive oxygen species (ROS) such as hydroxyl radicals, it may generate oxidative stress by overwhelming the intracellular antioxidant mechanisms (8). Oxidative stress may damage most cellular constituents by causing DNA-strand breakage, protein cross-linking, and lipid peroxidation (64). The physiological role of Prxs as a dam against oxidative stress is of particular importance in red blood cells in which Prxs are the second or third most abundant proteins (48). The assumption that Prxs protect against oxidative stress has been confirmed in recent reports demonstrating that mice with targeted disruptions of Prx genes are highly susceptible to oxidative stress-mediated toxicity. In Prx I knockout animals, Neumann and colleagues observed a hemolytic anemia with hemoglobin instability and Heinz body formation along with an increased incidence of various malignancies (51). Similarly, in Prx II-deficient animals, the life span of erythrocytes was drastically reduced, resulting in an anemia with lowered cellular hematocrit (43). In both Prx I and Prx II knockout animals, the generation of intracellular ROS in erythrocytes and in macrophages was markedly increased. Moreover, Prx VI knockout mice were found to have lower survival rates, as well as higher protein oxidation levels, with more severe tissue damage in organs such as kidney, liver, and lung (77). Interestingly, in Prx VI knockout animals, the gene expression levels of antioxidant enzymes such as catalase, glutathione peroxidase, and manganese superoxide dismutase (MnSOD) were not different from those of Prx VI wild-type animals, suggesting that Prx VI cannot be compensated for by other genes (77).

Hydrogen peroxide, however, not only may cause cellular oxidant damage, but at low levels may serve as physiological intracellular second messenger molecules involved in signal transduction cascades of various cell-surface receptors (13, 62, 76). Comparable to other second messengers such as cyclic nucleotides or inositol 3-phosphate, hydrogen peroxide that is generated by extracellular signals has to be eliminated in a timely manner after completion of its mission. In agreement with this concept, it was demonstrated that Prxs can regulate cellular signal transduction pathways via enzymatic elimination of hydrogen peroxide (62). In detail, it was demonstrated in transiently transfected cell lines that overexpression of Prx I and II diminished intracellular hydrogen peroxide levels that were increased in response to the growth factors platelet-derived growth factor or epidermal growth factor (33). Moreover, overexpression of Prx I and II inhibited hydrogen peroxide- and tumor necrosis factor-α (TNFα)-dependent activation of the transcription factor nuclear factor-κB (NF-κB) (33). In a more recent study, the regulatory role of Prx II for hydrogen peroxide signaling was confirmed in a model of Hela cells that were transfected with either wild-type or dominant negative forms of Prx II. In addition, Kang and co-workers demonstrated in cultured embryonic fibroblast cells from Prx II-deficient mice that overexpressed Prx II modified the hydrogen peroxide-dependent activation of the mitogen-activated protein kinases (MAPK) c-Jun N-terminal kinase (JNK) and p38 in response to TNFα. The authors concluded that Prxs may complement other antioxidant enzymes as modulators of intracellular redox signaling (34, 62). Others reported similar observations for the TNFα-dependent activation of the transcription factor activator protein-1 (AP-1), which was decreased by overexpression of Prx II in transfected endothelial cell cultures (70). Independently, in a cell culture model of thyroid cells, overexpressed Prx I and II were shown to eliminate hydrogen peroxide that was generated by treatment with thyrotropin. The increased expression of Prx genes protected these thyroid cells against hydrogen peroxide-mediated apoptosis (35). In a recent study on the Prx crystal structure, 2-cysteine Prxs were suggested to function as potential cellular sensor systems of whether or not hydrogen peroxide is a toxic oxidant or a beneficial signaling molecule (82). A model was proposed in which the sensitivity of eukaryotic 2-cysteine Prxs was quantitatively correlated with structural changes of these proteins. In this model, it was suggested that highly abundant 2-cysteine Prxs may keep cellular levels of hydrogen peroxide low in resting cells. By contrast, when intracellular levels of hydrogen peroxide are transiently increased, such as in cells treated with TNFα, oxidation of redox-sensitive cysteines of Prxs decreases their peroxidase enzyme activity and, in consequence, allows the generation of high levels of hydrogen peroxide for intracellular signaling. Therefore, these authors regard mammalian 2-cysteine Prxs as a floodgate for cellular peroxides that is opened under defined conditions (82). A surprising observation was made for Prx IV as to its regulation of the transcription factor NF-κB. Prx IV is the only Prx that is secreted by cells and is synonymous with thioredoxin peroxidase-related activator of NF-κB and JNK (TRANK) (17) and with the antioxidant enzyme 372 (32). In apparent contrast to other Prxs, Prx IV was shown to cause an activation of NF-κB via degradation of inhibitor of NF-κB (IκB) leading to NF-κB-dependent gene expression (17).

TISSUE- AND CELL-SPECIFIC DISTRIBUTION OF Prxs

The important physiological functions of Prxs are emphasized by the wide tissue expression of the corresponding family members. For an overview on the tissue expression of all Prx family members, we performed a UniGene database search (at the National Center for Biotechnology Information: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unigene). The highest number of hits for expressed sequence targets (ESTs in all cDNA libraries) was found for the Prx I gene with 2,383 EST sequences, the tissue representation of which is summarized in Table 1. A comparison of EST numbers for Prx I (= 100%) with those of other Prx family members indicated that Prx I is the most abundant and ubiquitous Prx (Prx I EST representation compared with one of the other Prx

Table 1. Tissue Representation of Mouse and Human ESTs for PRX I—UniGene Database Search

Organs and tissues	*ESTs of different individual cDNA libraries*
Central nervous system	Fetal brain, adult visual cortex, hippocampus, hypothalamus, pineal gland, cerebellum, spinal cord, oligodendroglia
Peripheral nervous system	Spinal ganglia, sciatic nerve, sympathetic trunk
Eye	Neural retina, pigmental epithelial cells, iris, lens
Inner ear	Organ of Corti
Respiratory tract	Nose-olfactory mucosa, lung (whole lung, epithelia, and alveoli)
Cardiovascular system	Heart and blood vessels such as aorta, basilary artery, other arteries and veins
Bone marrow and blood cells	Whole bone marrow, hemopoietic stem cells, macrophages, whole blood, B- and T-lymphocytes
Lymphatic organs	Thymus, spleen, and lymph nodes
Gastrointestinal system	Liver, gall bladder, pancreas, all parts of the intestines, stomach, and gastric epithelium
Urinary system	Kidney, urinary bladder
Endocrine organs	Pituitary, thyroid, parathyroid, and adrenal glands, and Islets of Langerhans
Male genital tract	Testis, spermatogonia, spermatocytes, Sertoli cells, prostate
Female genital tract	Mullerian duct, ovary, whole uterus, endometrium, placenta, amnion, decidual tissue, *in vitro* fertilized eggs, embryonic stem cells
Skin	Whole skin and melanocytes
Skeletal muscle	Tongue, nasopharynx, diaphragm, hind-limb muscles
Bone and joints	Maxilla and mandible, complete joints, synovial membrane
Other organs and tissues	Submandibular gland, adipose tissue
Tumors	Prostate tumors, embryonal testis tumors, embryonal carcinoma, squamous cell carcinoma, lung carcinoma, renal cell adenocarcinoma, hypernephroma, endometrial carcinoma, melanotic melanoma, leukemia, acute myeloid leukemia, Burkitt lymphoma, neuroblastoma, glioblastoma, retinoblastoma, rhabdomyosarcoma, chondrosarcoma, parathyroid tumors, insulinoma, adrenocorticoadenoma, pheochromocytomas, meningeomas

members is: Prx II = 52.98%, Prx III = 66.33%, Prx IV = 15.07%, Prx V = 18.98%, and Prx VI = 55.58%). EST clones for Prx I were found for almost all human and murine organs and tissues (see Table 1). EST clones for Prx I showed a particularly high representation in cDNA libraries made of mouse hypothalamus and primary Sertoli cell mRNA or human placenta, prostate tumor, and testis embryonal carcinoma, suggesting an important function of Prx I in these tissues. In addition, ESTs of Prx I were found in a large variety of different tumors, with the highest gene expression levels in prostate and embryonal testis tumors. The data agree with the widespread Prx tissue distribution in normal control animals and the high gene expression levels of different Prxs in tumor cell lines (3, 9, 14, 17, 24, 28, 32, 42, 44, 70, 71, 74, 75). Although mRNAs of Prxs are ubiquitously expressed, different members of the family exhibit a tissue-specific expression pattern. As an example, mRNA expression of Prx I was demonstrated at high levels in almost every tissue, whereas Prx IV exhibits a strong tissue-specific expression, with liver, pancreas, colon, prostate, testis, ovary, and muscle exhibiting high expression levels and small intestine, placenta, lung, kidney, spleen, and thymus lower expression levels (32).

Few morphological studies are available that deal with the quantitative analysis of Prx protein expression patterns in individual cell types of complex tissues and organs [skin, respiratory tract, brain (54); skin (40); nervous system (47); kidney (56); pancreatic β-cells (3); testis (39); lung (37); liver (24); prostate (75)]. In these studies, individual Prxs were found to have a characteristic cell type- and organ-specific expression pattern. It was shown that Prx I protein was widely expressed in various regions of the central and peripheral nervous system and exhibited a specific cell type-associated expression pattern (47). Prx I was particularly abundant in oligodendroglia cells and in Schwann cells, whereas astrocytes showed a weaker staining. Similarly, in rat liver, Prx I showed a broad expression in almost all cell types, with the highest staining intensities in sinusoidal lining cells (Kupffer cells, endothelial cells, and fat-storing cells) (24). Hepatocytes and bile duct epithelial cells were less strongly and heterogeneously labeled for Prx I. Lee and colleagues found that Prx I, II, and III were ubiquitously expressed in rat skin, however, with an isotype-specific expression pattern (40). In the epidermis, Prx I and II were expressed in all layers with increasing expression levels from the basal to the granular layer. Prx III was also expressed in all layers, however, with an opposite gradient (higher concentration in basal layers). After UV treatment, only Prx II showed a strong increase in the epidermis (40). Bast and coworkers demonstrated that Prx I and Prx II were present in pancreatic β-cells of the islets of Langerhans, whereas glucagon-producing cells were negative for these Prxs (3). Another example of the cell type-specific expression of distinct Prxs demonstrated that, in normal rat kidney, Prx I protein showed a moderate expression level in proximal and distal tubular cells, whereas Prx II, III, and V were strongly expressed in distal tubules. In addition, Prx V exhibited the highest expression level in the transitional epithelium, and red blood cells in glomeruli capillaries were intensively stained only for Prx II and IV (56). Similar distinct expression patterns for Prxs were reported for lung tissue (37) in which all six family members were mainly expressed in epithelial cells or in alveolar macrophages. In this respect, the bronchial epithelium showed a moderate to high expression of Prx I, III, V, and VI, and the alveolar epithelium mainly expressed Prx V and VI and alveolar macrophages Prx I and III (37).

