The role of peroxiredoxins in cancer (Review)

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Abstract. Peroxiredoxins (PRDXs) are a ubiquitously expressed family of small (22-27 κDa) non-seleno peroxidases that catalyze the peroxide reduction of H_2O_2, organic hydroperoxides and peroxynitrite. They are highly involved in the control of various physiological functions, including cell growth, differentiation, apoptosis, embryonic development, lipid metabolism, the immune response, as well as cellular homeostasis. Although the protective role of PRDXs in cardiovascular and neurological diseases is well established, their role in cancer remains controversial. Increasing evidence suggests the involvement of PRDXs in carcinogenesis and in the development of drug resistance. Numerous types of cancer cells, in fact, are characterized by an increase in reactive oxygen species (ROS) production, and often exhibit an altered redox environment compared with normal cells. The present review focuses on the complex association between oxidant balance and cancer, and it provides a brief account of the involvement of PRDXs in tumorigenesis and in the development of chemoresistance.

Contents

1. Oxidative stress and the role of H_2O_2 as a second messenger

Life in an oxygen-rich environment has to deal with the danger of oxidative stress. Oxidative stress represents a biochemical state characterized by an excessive presence of free radicals and reactive metabolites potentially harmful for the organism (1,2). Free radicals are highly reactive chemical species, typically with a short half-life, consisting of an atom or a molecule containing one or more unpaired electrons. These electrons give a significant reactivity to the radical, making it able to bind to other radicals or subtract an electron from other molecules nearby. Reactive oxygen species (ROS) are the most important class of free radicals that are produced by organisms: Elevated levels result from an imbalance between the production of oxidants and their elimination by the antioxidant system protecting the organism. The superoxide anion radical (O2=) is one of the best known ROS. Its metabolites, such as the hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2), are very reactive (3). Reactive nitrogen species (RNS) are another family of free radicals (with antimicrobial action), derived from nitric oxide (•NO) and superoxide anion (O2=), that, acting together with ROS, can damage cells. Not surprisingly, in humans, associations between the level of oxidative stress and serious diseases, including diabetes mellitus, atherosclerosis, hypertension, inflammatory diseases, neurodegenerative disorders and cancer, are well known (1,2,4) (Fig. 1).

During normal cell metabolism, the production of ATP by aerobic respiration in mitochondria constantly produces ROS and RNS, such as the by-products of oxidative phosphorylation.

At low to moderate concentrations, ROS exert an important positive role in several physiological processes, including defense against infectious agents and cell signaling (5), although at high concentrations they are able to react with many cellular components, such as nucleic acids, proteins and lipids, causing DNA damage that escapes the DNA repair system. For this reason, their concentration needs to be strictly controlled. In numerous organisms, ROS, and especially H_2O_2, are signaling molecules able to cross the membranes, to function as second messengers inside the cell, and to induce specific signal transduction pathways. Furthermore, ROS and RNS are able to control the activity of enzymes by triggering several post-translational modifications, such as disulfide bond formation, thiol oxidation to sulfenic/sulfinic/sulfonic acid, glutathionylation, nitrosylation and carbonylation. Several studies have reported that cell stimulation by a variety of growth factors, cytokines and G-protein-coupled receptors generates intracellular H_2O_2, e.g. (6), so that it may be difficult to resolve whether the cell is being subjected to H_2O_2-dependent signaling

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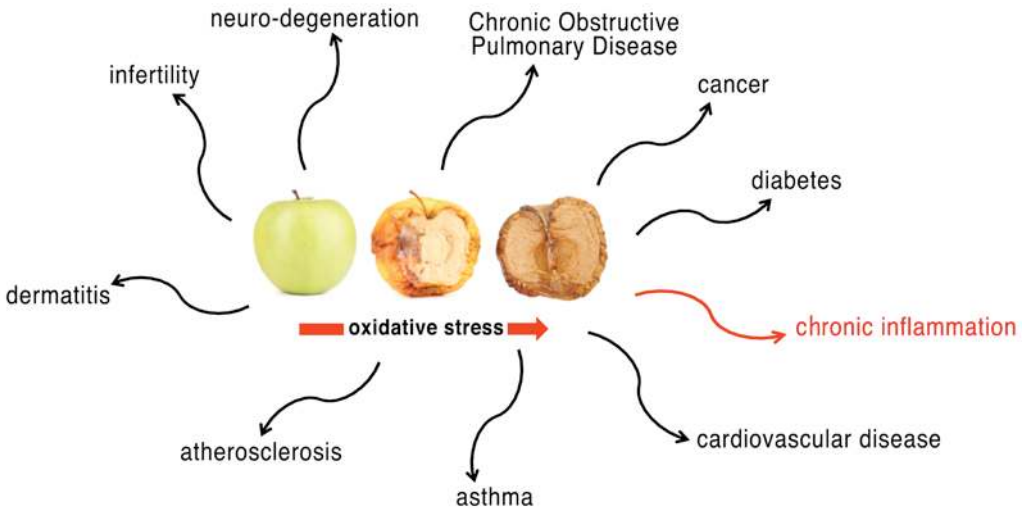