SUBCELLULAR LOCALIZATION OF Prx PROTEINS

Cellular production of ROS occurs from both enzymatic and nonenzymatic sources. As ROS formation can occur as a "by-product" or as escape of electrons during electron transfer reactions in any electron-transfer system, ROS are produced due to normal cellular metabolism in a variety of subcellular localizations, such as in mitochondria (respiratory complexes), peroxisomes (several different peroxisomal oxidases and membrane proteins), smooth endoplasmic reticulum (cytochrome P450 and b5 families of proteins), nuclear membranes (cytochrome oxidases), and the cytoplasm (xanthine oxidase, aldehyde oxidase, dihydroorotate dehydrogenase, flavoprotein dehydrogenase, tryptophan dioxygenase) (76). Therefore, it is necessary that appropriate antioxidative systems are present at the sites of intracellular ROS production to protect against oxidative stress-mediated cell damage and to maintain the homeostasis of the cellular metabolic pathways. Due to the important function of antioxidative systems for normal life, different enzyme systems that are located at different subcellular sites occur simultaneously in the cell (72, 76). Whether these various enzymes have complementary functions for the metabolism of ROS in various subcellular compartments, however, is not understood completely.

Similar to glutathione peroxidases, Prxs are present in all subcellular compartments (for a review, see 83), but reports on the localization of Prxs in different subcellular compartments are controversial (24, 33, 56, 77, 83). This may be explained by the fact that distinct species, tissues, and cells have been used and different methods have been applied for studying the subcellular localization of Prxs. Indeed, by application of differential centrifugation for the isolation of crude organelles, which is applied mostly for biochemical studies dealing with the subcellular localization of Prxs, other organelles may "contaminate" the cell fractions used for western blotting. In addition, some of the organelles, such as peroxisomes, are sensitive to homogenization methods, and matrix proteins may leak and be found in the cytosolic fractions. In contrast, if antibodies are monospecific for individual Prx proteins, postembedding immunocytochemical localization is a reliable method for subcellular localization of the corresponding proteins. With this method, we were able to show in normal rat liver that Prx I is not only expressed in the cytoplasm and nucleus, but is also present in the matrix of mitochondria and in peroxisomes (Fig. 1). Therefore,

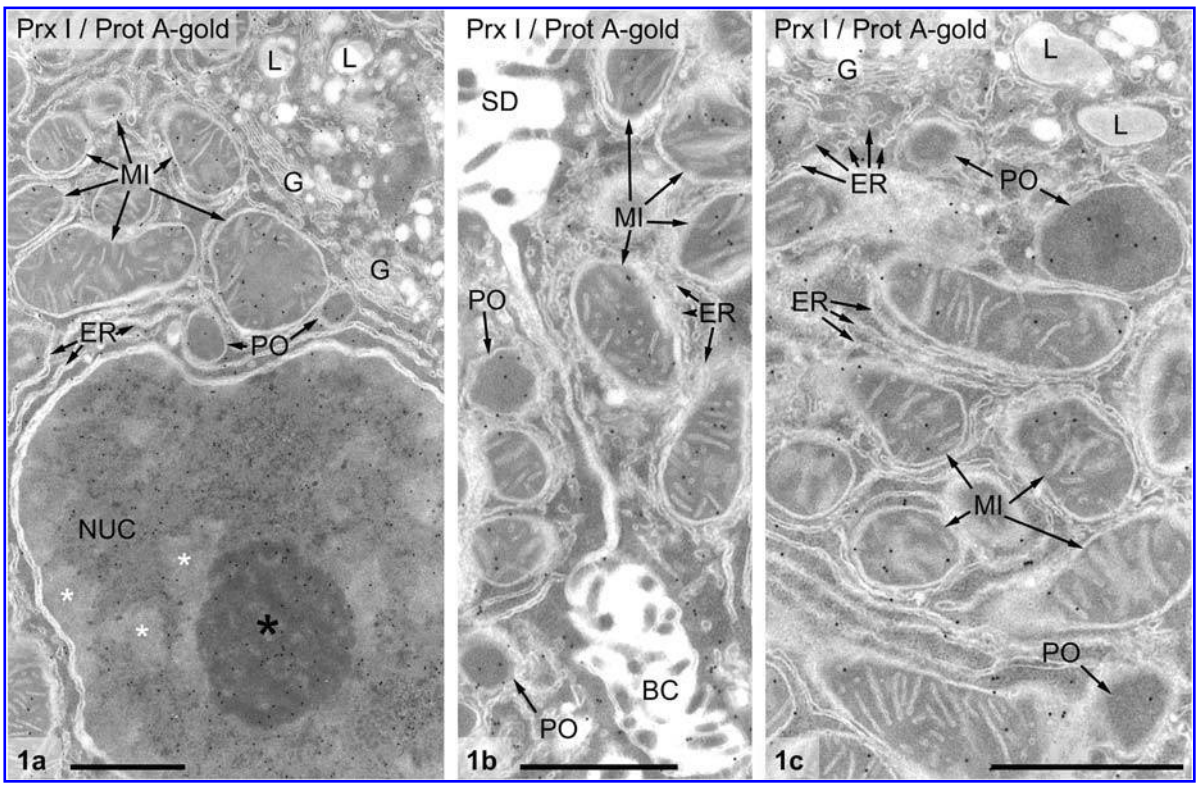

FIG. 1. Electron micrographs of hepatocytes depicting the subcellular localization of Prx I in rat liver (postembedding protein A-Gold method on LR White sections). (a) Low-magnification view of a hepatocyte showing the multicompartmental localization of Prx I in the nucleus (NUC), mitochondria (MI), peroxisomes (PO), and cytoplasm. In the nucleus, only the euchromatin and the nucleolus (large black asterisk) are labeled. Areas with heterochromatin (small white asterisks) are empty. Endoplasmic reticulum (ER), the Golgi apparatus (G), and lysosomes (L) are not labeled. Bar = 1 μm. **(b** and **c)** Two different higher magnification views of hepatocytes labeled for Prx I. Note the heterogeneous labeling of mitochondria (MI) and peroxisomes (PO). Cytoplasmic labeling is also seen in close vicinity to the outer surface of segments of the endoplasmic reticulum (ER). Lysosomes (L), the lumen of the bile canaliculus (BC), and the space of Disse (SD) are not labeled, showing the high specificity of the antibody reaction. Bars = 1 μm.

Prx I is not only the member of the Prx family with the widest tissue distribution, but is also widely distributed in intracellular organelles (24). In addition to Prx I, Prx V was found in various intracellular organelles, such as the cytoplasm, peroxisomes, mitochondria, and to a lesser extent the nucleus (2, 66).

In comparison with the wide intracellular distribution of Prx I and V, other Prxs exhibit a more restricted subcellular localization, such as Prx II, which is only present in the nucleus and the cytoplasm (83). Prx IV, which is actively secreted by the secretory apparatus, is present in the cytoplasm and in lysosomes (56, 83). The lysosomal localization of Prx IV in kidney tubules, however, could be interpreted as reuptake of this Prx from the extracellular space. The only Prxs located in a single compartment are Prx III (mitochondria) and Prx VI in the cytoplasm (56, 77, 83).

REGULATION OF Prx GENE EXPRESSION AND ACTIVITY

The regulation of Prx activity occurs at the level of gene expression and by posttranslational protein modification and has received a great deal of attention in recent reports.

Regulation of Prx gene expression

Prx I gene expression is up-regulated by a large variety of oxidative stress stimuli in mouse peritoneal macrophages (26). Similarly, it was also shown by others that Prx I gene expression was induced by the prooxidant heme and by various heavy metals in cultured hepatic cells (22), as well as by lipopolysaccharide (LPS) in rat liver tissue macrophages (Fig. 2) (23). In these studies, it was demonstrated that the induction of Prx I gene expression by the above-mentioned stress stimuli occurred in coordination with that of heme oxygenase-1. Heme oxygenase-1 is the inducible isoform of the rate-limiting enzyme of heme degradation and a well-known stress-inducible gene (46, 57). A parallel induction of Prx I and heme oxygenase-1 gene expression was also observed after exposure of cultured vascular smooth muscle cells to oxidized low-density lipoproteins (73) and in an *in vivo* rat model around hemorrhagic brain regions (50). Therefore, the coordinate induction of Prx I and heme oxygenase-1 seems to be a general adaptive response of the cell to protect against oxidative stress. In addition, stress-dependent induction of Prx gene expression has also been observed for other Prxs, such as Prx II or Prx VI (3, 36).

What are the molecular mechanisms that are involved in the transcriptional induction of Prx gene expression by oxidative stress? A major role for the regulation of Prx I gene expression by electrophilic and ROS-producing agents has been ascribed to the transcription factor NF-E2-related-factor 2 (Nrf2) (Fig. 2). Nrf2 is a key regulator of oxidative stress-dependent gene expression via its DNA-binding activity to the antioxidant response element (ARE) (52). In cultured peritoneal macrophages of Nrf2-deficient mice, Prx I gene expression was not induced by stress stimuli (29). The activity of Nrf2 was proposed to be mediated via the cytosolic protein Keap1, which interacts with the regulatory N-terminal domain of this transcription factor and may thus function as a crucial sensor system for oxidative stress. It was demonstrated that oxidative stress antagonized inhibition of Nrf2 by Keap1 and enhanced the shuttle of Nrf2 into the nucleus, thereby leading to Nrf2-mediated gene expression (30) (Fig. 2). Although Nrf2 is a key regulator of Prx I gene expression, other transcription factors are also involved in gene regulation of Prx I. It was shown that Prx I gene expression is transcriptionally up-regulated by the phorbol ester 12-*O*-tetradecanoylphorbol 13-acetate (TPA) via an AP-1-dependent mechanism by the interaction with TPA recognition elements of the rat Prx I gene promoter region (18) (Fig. 2).

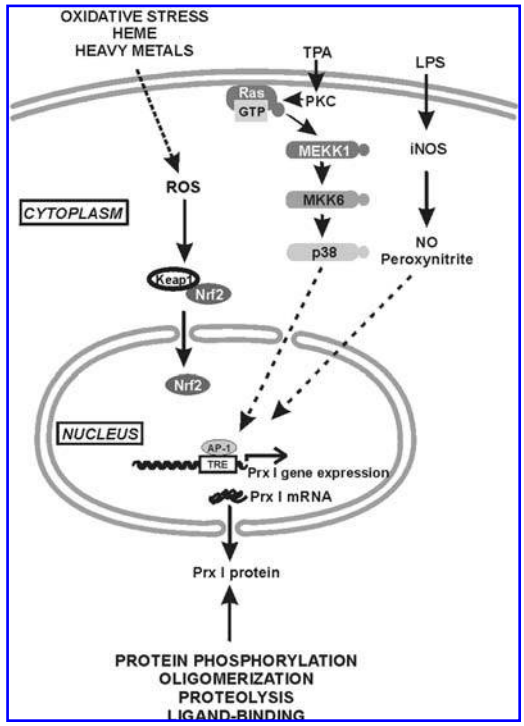

FIG. 2. Signal transduction pathways and molecular mechanisms of the regulation of Prx I gene expression and activity. Schematic representation of the known signaling cascades and molecular mechanisms that are involved in the regulation of Prx I gene expression and posttranslational modifications. iNOS, inducible nitric oxide synthase; MEKK1, MAPK/ERK kinase kinase; MKK, MAPK kinase; TRE, TPA response element.

Posttranslational mechanisms of Prx regulation

Prx activity is modified not only by the regulation of gene expression, but also by posttranslational mechanisms. These mechanisms comprise protein phosphorylation, redox-dependent oligomerization, proteolysis, and modification by ligand binding (Fig. 2). It was demonstrated that Prx I, II, III, and IV are phosphorylated at a threonine residue of a specific phosphorylation recognition sequence via the cyclin-dependent kinase Cdc2 (10). This Cdc2-mediated phosphorylation was shown to inhibit the peroxidase activity of Prxs. The potential mechanism(s) of how phosphorylation decreases peroxidase activity could be the introduction of a negatively charged phos-

phate group that may modulate the peroxidatic active site via an unfavorable electrostatic effect (10). Prxs also form dimers and decamers, which is facilitated by factors such as ionic strength or low pH. Oligomerization of Prxs seems to be primarily affected by changes of the redox-active disulfide center. A direct functional link of the redox state and oligomerization was reported for Prxs in bacteria (60, 81). Moreover, it was found that proteolysis of the C-terminal end of a typical 2-cysteine Prx led to a higher resistance to overoxidation and, subsequently, to an inactivation of peroxidase enzyme activity. The targeted truncation of 2-cysteine Prxs prevented the peroxide-mediated inactivation in response to increased peroxide levels (38). Prx activity can also be affected by ligands such as heme and cyclophilin A that noncovalently bind to these proteins. As mentioned, Prx I was initially identified as a heme-binding protein with high binding affinity for this tetrapyrrole (31). Others demonstrated that incubation of Prx I with heme markedly decreased the peroxidase activity of Prx I *in vitro* (27). In addition, Prx activity of Prx VI was shown to be increased by the interaction with cyclophilin A (41). In summary, the large variety of posttranslational modifications of Prxs and their functional consequences suggest a high versatility of these enzymes as regulators of the cellular redox homeostasis.

SIGNALING PATHWAYS INVOLVED IN THE REGULATION OF Prx ACTIVITY

Few reports have been published on the signal transduction pathways that are involved in the regulation of Prx gene expression and activity. LPS was shown to induce Prx I gene expression via a nitric oxide (NO)-dependent signaling cascade in cultured rat liver tissue macrophages (Fig. 2) possibly via the up-regulation of the inducible NO synthase (23). A regulatory role of a NO-dependent signaling pathway was shown by others for the induction of Prx I and II gene expression in a pancreatic islet cell line (3). In addition, activation of the protein kinase C (PKC) signaling cascade was found to mediate the induction of Prx I gene expression. PKC is a central signaling molecule involved in cellular redox-dependent signaling cascades (15). The PKC family contains at least 11 phospholipid-dependent serine-threonine kinases that are divided into three major categories according to the cofactors that are required for optimal catalytic activity (53). PKCδ was shown to mediate the posttranslational induction of Prx I expression by sodium arsenate in cultured osteoblast cells (44). More recently, it was also reported that PKC is involved in the induction of Prx I gene expression by the phorbol ester TPA in cultured macrophage cells (18). TPA-dependent induction of Prx I gene expression was found to be mediated via the small GTP-binding protein Ras, which in turn activates the downstream p38 MAPK signaling pathway (Fig. 2).

Prxs AND THE CELL CYCLE

It has been known for many years that cellular generation of ROS and the redox state of the cell play a crucial role for the regulation of the cell cycle and cell proliferation (for reviews, see 63, 67). Consequently, antioxidant enzymes such as glutathione peroxidase or MnSOD have been suggested to be involved in the regulation of the cell cycle (55). Evidence for a ROS-dependent regulation of the cell cycle was presented by Irani and colleagues (25). These authors demonstrated that overexpression of a constitutively active H-RasV12 mutant produced large amounts of ROS that mediated cell-cycle progression of fibroblast cell cultures. Cell-cycle progression in this experimental setting was inhibited by the chemical antioxidant *N*-acetyl-L-cysteine (25). In mouse embryo fibroblasts, it was found that the cellular levels of ROS correlated with the cell-cycle period and overexpressed MnSOD inhibited cell proliferation (45).

A link of Prx I to cell proliferation was presented in one of the early reports on Prx I. It was demonstrated that Prx I gene expression was markedly higher in Ras-transformed epithelial cells in comparison with control cells and, thus, was termed pag (58). The correlation of increased Prx I gene expression with cell proliferation was confirmed in the human promyelocytic cell line HL60, which can be stimulated to undergo growth arrest after treatment with dimethyl sulfoxide. In HL60 cells, Prx I gene expression decreased in a time-dependent manner upon exposure to dimethyl sulfoxide and was hardly detectable when these cells reached differentiation (58). In an attempt to distinguish the mechanisms of Prx I gene induction either by cell proliferation or by oxidative stress, a lymphoma cell line was used that can be stimulated to proliferate by treatment with prolactin (59). In this study, Prx I was shown to reach a maximum of gene expression when NB2 cells were in the S-phase after exposure to prolactin (Fig. 3). It still needs to be clarified, however, whether the up-regulation of Prx gene expression and the induction of cell proliferation by oxidative stress are directly linked.

Prx I was also demonstrated to interact with the oncogene products c-Abl and c-Myc, both of which play crucial roles for the regulation of cell proliferation. With a yeast two-hybrid screen, Prx I was identified to interact with the Src homology 3 domain of c-Abl (79) and to regulate the c-Abl tyrosine kinase activity. As the c-Abl Src homology 3 domain is assumed to suppress the intrinsic transforming ability of

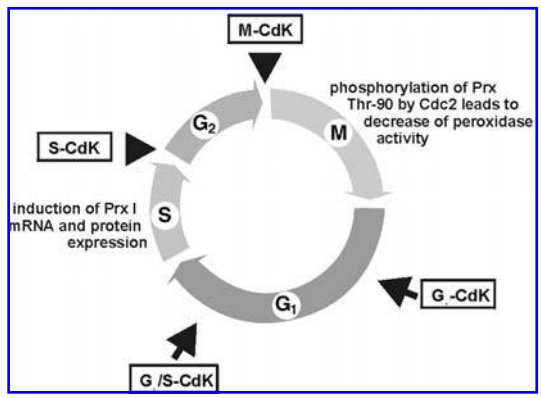

FIG. 3. A schematic representation of the four major cell-cycle periods and the cyclin/CdK complexes that regulate progression through each period. The known interactions of Prxs with the cell-cycle periods are indicated.

c-Abl, it is conceivable that the reversible interaction of Prx I with c-Abl may function as a key regulator of the cell cycle. Independently, Prx I was also found to bind to c-Myc, specifically to the highly conserved Myc box II of the c-Myc transactivating domain (49). Overexpression of Prx I was demonstrated to cause a marked increase of cell size in conjunction with protective effects against apoptosis during oxidative stress. Moreover, a number of specific c-Myc target genes were found to be down-regulated by overexpressed Prx I (49).

As mentioned above, Prxs were shown to be specifically phosphorylated at the threonine-90 residue via the cyclin-dependent kinase Cdc2 and, as a consequence, a decrease of the Prx peroxidase activity was observed (Fig. 3) (10). Phosphorylated Prx I was demonstrated to occur during mitosis, but not during the interphase. Therefore, it was proposed that the phosphorylation of Prx could be an important switch for the up-regulation of cellular levels of hydrogen peroxide, resulting in a progression of the cell cycle.

Prxs AND APOPTOSIS

Progression of the cell cycle and apoptosis are tightly interrelated processes, and deregulation of Cdc2 kinase activity in mammalian cells was shown to trigger the apoptotic machinery leading to caspase-3 activation and apoptosis (16). One of the cytokines reported to induce ROS during intracellular signaling is TNFα, which, in turn, induces apoptosis by binding to the death domain containing receptor TNFα receptor-1 (11). In this process, TNFα activates NF-κB, a transcription factor mediating also ROS-dependent gene activation (65, 76). Overexpression of Prx II was found to inhibit the activation of NF-κB after stimulation with extracellular added hydrogen peroxide (33), and overexpression of this protein in Molt-4 leukemia cells was protective against apoptosis by serum deprivation, ceramide, or etoposide (84). In this study, Prx II was also shown to prevent cytochrome *c* release from mitochondria and to inhibit lipid peroxidation. Therefore, it is interesting to note that only the mitochondrial overexpression of Prx V had beneficial effects on cells exposed to external peroxides (2). Furthermore, in rat hepatocytes, endogenous Prx I and Prx II expression levels were shown to be reduced during glycochenodeoxycholic acid-induced cell death mediated by ROS generation and NF-κB activation (12). In conclusion, it appears that high levels of Prxs inhibit apoptosis and induce cell proliferation.

Prxs AND CANCER

Oxidative stress plays a crucial role in the pathogenesis of various malignant tumors (1, 78). Carcinogenesis by oxidant stress appears to be caused mainly by excessive generation of ROS leading to structural changes of DNA, such as base-pair mutations, deletions, insertions, or rearrangements (21). Moreover, ROS may directly activate cytoplasmic and nuclear signal transduction pathways that are associated with malignant transformation (4). Therefore, antioxidant enzymes have been suggested to play a functional role in carcinogenesis. Indeed, it was previously demonstrated that overexpression of MnSOD inhibits the cellular proliferation of various cancer cell lines (55). Due to their peroxidase enzyme activity, Prxs may have a similar function. An important role of Prxs for carcinogenesis was suggested in a recent report in which Prx I knockout mice exhibited an increased frequency of malignant tumors such as lymphomas, sarcomas, and carcinomas (51). These authors also observed that murine embryonic fibroblasts from Prx I-deficient mice not only exhibited a lower survival rate after exposure to oxidative stress, but also had higher levels of endogenous ROS in response to peroxide treatment. Overall, the data of this report are consistent with an important role of Prx I as tumor suppressor.

SUMMARY AND CONCLUSIONS

Prxs are a family of multifunctional proteins that are involved in the cellular protection against oxidative stress, modulation of intracellular signaling, and regulation of cell proliferation. Prxs exhibit a cell- and tissue-specific gene expression pattern and are upregulated by oxidative stress stimuli. The important functions of Prxs in a variety of physiological and pathophysiological experimental models and in Prx knockout animals suggest that the regulation of these proteins may represent a novel target for therapeutic interventions. To achieve this goal, a more detailed understanding of the regulatory mechanisms and signaling pathways that control Prx gene expression and activity is necessary.

ACKNOWLEDGMENT S

We thank Dr. H. Dariush Fahimi (University of Heidelberg, Germany) for providing us with original negatives of electron micrographs for Prx I labeling. S.I. was supported by grant SFB 402 A8.

ABBREVIATIONS

AP-1, activator protein-1; EST, expressed sequence target; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MnSOD, manganese superoxide dismutase; NF-κB, nuclear factor-κB; NO, nitric oxide; Nrf2, NF-E2-related factor 2; pag, proliferation-associated gene; PKC, protein kinase C; Prx, peroxiredoxin; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol 13-acetate.

REFERENCES

1. Ames BN, Gold LS, and Willett WC. The causes and prevention of cancer. *Proc Natl Acad Sci U S A* 92: 5258–5265, 1995.
2. Banmeyer I, Marchand C, Verhaeghe C, Vucic B, Rees JF, and Knoops B. Overexpression of human peroxiredoxin 5 in subcellular compartments of Chinese hamster ovary

cells: effects on cytotoxicity and DNA damage caused by peroxides. *Free Radic Biol Med* 36: 65–77, 2004.
3. Bast A, Wolf G, Oberbaumer I, and Walther R. Oxidative and nitrosative stress induces peroxiredoxins in pancreatic beta cells. *Diabetologia* 45: 867–876, 2002.
4. Cerutti PA. Oxy-radicals and cancer. *Lancet* 344: 862–863, 1994.
5. Chae HZ, Kim IH, Kim K, and Rhee SG. Cloning, sequencing, and mutation of thiol-specific antioxidant gene of *Saccharomyces cerevisiae*. *J Biol Chem* 268: 16815–16821, 1993.
6. Chae HZ, Robison K, Poole LB, Church G, Storz G, and Rhee SG. Cloning and sequencing of thiol-specific antioxidant from mammalian brain: alkyl hydroperoxide reductase and thiol-specific antioxidant define a large family of antioxidant enzymes. *Proc Natl Acad Sci U S A* 91: 7017–7021, 1994.
7. Chae HZ, Uhm TB, and Rhee SG. Dimerization of thiol-specific antioxidant and the essential role of cysteine 47. *Proc Natl Acad Sci USA* 91: 7022–7026, 1994.
8. Chance B, Sies H, and Boveris A. Hydroperoxide metabolism in mammalian organs. *Physiol Rev* 59: 527–605, 1979.
9. Chang JW, Jeon HB, Lee JH, Yoo JS, Chun JS, Kim JH, and Yoo YJ. Augmented expression of peroxiredoxin I in lung cancer. *Biochem Biophys Res Commun* 289: 507–512, 2001.
10. Chang TS, Jeong W, Choi SY, Yu S, Kang SW, and Rhee SG. Regulation of peroxiredoxin I activity by Cdc2-mediated phosphorylation. *J Biol Chem* 277: 25370–25376, 2002.
11. Chen G and Goeddel DV. TNF-R1 signaling: a beautiful pathway. *Science* 296: 1634–1635, 2002.
12. Chu SH, Lee-Kang J, Lee KH, and Lee K. Roles of reactive oxygen species, NF-kappaB, and peroxiredoxins in glycochenodeoxycholic acid-induced rat hepatocytes death. *Pharmacology* 69: 12–19, 2003.
13. Finkel T. Oxygen radicals and signaling. *Curr Opin Cell Biol* 10: 248–253, 1998.
14. Fujii T, Fujii J, and Taniguchi N. Augmented expression of peroxiredoxin VI in rat lung and kidney after birth implies an antioxidative role. *Eur J Biochem* 268: 218–225, 2001.
15. Gopalakrishna R and Jaken S. Protein kinase C signaling and oxidative stress. *Free Radic Biol Med* 28: 1349–1361, 2000.
16. Gu L, Zheng H, Murray SA, Ying H, and Jim Xiao ZX. Deregulation of Cdc2 kinase induces caspase-3 activation and apoptosis. *Biochem Biophys Res Commun* 302: 384–391, 2003.
17. Haridas V, Ni J, Meager A, Su J, Yu GL, Zhai Y, Kyaw H, Akama KT, Hu J, Van Eldik LJ, and Aggarwal BB. TRANK, a novel cytokine that activates NF-kappa B and c-Jun N-terminal kinase. *J Immunol* 161: 1–6, 1998.
18. Hess A, Wijayanti N, Neuschäfer-Rube AP, Katz N, Kietzmann T, and Immenschuh S. Phorbol ester-dependent activation of peroxiredoxin I gene expression via a protein kinase C, Ras, p38 mitogen-activated protein kinase signaling pathway. *J Biol Chem* 278: 45419–45434, 2003.
19. Hirotsu S, Abe Y, Okada K, Nagahara N, Hori H, Nishino T, and Hakoshima T. Crystal structure of a multifunctional 2-Cys peroxiredoxin heme-binding protein 23 kDa/proliferation-associated gene product. *Proc Natl Acad Sci U S A* 96: 12333–12338, 1999.
20. Hofmann B, Hecht H-J, and Flohe L. Peroxiredoxins. *Biol Chem* 383: 347–364, 2002.
21. Imlay JA and Linn S. DNA damage and oxygen radical toxicity. *Science* 240: 1302–1309, 1988.
22. Immenschuh S, Iwahara S-I, Satoh H, Nell C, Katz N, and Muller-Eberhard U. Expression of the mRNA of heme-binding protein 23 is coordinated with that of heme oxygenase-1 by heme and heavy metals in primary rat hepatocytes and hepatoma cells. *Biochemistry* 34: 13407–13411, 1995.
23. Immenschuh S, Stritzke J, Iwahara S-I, and Ramadori G. Up-regulation of heme-binding protein 23 (HBP23) gene expression by lipopolysaccharide is mediated via a nitric oxide-dependent signaling pathway in rat Kupffer cells. *Hepatology* 30: 118–127, 1999.
24. Immenschuh S, Baumgart-Vogt E, Tan M, Iwahara S, Ramadori G, and Fahimi HD. Differential cellular and subcellular localization of heme-binding protein 23/peroxiredoxin I and heme oxygenase-1 in rat liver. *J Histochem Cytochem* 51: 1621–1631, 2003.
25. Irani K, Xia Y, Zweier JL, Sollott SJ, Der CJ, Fearon ER, Sundaresan M, Finkel T, and Goldschmidt-Clermont PJ. Mitogenic signaling mediated by oxidants in Ras-transformed fibroblasts. *Science* 275: 1649–1652, 1997.
26. Ishii T, Yamada M, Sato H, Matsue M, Taketani S, Nakayama K, Sugita Y, and Bannai S. Cloning and characterization of a 23-kDa stress induced mouse peritoneal macrophage protein. *J Biol Chem* 268: 18633–18636, 1993.
27. Ishii T, Kawane T, Taketani S, and Bannai S. Inhibition of the thiol-specific antioxidant activity of rat liver MSP23 protein by hemin. *Biochem Biophys Res Commun* 216: 970–975, 1995.
28. Ishii T, Itoh K, Akasaka J, Yanagawa T, Takahashi S, Yoshida H, Bannai S, and Yamamoto M. Induction of murine intestinal and hepatic peroxiredoxin MSP23 by dietary butylated hydroxyanisole. *Carcinogenesis* 21: 1013–1016, 2000.
29. Ishii T, Itoh K, Takahashi S, Sato H, Yanagawa T, Katoh Y, Bannai S, and Yamamoto M. Transcription factor Nrf2 coordinately regulates a group of oxidative stress-inducible genes in macrophages. *J Biol Chem* 275: 16023–16029, 2000.
30. Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD, and Yamamoto M. Keap1 represses nuclear activation of antioxidant response elements by Nrf2 through binding to the amino-terminal Neh2 domain. *Genes Dev* 13: 76–86, 1999.
31. Iwahara S, Satoh H, Song D-X, Webb J, Burlingame AL, Nagae Y, and Muller-Eberhard U. Purification, characterization and cloning of a heme-binding protein (23 kDa) in rat liver cytosol. *Biochemistry* 34: 13398–13406, 1995.
32. Jin DY, Chae HZ, Rhee SG, and Jeang KT. Regulatory role for a novel human thioredoxin peroxidase in NF-kappaB activation. *J Biol Chem* 272: 30952–30961, 1997.
33. Kang SW, Chae HZ, Seo MS, Kim K, Baines IC, and Rhee SG. Mammalian peroxiredoxin isoforms can reduce hydrogen peroxide generated in response to growth factors

and tumor necrosis factor-alpha. *J Biol Chem* 273: 6297–6302, 1998.
34. Kang SW, Chang TS, Lee TH, Kim ES, Yu DY, and Rhee SG. Cytosolic peroxiredoxin attenuates the activation of JNK and p38 but potentiates that of ERK in HeLa cells stimulated with tumor necrosis factor-α. *J Biol Chem* 279: 2535–2543, 2004.
35. Kim H, Lee TH, Park ES, Suh JM, Park SJ, Chung HK, Kwon OY, Kim YK, Ro HK, and Shong M. Role of peroxiredoxins in regulating intracellular hydrogen peroxide and hydrogen peroxide-induced apoptosis in thyroid cells. *J Biol Chem* 275: 18266–18270, 2000.
36. Kim HS, Manevich Y, Feinstein SI, Pak JH, Ho YS, and Fisher AB. Induction of 1-Cys peroxiredoxin expression by oxidative stress in lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 285: L363–L369, 2003.
37. Kinnula VL, Lehtonen S, Kaarteenaho-Wiik R, Lakari E, Paakko P, Kang SW, Rhee SG, and Soini Y. Cell specific expression of peroxiredoxins in human lung and pulmonary sarcoidosis. *Thorax* 57: 157–164, 2002.
38. Koo KH, Lee S, Jeong SY, Kim ET, Kim HJ, Kim K, Song K, and Chae HZ. Regulation of thioredoxin peroxidase activity by C-terminal truncation. *Arch Biochem Biophys* 397: 312–318, 2002.
39. Lee K, Park JS, Kim YJ, Soo Lee YS, Sook Hwang TS, Kim DJ, Park EM, and Park YM. Differential expression of Prx I and II in mouse testis and their up-regulation by radiation. *Biochem Biophys Res Commun* 296: 337–342, 2002.
40. Lee SC, Chae HZ, Lee JE, Kwon BD, Lee JB, Won YH, Ahn KY, and Kim YP. Peroxiredoxin is ubiquitously expressed in rat skin: isotype-specific expression in the epidermis and hair follicle. *J Invest Dermatol* 115: 1108–1114, 2000.
41. Lee SP, Hwang YS, Kim YJ, Kwon KS, Kim HJ, Kim K, and Chae HZ. Cyclophilin A binds to peroxiredoxins and activates its peroxidase activity. *J Biol Chem* 276: 29826–29832, 2001.
42. Lee TH, Yu SL, Kim SU, Lee KK, Rhee SG, and Yu DY. Characterization of mouse peroxiredoxin I genomic DNA and its expression. *Gene* 239: 243–250, 1999.
43. Lee TH, Kim SU, Yu SL, Kim SH, Park DS, Moon HB, Dho SH, Kwon KS, Kwon HJ, Han YH, Jeong S, Kang SW, Shin HS, Lee KK, Rhee SG, and Yu DY. Peroxiredoxin II is essential for sustaining life span of erythrocytes in mice. *Blood* 101: 5033–5038, 2003.
44. Li B, Ishii T, Tan CP, Soh JW, and Goff SP. Pathways of induction of peroxiredoxin I expression in osteoblasts: roles of p38 mitogen-activated protein kinase and protein kinase C. *J Biol Chem* 277: 12418–12422, 2002.
45. Li N and Oberley TD. Modulation of antioxidant enzymes, reactive oxygen species, and glutathione levels in manganese superoxide dismutase-overexpressing NIH/3T3 fibroblasts during the cell cycle. *J Cell Physiol* 177: 148–160, 1998.
46. Maines MD. The heme oxygenase system: a regulator of second messenger gases. *Annu Rev Pharmacol Toxicol* 37: 517–554, 1997.
47. Mizusawa H, Ishii T, and Bannai S. Peroxiredoxin I (macrophage 23 kDa stress protein) is highly and widely expressed in the rat nervous system. *Neurosci Lett* 283: 57–60, 2000.
48. Moore RB, Mankad MV, Shriver SK, Mankad VN, and Plishker GA. Reconstitution of Ca^{2+}-dependent K^+ transport in erythrocyte membrane vesicles requires a cytoplasmic protein. *J Biol Chem* 266: 18964–18968, 1991.
49. Mu ZM, Yin XY, and Prochownik EV. Pag, a putative tumor suppressor, interacts with the Myc box II domain of c-Myc and selectively alters its biological function and target gene expression. *J Biol Chem* 277: 43175–43184, 2002.
50. Nakaso K, Kitayama M, Mizuta E, Fukuda H, Ishii T, Nakashima K, and Yamada K. Co-induction of heme oxygenase-1 and peroxiredoxin I in astrocytes and microglia around hemorrhagic region in the rat brain. *Neurosci Lett* 293: 49–52, 2000.
51. Neumann CA, Krause DS, Carman CV, Das S, Dubey DP, Abraham JL, Bronson RT, Fujiwara Y, Orkin SH, and Van Etten RA. Essential role for the peroxiredoxin Prdx1 in erythrocyte antioxidant defence and tumour suppression. *Nature* 424: 561–565, 2003.
52. Nguyen T, Sherratt PJ, and Pickett CB. Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. *Annu Rev Pharmacol Toxicol* 43: 233–260, 2003.
53. Nishizuka Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. *Science* 258: 607–614, 1992.
54. Novoselov SV, Peshenko IV, Popov VI, Novoselov VI, Bystrova MF, Evdokimov VJ, Kamzalov SS, Merkulova MI, Shuvaeva TM, Lipkin VM, and Fesenko EE. Localization of 28-kDa peroxiredoxin in rat epithelial tissues and its antioxidant properties. *Cell Tissue Res* 298: 471–480, 1999.
55. Oberley TD. Oxidative damage and cancer. *Am J Pathol* 160: 403–408, 2002.
56. Oberley TD, Verwiebe E, Zhong W, Kang SW, and Rhee SG. Localization of the thioredoxin system in normal rat kidney. *Free Radic Biol Med* 30: 412–424, 2001.
57. Otterbein LE and Choi AM. Heme oxygenase: colors of defense against cellular stress. *Am J Physiol Lung Cell Mol Physiol* 279: L1029–L1037, 2000.
58. Prosperi MT, Ferbus D, Karczinski I, and Goubin G. A human cDNA corresponding to a gene overexpressed during cell proliferation encodes a product sharing homology with amoebic and bacterial proteins. *J Biol Chem* 268: 11050–11056, 1993.
59. Prosperi MT, Ferbus D, Rouillard D, and Goubin G. The pag gene product, a physiological inhibitor of c-abl tyrosine kinase, is overexpressed in cells entering S phase and by contact with agents inducing oxidative stress. *FEBS Lett* 423: 39–44, 1998.
60. Reynolds CM, Meyer J, and Poole LB. An NADH-dependent bacterial thioredoxin reductase-like protein in conjunction with a glutaredoxin homologue form a unique peroxiredoxin (AhpC) reducing system in *Clostridium pasteurianum*. *Biochemistry* 41: 1990–2001, 2002.
61. Rhee SG, Kang SW, Netto LE, Seo MS, and Stadtman ER. A family of novel peroxidases, peroxiredoxins. *Biofactors* 10: 207–209, 1999.
62. Rhee SG, Chang TS, Bae YS, Lee SR, and Kang SW. Cellular regulation by hydrogen peroxide. *J Am Soc Nephrol* 14: S211–S215, 2003.

63. Sauer H, Wartenberg M, and Hescheler J. Reactive oxygen species as intracellular messengers during cell growth and differentiation. *Cell Physiol Biochem* 11: 173–186, 2001.
64. Scandalios JG. *Oxidative Stress and the Molecular Biology of Antioxidant Defenses*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1997.
65. Schreck R, Rieber P, and Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappaB transcription factor and HIV-1. *EMBO J* 10: 2247–2258, 1991.
66. Seo MS, Kang SW, Kim K, Baines IC, Lee TH, and Rhee SG. Identification of a new type of mammalian peroxiredoxin that forms an intramolecular disulfide as a reaction intermediate. *J Biol Chem* 275: 20346–20354, 2000.
67. Shackelford RE, Kaufmann WK, and Paules RS. Oxidative stress and cell cycle checkpoint function. *Free Radic Biol Med* 28: 1387–1404, 2000.
68. Shau H, Gupta RK, and Golub SH. Identification of a natural killer enhancing factor (NKEF) from human erythroid cells. *Cell Immunol* 147: 1–11, 1993.
69. Shau H, Butterfield LH, Chiu R, and Kim A. Cloning and sequence of candidate human natural killer-enhancing factor genes. *Immunogenetics* 40: 129–134, 1994.
70. Shau H, Huang AC, Faris M, Nazarian R, de Vellis J, and Chen W. Thioredoxin peroxidase (natural killer enhancing factor) regulation of activator protein-1 function in endothelial cells. *Biochem Biophys Res Commun* 249: 683–686, 1998.
71. Shin DH, Fujiki K, Nakao M, and Yano T. Organization of the NKEF gene and its expression in the common carp (*Cyprinus carpio*). *Dev Comp Immunol* 25: 597–606, 2001.
72. Singh I. Mammalian peroxisomes: metabolism of oxygen and reactive oxygen species. *Ann N Y Acad Sci* 804: 612–627, 1996.
73. Siow RCM, Ishii T, Sato H, Taketani S, Leake DS, Sweiry JH, Pearson JD, Bannai S, and Mann GE. Induction of the antioxidant stress proteins heme oxygenase-1 and MSP23 by stress agents and oxidised LDL in cultured vascular smooth muscle cells. *FEBS Lett* 368: 239–242, 1995.
74. Sparling NE and Phelan SA. Identification of multiple transcripts for antioxidant protein 2 (Aop2): differential regulation by oxidative stress and growth factors. *Redox Rep* 8: 87–94, 2003.
75. Tam NNC, Gao Y, Leung Y-K, and Ho S-M. Androgenic regulation of oxidative stress in the rat prostate. Involvement of NAD(P)H oxidases and antioxidant defense machinery during prostatic involution and regrowth. *Am J Pathol* 163: 2513–2522, 2003.
76. Thannickal VJ and Fanburg BL. Reactive oxygen species in cell signaling. *Am J Physiol Lung Cell Mol Physiol* 279: L1005–L1028, 2000.
77. Wang X, Phelan SA, Forsman-Semb K, Taylor EF, Petros C, Brown A, Lerner CP, and Paigen B. Mice with targeted mutation of peroxiredoxin 6 develop normally but are susceptible to oxidative stress. *J Biol Chem* 278: 25179–25190, 2003.
78. Weitzman SA and Gordon LI. Inflammation and cancer: role of phagocyte-generated oxidants in carcinogenesis. *Blood* 76: 655–663, 1990.
79. Wen S-T and Van Etten RA. The pag gene product, a stress-induced protein with antioxidant properties, is an Abl SH3-binding protein and a physiological inhibitor of c-Abl tyrosine kinase activity. *Genes Dev* 11: 2456–2467, 1997.
80. Woo HA, Chae HZ, Hwang SC, Yang KS, Kang SW, Kim K, and Rhee SG. Reversing the inactivation of peroxiredoxins caused by cysteine sulfinic acid formation. *Science* 300: 653–656, 2003.
81. Wood ZA, Poole LB, Hantgan RR, and Karplus PA. Dimers to doughnuts: redox-sensitive oligomerization of 2-cysteine peroxiredoxins. *Biochemistry* 41: 5493–5504, 2002.
82. Wood ZA, Poole LB, and Karplus PA. Peroxiredoxin evolution and the regulation of hydrogen peroxide signaling. *Science* 300: 650–653, 2003.
83. Wood ZA, Schroder E, Harris JR, and Poole LB. Structure, mechanism and regulation of peroxiredoxins. *Trends Biochem Sci* 28: 32–40, 2003.
84. Zhang P, Liu B, Kang SW, Seo MS, Rhee SG, and Obeid LM. Thioredoxin peroxidase is a novel inhibitor of apoptosis with a mechanism distinct from that of Bcl-2. *J Biol Chem* 272: 30615–30618, 1997.

Address reprint requests to:
Stephan Immenschuh, M.D.
Institut für Klinische Immunologie und Transfusionsmedizin
Justus-Liebig-Universität Giessen
Langhansstr. 7
35392 Giessen, Germany

E-mail: Stephan.Immenschuh@immunologie.med.uni-giessen.de

Received for publication September 3, 2004; accepted November 30, 2004.

This article has been cited by:

1. Magnus G. Olsson , Maria Allhorn , Leif Bülow , Stefan R. Hansson , David Ley , Martin L. Olsson , Artur Schmidtchen , Bo Åkerström . 2012. Pathological Conditions Involving Extracellular Hemoglobin: Molecular Mechanisms, Clinical Significance, and Novel Therapeutic Opportunities for #1-Microglobulin. *Antioxidants & Redox Signaling* **17**:5, 813-846. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
2. S. Yan, S. Chen, Z. Li, H. Wang, T. Huang, X. Wang, J. Wang. 2012. Biochemical characterization of human peroxiredoxin 2, an antioxidative protein. *Acta Biochimica et Biophysica Sinica* **44**:9, 759-764. [CrossRef]
3. Hongqiao Zhang, Henry Jay Forman. 2012. Glutathione synthesis and its role in redox signaling. *Seminars in Cell & Developmental Biology* **23**:7, 722-728. [CrossRef]
4. Catherine Putonti, Bryan Quach, Rachel A. Kooistra, Stefan M. Kanzok. 2012. The evolution and putative function of phosducin-like proteins in the malaria parasite Plasmodium. *Infection, Genetics and Evolution* . [CrossRef]
5. Young-Eun Cho, Sang-Hyun Kim, Moon-Chang Baek. 2012. Proteome profiling of tolbutamide-treated rat primary hepatocytes using nano LC-MS/MS and label-free protein quantitation. *ELECTROPHORESIS* **33**:18, 2806-2817. [CrossRef]
6. Qian Liu, Xiaoping Zhao, Xiaoyan Lu, Xiaohui Fan, Yi Wang. 2012. Proteomic Study on Usnic-Acid-Induced Hepatotoxicity in Rats. *Journal of Agricultural and Food Chemistry* **60**:29, 7312-7317. [CrossRef]
7. L M Dittmann, A Danner, J Gronych, M Wolter, K Stühler, M Grzendowski, N Becker, J Bageritz, V Goidts, G Toedt, J Felsberg, M C Sabel, S Barbus, G Reifenberger, P Lichter, B Tews. 2012. Downregulation of PRDX1 by promoter hypermethylation is frequent in 1p/19q-deleted oligodendroglial tumours and increases radio- and chemosensitivity of Hs683 glioma cells in vitro. *Oncogene* **31**:29, 3409-3418. [CrossRef]
8. Xingang Yuan, Liling Liu, Yalan Pu, Xuan Zhang, Xiaomeng He, Yuexian Fu. 2012. 2,3,7,8-Tetrachlorodibenzo-p-dioxin induces a proteomic pattern that defines cleft palate formation in mice. *Food and Chemical Toxicology* **50**:7, 2270-2274. [CrossRef]
9. Tae-Ho Kwon, Ying-Hao Han, So Gun Hong, Doo Jae Lee, Hye-Lin Ha, Sang Won Kang, Wei Li, Do Young Yoon, Dae-Yeul Yu. 2012. Reactive oxygen species mediated DNA damage is essential for abnormal erythropoiesis in peroxiredoxin II -/- mice. *Biochemical and Biophysical Research Communications* **424**:1, 189-195. [CrossRef]
10. Fei Yin , Harsh Sancheti , Enrique Cadenas . Mitochondrial Thiols in the Regulation of Cell Death Pathways. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
11. Hyeran Won , Sangbin Lim , Miran Jang , Yeonghwan Kim , Md Abdur Rashid , K.R. Jyothi , Amarjargal Dashdorj , Insug Kang , Joohun Ha , Sung Soo Kim . 2012. Peroxiredoxin-2 Upregulated by NF-#B Attenuates Oxidative Stress During the Differentiation of Muscle-Derived C2C12 Cells. *Antioxidants & Redox Signaling* **16**:3, 245-261. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
12. Jose Antonio Reales-Calderón, Laura Martínez-Solano, Montserrat Martínez-Gomariz, César Nombela, Gloria Molero, Concha Gil. 2012. Sub-proteomic study on macrophage response to Candida albicans unravels new proteins involved in the host defense against the fungus. *Journal of Proteomics* . [CrossRef]
13. Kevin Goncalves, Katie Sullivan, Shelley Phelan. 2012. Differential Expression and Function of Peroxiredoxin 1 and Peroxiredoxin 6 in Cancerous MCF-7 and Noncancerous MCF-10A Breast Epithelial Cells. *Cancer Investigation* **30**:1, 38-47. [CrossRef]
14. Chia-Yen Hsiao, Ching-Yi Hung, Tung-Hu Tsai, Kin-Fu Chak. 2012. A Study of the Wound Healing Mechanism of a Traditional Chinese Medicine, Angelica sinensis, Using a Proteomic Approach. *Evidence-Based Complementary and Alternative Medicine* **2012**, 1-14. [CrossRef]
15. Hongqiao Zhang, Henry Jay Forman. 2012. Glutathione synthesis and its role in redox signaling. *Seminars in Cell & Developmental Biology* . [CrossRef]
16. Regina Brigelius-Flohé , Leopold Flohé . 2011. Basic Principles and Emerging Concepts in the Redox Control of Transcription Factors. *Antioxidants & Redox Signaling* **15**:8, 2335-2381. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
17. Takumi Satoh, Tayebeh Rezaie, Masaaki Seki, Carmen R. Sunico, Takahito Tabuchi, Tomomi Kitagawa, Mika Yanagitai, Mutsumi Senzaki, Chihiro Kosegawa, Hideharu Taira, Scott R. McKercher, Jennifer K. Hoffman, Gregory P. Roth, Stuart A. Lipton. 2011. Dual neuroprotective pathways of a pro-electrophilic compound via HSF-1-activated heat-shock proteins and Nrf2-activated phase 2 antioxidant response enzymes. *Journal of Neurochemistry* no-no. [CrossRef]

18. Marilize Roes-Hill, Nuraan Khan, Stephanie Gail Burton. 2011. Actinobacterial Peroxidases: an Unexplored Resource for Biocatalysis. *Applied Biochemistry and Biotechnology* **164**:5, 681-713. [CrossRef]
19. Kahina Abbas, Jacques Breton, Anne-Gaelle Planson, Cécile Bouton, Jérome Bignon, Cendrine Seguin, Sylvie Riquier, Michel B. Toledano, Jean-Claude Drapier. 2011. Nitric oxide activates an Nrf2/sulfiredoxin antioxidant pathway in macrophages. *Free Radical Biology and Medicine* **51**:1, 107-114. [CrossRef]
20. F. Yu, M. Kang, F. Meng, X. Guo, B. Xu. 2011. Molecular cloning and characterization of a thioredoxin peroxidase gene from Apis cerana cerana. *Insect Molecular Biology* **20**:3, 367-378. [CrossRef]
21. Anamika Basu, Hiya Banerjee, Heather Rojas, Shannalee R. Martinez, Sourav Roy, Zhenyu Jia, Michael B. Lilly, Marino De León, Carlos A. Casiano. 2011. Differential expression of peroxiredoxins in prostate cancer: Consistent upregulation of PRDX3 and PRDX4. *The Prostate* **71**:7, 755-765. [CrossRef]
22. Géraldine Dubreuil, Emeline Deleury, Marc Magliano, Maëlle Jaouannet, Pierre Abad, Marie-Noëlle Rosso. 2011. Peroxiredoxins from the plant parasitic root-knot nematode, Meloidogyne incognita, are required for successful development within the host. *International Journal for Parasitology* **41**:3-4, 385-396. [CrossRef]
23. Pascal Dammeyer, Elias S.J. Arnér. 2011. Human Protein Atlas of redox systems — What can be learnt?. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1810**:1, 111-138. [CrossRef]
24. Yu-Il Lee, Woo-Dae Kang, Mi-Young Kim, Moon-Kyoung Cho, Sang-Young Chun. 2011. Expression of peroxiredoxin I regulated by gonadotropins in the rat ovary. *Clinical and Experimental Reproductive Medicine* **38**:1, 18. [CrossRef]
25. Marilisa Sulpizio, Stefano Falone, Fernanda Amicarelli, Marco Marchisio, Fabrizio Di Giuseppe, Enrica Eleuterio, Carmine Di Ilio, Stefania Angelucci. 2011. Molecular basis underlying the biological effects elicited by extremely low-frequency magnetic field (ELF-MF) on neuroblastoma cells. *Journal of Cellular Biochemistry* n/a-n/a. [CrossRef]
26. Antje Bast, Saskia F. Erttmann, Reinhard Walther, Ivo Steinmetz. 2010. Influence of iNOS and COX on peroxiredoxin gene expression in primary macrophages. *Free Radical Biology and Medicine* **49**:12, 1881-1891. [CrossRef]
27. Milena Bertolotti , Sun Hee Yim , Jose M. Garcia-Manteiga , Silvia Masciarelli , Yoo-Jin Kim , Min-Hee Kang , Yoshihito Iuchi , Junichi Fujii , Roberta Vené , Anna Rubartelli , Sue Goo Rhee , Roberto Sitia . 2010. B- to Plasma-Cell Terminal Differentiation Entails Oxidative Stress and Profound Reshaping of the Antioxidant Responses. *Antioxidants & Redox Signaling* **13**:8, 1133-1144. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
28. Victor T.K. Chen, Chuen-Lin Huang, Yi-Chao Lee, Wei-Chen Liao, Nai-Kuei Huang. 2010. The roles of the thioredoxin system and peroxiredoxins in 1-methyl-4-phenyl-pyridinium ion-induced cytotoxicity in rat pheochromocytoma cells. *Toxicology in Vitro* **24**:6, 1577-1583. [CrossRef]
29. S. Reuter, S. Reiermann, R. Worner, R. Schroter, B. Edemir, F. Buck, S. Henning, J. Peter-Katalinic, B. Vollenbroker, K. Amann, H. Pavenstadt, E. Schlatter, G. Gabriels. 2010. IF/TA-related metabolic changes--proteome analysis of rat renal allografts. *Nephrology Dialysis Transplantation* **25**:8, 2492-2501. [CrossRef]
30. Lei Cui, Fang Li, Qingchuan Zhao, Zhili Li. 2010. Screening and Verification of Differentially Expressed Proteins from Pancreatic Cancer Tissue. *Chinese Journal of Chemistry* **28**:6, 884-890. [CrossRef]
31. 2010. Induction of peroxiredoxin I gene expression by LPS involves the Src/PI3K/JNK signalling pathway. *Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms* **1799**:5-6, 402-410. [CrossRef]
32. Ana P. D. Demasi, Ana F. Costa, Albina Altemani, Cristiane Furuse, Ney S. Araújo, Vera C. Araújo. 2010. Glucose transporter protein 1 expression in mucoepidermoid carcinoma of salivary gland: correlation with grade of malignancy. *International Journal of Experimental Pathology* **91**:2, 107-113. [CrossRef]
33. Ji-Sun Kim, Mi-Ae Bang, Song-Mi Lee, Ho-Zoon Chae, Kang-Hwa Kim. 2010. Distinct functional roles of peroxiredoxin isozymes and glutathione peroxidase from fission yeast, Schizosaccharomyces pombe. *BMB Reports* **43**:3, 170-175. [CrossRef]
34. Raffaella Gozzelino, Viktoria Jeney, Miguel P. Soares. 2010. Mechanisms of Cell Protection by Heme Oxygenase-1. *Annual Review of Pharmacology and Toxicology* **50**:1, 323-354. [CrossRef]
35. Suzy A.A. Comhair , Serpil C. Erzurum . 2010. Redox Control of Asthma: Molecular Mechanisms and Therapeutic Opportunities. *Antioxidants & Redox Signaling* **12**:1, 93-124. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
36. Jhang Ho Pak, Ju Hyun Moon, Seung-Jun Hwang, Shin-Hyeong Cho, Sang-Beom Seo, Tong-Soo Kim. 2009. Proteomic analysis of differentially expressed proteins in human cholangiocarcinoma cells treated with Clonorchis sinensis excretoryâsecretory products. *Journal of Cellular Biochemistry* **108**:6, 1376-1388. [CrossRef]

37. Seung Bum Lee, Jin-Nyoung Ho, Sung Hwan Yoon, Ga Young Kang, Sang-Gu Hwang, Hong-Duck Um. 2009. Peroxiredoxin 6 promotes lung cancer cell invasion by inducing urokinase-type plasminogen activator via p38 kinase, phosphoinositide 3-kinase, and Akt. *Molecules and Cells* **28**:6, 583-588. [CrossRef]
38. Maja Ludvigsen, Christian Jacobsen, Arvid B. Maunsbach, Bent Honoré. 2009. Identification and characterization of novel ERC-55 interacting proteins: Evidence for the existence of several ERC-55 splicing variants; including the cytosolic ERC-55-C. *PROTEOMICS* **9**:23, 5267-5287. [CrossRef]
39. Md. Kaimul Ahsan , Istvan Lekli , Diptarka Ray , Junji Yodoi , Dipak K. Das . 2009. Redox Regulation of Cell Survival by the Thioredoxin Superfamily: An Implication of Redox Gene Therapy in the Heart. *Antioxidants & Redox Signaling* **11**:11, 2741-2758. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
40. T. M. Shuvaeva, V. I. Novoselov, E. E. Fesenko, V. M. Lipkin. 2009. Peroxiredoxins, a new family of antioxidant proteins. *Russian Journal of Bioorganic Chemistry* **35**:5, 523-537. [CrossRef]
41. Pablo E. Vivas-Mejía, Bulent Ozpolat, Xian Chen, Gabriel Lopez-Berestein. 2009. Downregulation of the c-MYC target gene, peroxiredoxin III, contributes to arsenic trioxide-induced apoptosis in acute promyelocytic leukemia. *International Journal of Cancer* **125**:2, 264-275. [CrossRef]
42. Nina A. Bonekamp, Alfred Völkl, H. Dariush Fahimi, Michael Schrader. 2009. Reactive oxygen species and peroxisomes: Struggling for balance. *BioFactors* **35**:4, 346-355. [CrossRef]
43. Ana P. D. Demasi, Cristiane Furuse, Albina Altemani, José L. C. Junqueira, Paulo R. G. Oliveira, Vera C. Araújo. 2009. Peroxiredoxin I is overexpressed in oncocytic lesions of salivary glands. *Journal of Oral Pathology & Medicine* **38**:6, 514-517. [CrossRef]
44. Martin Aran, Diego S. Ferrero, Eduardo Pagano, Ricardo A. Wolosiuk. 2009. Typical 2-Cys peroxiredoxins - modulation by covalent transformations and noncovalent interactions. *FEBS Journal* **276**:9, 2478-2493. [CrossRef]
45. Srikanth Karnati, Eveline Baumgart-Vogt. 2009. Peroxisomes in airway epithelia and future prospects of these organelles for pulmonary cell biology. *Histochemistry and Cell Biology* **131**:4, 447-454. [CrossRef]
46. Francesc X. Soriano, Paul Baxter, Lyndsay M. Murray, Michael B. Sporn, Thomas H. Gillingwater, Giles E. Hardingham. 2009. Transcriptional regulation of the AP-1 and Nrf2 target gene sulfiredoxin. *Molecules and Cells* **27**:3, 279-282. [CrossRef]
47. Frank J. Berendt, Thomas Fröhlich, Patrick Bolbrinker, Marc Boelhauve, Tuna Güngör, Felix A. Habermann, Eckhard Wolf, Georg J. Arnold. 2009. Highly sensitive saturation labeling reveals changes in abundance of cell cycle-associated proteins and redox enzyme variants during oocyte maturation in vitro. *PROTEOMICS* **9**:3, 550-564. [CrossRef]
48. E. V. Kalinina, N. N. Chernov, A. N. Saprin. 2008. Involvement of thio-, peroxi-, and glutaredoxins in cellular redox-dependent processes. *Biochemistry (Moscow)* **73**:13, 1493-1510. [CrossRef]
49. Kahina Abbas, Jacques Breton, Jean-Claude Drapier. 2008. The interplay between nitric oxide and peroxiredoxins. *Immunobiology* **213**:9-10, 815-822. [CrossRef]
50. Agnese Viganò, Marilena Ripamonti, Sara De Palma, Daniele Capitanio, Michele Vasso, Robin Wait, Carsten Lundby, Paolo Cerretelli, Cecilia Gelfi. 2008. Proteins modulation in human skeletal muscle in the early phase of adaptation to hypobaric hypoxia. *PROTEOMICS* **8**:22, 4668-4679. [CrossRef]
51. Y GO, D JONES. 2008. Redox compartmentalization in eukaryotic cells. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1273-1290. [CrossRef]
52. Francesc X. Soriano, Frédéric Léveillé, Sofia Papadia, Larry G. Higgins, James Varley, Paul Baxter, John D. Hayes, Giles E. Hardingham. 2008. Induction of sulfiredoxin expression and reduction of peroxiredoxin hyperoxidation by the neuroprotective Nrf2 activator 3H-1,2-dithiole-3-thione. *Journal of Neurochemistry* **107**:2, 533-543. [CrossRef]
53. Eda Bener Aksam, Helmut Jungwirth, Sepp D. Kohlwein, Julia Ring, Frank Madeo, Marten Veenhuis, Ida J. van der Klei. 2008. Absence of the peroxiredoxin Pmp20 causes peroxisomal protein leakage and necrotic cell death. *Free Radical Biology and Medicine* **45**:8, 1115-1124. [CrossRef]
54. Byungki Jang, Eunah Kim, Jin-Kyu Choi, Jae-Kwang Jin, Jae-Il Kim, Akihito Ishigami, Naoki Maruyama, Richard I. Carp, Yong-Sun Kim, Eun-Kyoung Choi. 2008. Accumulation of Citrullinated Proteins by Up-Regulated Peptidylarginine Deiminase 2 in Brains of Scrapie-Infected Mice. *The American Journal of Pathology* **173**:4, 1129-1142. [CrossRef]
55. Claudia Röhl, Elisabeth Armbrust, Karola Kolbe, Ralph Lucius, Edmund Maser, Simone Venz, Michael Gülden. 2008. Activated microglia modulate astroglial enzymes involved in oxidative and inflammatory stress and increase the resistance of astrocytes to oxidative stressin Vitro. *Glia* **56**:10, 1114-1126. [CrossRef]

56. Gerty Schreibelt, Jack van Horssen, Reiner F. Haseloff, Arie Reijerkerk, Susanne M.A. van der Pol, Orm Nieuwenhuizen, Eberhard Krause, Ingolf E. Blasig, Christine D. Dijkstra, Eric Ronken, Helga E. de Vries. 2008. Protective effects of peroxiredoxin-1 at the injured blood–brain barrier. *Free Radical Biology and Medicine* **45**:3, 256-264. [CrossRef]
57. R. B. Parmigiani, W. S. Xu, G. Venta-Perez, H. Erdjument-Bromage, M. Yaneva, P. Tempst, P. A. Marks. 2008. HDAC6 is a specific deacetylase of peroxiredoxins and is involved in redox regulation. *Proceedings of the National Academy of Sciences* **105**:28, 9633-9638. [CrossRef]
58. Zhongmin Zou, Huiqin Sun, Yongping Su, Tianmin Cheng, Chengji Luo. 2008. Progress in Research on Radiation Combined Injury in China. *Radiation Research* **169**:6, 722-729. [CrossRef]
59. Yuan Li, Xue Qin, Jiefeng Cui, Zhi Dai, Xiaonan Kang, Haiying Yue, Yu Zhang, Jianjia Su, Ji Cao, Chao Ou, Chun Yang, Xiaoxian Duan, Huifen Yue, Yinkun Liu. 2008. Proteome analysis of aflatoxin B1-induced hepatocarcinogenesis in tree shrew (Tupaia belangeri chinensis) and functional identification of candidate protein peroxiredoxin II. *PROTEOMICS* **8**:7, 1490-1501. [CrossRef]
60. Douglas B. Vasey, C. Roland Wolf, Thomas MacArtney, Ken Brown, C. Bruce A. Whitelaw. 2008. p21-LacZ reporter mice reflect p53-dependent toxic insult. *Toxicology and Applied Pharmacology* **227**:3, 440-450. [CrossRef]
61. J CHAE, Y CHO, S CHO, J KIM, Y HAN, D KOO, K LEE. 2008. Proteomic analysis of pancreas derived from adult cloned pig. *Biochemical and Biophysical Research Communications* **366**:2, 379-387. [CrossRef]
62. Nastiti Wijayanti, Srivatsava Naidu, Thomas Kietzmann, Stephan Immenschuh. 2008. Inhibition of phorbol ester-dependent peroxiredoxin I gene activation by lipopolysaccharide via phosphorylation of RelA/p65 at serine 276 in monocytes. *Free Radical Biology and Medicine* **44**:4, 699-710. [CrossRef]
63. Filomena G. Ottaviano, Diane E. Handy, Joseph Loscalzo. 2008. Redox Regulation in the Extracellular Environment. *Circulation Journal* **72**:1, 1-16. [CrossRef]
64. Radhika A. Vaishnav, Marilyn L. Getchell, Liping Huang, Matthew A. Hersh, Arnold J. Stromberg, Thomas V. Getchell. 2008. Cellular and molecular characterization of oxidative stress in olfactory epithelium of Harlequin mutant mouse. *Journal of Neuroscience Research* **86**:1, 165-182. [CrossRef]
65. T.-B. Kim, S. Y. Kim, K.-A. Moon, C.-S. Park, M. K. Jang, E. S. Yun, Y. S. Cho, H.-B. Moon, K.-Y. Lee. 2007. Five-aminoimidazole-4-carboxamide-1-#-4-ribofuranoside attenuates poly (I:C)-induced airway inflammation in a murine model of asthma. *Clinical & Experimental Allergy* **37**:11, 1709-1719. [CrossRef]
66. M TRUJILLO, A CLIPPE, B MANTA, G FERRERSUETA, A SMEETS, J DECLERCQ, B KNOOPS, R RADI. 2007. Pre-steady state kinetic characterization of human peroxiredoxin 5: Taking advantage of Trp84 fluorescence increase upon oxidation. *Archives of Biochemistry and Biophysics* **467**:1, 95-106. [CrossRef]
67. Federica Boraldi, Giulia Annovi, Fabio Carraro, Antonella Naldini, Roberta Tiozzo, Pascal Sommer, Daniela Quaglino. 2007. Hypoxia influences the cellular cross-talk of human dermal fibroblasts. A proteomic approach. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1774**:11, 1402-1413. [CrossRef]
68. J SMIRNOVA, L ZHUKOVA, A WITKIEWICZKUCHARCZYK, E KOPERA, J OLEDZKI, A WYSLOUCHCIESZYNSKA, P PALUMAA, A HARTWIG, W BAL. 2007. Quantitative electrospray ionization mass spectrometry of zinc finger oxidation: The reaction of XPA zinc finger with H2O2. *Analytical Biochemistry* **369**:2, 226-231. [CrossRef]
69. Toshimitsu Niwa. 2007. Protein glutathionylation and oxidative stress#. *Journal of Chromatography B* **855**:1, 59-65. [CrossRef]
70. Heidrun D. Gerr, Michele L. Nassin, Elizabeth M. Davis, Nimanthi Jayathilaka, Mary E. Neilly, Brigitte Schlegelberger, Yanming Zhang, Janet D. Rowley. 2007. Cytogenetic and molecular study of the PRDX4 gene in a t(X;18)(p22;q23): a cautionary tale. *Cancer Genetics and Cytogenetics* **176**:2, 131-136. [CrossRef]
71. Sandy Thijssen, Ann Cuypers, John Maringwa, Karen Smeets, Nele Horemans, Ivo Lambrichts, Emmy Van Kerkhove. 2007. Low cadmium exposure triggers a biphasic oxidative stress response in mice kidneys. *Toxicology* **236**:1-2, 29-41. [CrossRef]
72. Pan-Kyeom Kim, Mi-Ryung Kim, Hyun-Jung Kim, Hyun-Syuk Yoo, Ji-Soo Kim, Eun-Hee Cho, Chan-Wha Kim. 2007. Proteome analysis of the rat hepatic stellate cells under high concentrations of glucose. *PROTEOMICS* **7**:13, 2184-2188. [CrossRef]
73. Albert Mulenga, Maria Blandon, Rabuesak Khumthong. 2007. The molecular basis of the Amblyomma americanum tick attachment phase. *Experimental and Applied Acarology* **41**:4, 267-287. [CrossRef]

74. Daniela Cecconi, Massimo Donadelli, Sara Rinalducci, Lello Zolla, Maria Teresa Scupoli, Aldo Scarpa, Marta Palmieri, Pier Giorgio Righetti. 2007. Proteomic analysis of pancreatic endocrine tumor cell lines treated with the histone deacetylase inhibitor trichostatin A. *PROTEOMICS* **7**:10, 1644-1653. [CrossRef]
75. Amit Chaudhary, Tibor Pechan, Kristine L. Willett. 2007. Differential protein expression of peroxiredoxin I and II by benzo(a)pyrene and quercetin treatment in 22Rv1 and PrEC prostate cell lines. *Toxicology and Applied Pharmacology* **220**:2, 197-210. [CrossRef]
76. Bridget M. Gallagher, Shelley A. Phelan. 2007. Investigating transcriptional regulation of Prdx6 in mouse liver cells. *Free Radical Biology and Medicine* **42**:8, 1270-1277. [CrossRef]
77. Dalia Luna-Moreno, Olivia Vázquez-Martínez, Adrián Báez-Ruiz, Jorge Ramírez, Mauricio Díaz-Muñoz. 2007. Food restricted schedules promote differential lipoperoxidative activity in rat hepatic subcellular fractions. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology* **146**:4, 632-643. [CrossRef]
78. H CHEN, Y LEE, C HUANG, H LIU, W LIAO, W LAI, Y LIN, N HUANG. 2007. Methamphetamine downregulates peroxiredoxins in rat pheochromocytoma cells. *Biochemical and Biophysical Research Communications* **354**:1, 96-101. [CrossRef]
79. L XIN, W CAO, X FEI, Y WANG, W LIU, B LIU, Z ZHU. 2007. Applying proteomic methodologies to analyze the effect of methionine restriction on proliferation of human gastric cancer SGC7901 cells. *Clinica Chimica Acta* **377**:1-2, 206-212. [CrossRef]
80. O. N. Oktyabrsky, G. V. Smirnova. 2007. Redox regulation of cellular functions. *Biochemistry (Moscow)* **72**:2, 132-145. [CrossRef]
81. Lisa Wen, Hui-Ming Huang, Rong-Huay Juang, Chi-Tsai Lin. 2007. Biochemical characterization of 1-Cys peroxiredoxin from Antrodia camphorata. *Applied Microbiology and Biotechnology* **73**:6, 1314-1322. [CrossRef]
82. Paul A. Fowler, Jenny Tattum, Siladitya Bhattacharya, Thomas Klonisch, Sabine Hombach-Klonisch, Rafet Gazvani, Richard G. Lea, Iain Miller, William G. Simpson, Phillip Cash. 2007. An investigation of the effects of endometriosis on the proteome of human eutopic endometrium: A heterogeneous tissue with a complex disease. *PROTEOMICS* **7**:1, 130-142. [CrossRef]
83. Fatiha Tabet, Rhian M. TouyzReactive Oxygen Species, Oxidative Stress, and Vascular Biology in Hypertension 337-347. [CrossRef]
84. Pamela Maher . 2006. Redox Control of Neural Function: Background, Mechanisms, and Significance. *Antioxidants & Redox Signaling* **8**:11-12, 1941-1970. [Abstract] [Full Text PDF] [Full Text PDF with Links]
85. Ulrika A. Petersson, Thomas Kieselbach, José G. García-Cerdán, Wolfgang P. Schröder. 2006. The Prx Q protein of Arabidopsis thaliana is a member of the luminal chloroplast proteome. *FEBS Letters* **580**:26, 6055-6061. [CrossRef]
86. Stanley Muravchick, Richard J. Levy. 2006. Clinical Implications of Mitochondrial Dysfunction. *Anesthesiology* **105**:4, 819-837. [CrossRef]
87. J BERGES, G RICKARDS, A RAUK, C HOUEELEVIN. 2006. QM/MM study of electron addition on protein disulfide bonds. *Chemical Physics Letters* **421**:1-3, 63-67. [CrossRef]
88. Dr. Irfan Rahman , Se-Ran Yang , Saibal K. Biswas . 2006. Current Concepts of Redox Signaling in the Lungs. *Antioxidants & Redox Signaling* **8**:3-4, 681-689. [Abstract] [Full Text PDF] [Full Text PDF with Links]
89. Tina M.L. Peterson, Shirley Luckhart. 2006. A mosquito 2-Cys peroxiredoxin protects against nitrosative and oxidative stresses associated with malaria parasite infection. *Free Radical Biology and Medicine* **40**:6, 1067-1082. [CrossRef]
90. Emily C. Rothstein , Pamela A. Lucchesi . 2005. Redox Control of the Cell Cycle: A Radical Encounter. *Antioxidants & Redox Signaling* **7**:5-6, 701-703. [Citation] [Full Text PDF] [Full Text PDF with Links]