Figure 1. Oxidative stress and human diseases. Oxidative stress plays a role in many pathological processes.

or to oxidative stress. Aerobic organisms are equipped with nonenzymatic (ascorbate, glutathione, tocopherol and carotenoid) or enzymatic [catalase (CAT), ascorbate peroxidase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and peroxiredoxin] antioxidant systems to neutralize ROS and RNS in the cells and to finely control their concentrations.

2. A special class of antioxidant enzymes: The peroxiredoxins

One of the most important enzyme systems that, together with SOD, CAT and GPx, act in the defense against oxidative stress is the 'peroxiredoxin' (PRDX) family (7,8).

PRDXs have been identified in numerous organisms and constitute a ubiquitous family of thiol-dependent peroxidases, catalyzing the reduction of H_2O_2, alkyl hydroperoxides and peroxynitrite to water, the corresponding alcohol and nitrite, respectively (9-11), emerging as arguably the most important and widespread peroxide and peroxynitrite scavenging enzymes in all of biology (12,13). Their role was long overshadowed by well-studied oxidative stress defense enzymes such as catalase and glutathione peroxidase, considered for a long time to be the major enzymes responsible for protecting cells against hydroperoxides.

Unlike heme-dependent catalase and the selenium-dependent glutathione peroxidase, PRDXs do not require cofactors. They were identified approximately 27 years ago in yeast (14) and 25 years ago in mammals (15), and are functionally conserved in all three phylogenetic domains: Archaea, Bacteria and Eukaryota, stressing the importance of the existence of systems protecting against ROS for the evolution of living organisms (16) (Table I).

PRDXs have been classified into the following subgroups on the basis of functional site sequence similarity (17): Prx1/PRDX1, Prx5/PRDX5 and Prx6/PRDX6 (18). The phylogenetic distribution of PRDXs demonstrates the widest biological distribution for the Prx1/PRDX1 and Prx6/PRDX6 subfamilies; Prx5/PRDX5 members are apparently lost in archaea (Table I).

PRDXs of different subgroups vary in their oligomerization states, conformational flexibility, and certain secondary structural elements. In addition, most organisms possess multiple isoforms (19): In humans, for example, six different isoforms of PRDX are present (20), four PRDX1 subtypes, one PRDX5 subtype and one PRDX6 subtype.

PRDX1, PRDX2, PRDX3, PRDX5 and PRDX6 are localized in the cytosol, in the mitochondria, in the nuclei and in the peroxisomes (21-23), whereas PRDX4 is mainly present in the endoplasmic reticulum, or it is secreted (24).

The catalytic activity of PRDXs is crucially dependent on a conserved peroxidatic Cys (C_p) residue contained within a universally conserved Pxxx(T/S)xxC active-site motif in the amino-terminal portion of the protein (17), which corresponds to Cys-47 in yeast cytosolic thioredoxin peroxidase I (cTPx I) (15). Five out of six human PRDXs also contain an additional conserved Cys in the carboxy-terminal region, which corresponds to Cys-170 in yeast thiol-specific antioxidant (TSA) (15), termed resolving cysteine (C_r). Depending on the PRDX, the C_r may be located within the same chain of C_p or in the chain of another subunit, therefore human PRDXs are classified into three classes: i) Typical 2-Cys PRDXs, which include PRDX1-4, ii) atypical 2-Cys PRDX and PRDX5, and iii) 1-Cys PRDX and PRDX6 (25). The typical 2-Cys PRDXs are obligate homodimers containing two identical active sites, bringing the two redox-active cysteines (C_p and C_r) into close proximity (26). By contrast, atypical 2-Cys PRDXs form an intramolecular disulfide intermediate by reacting the amino-terminal sulfenic acid (Cys-47) with a carboxy-terminal Cys-SH (Cys-151) of the same molecule that is able to be reduced by thioredoxin (27).

PRDX6 is the only known mammalian member of the 1-Cys subgroup. The mechanism by which its sulfenic acid form is reduced has yet to be fully elucidated (27), but Monteiro *et al* (28) have unequivocally demonstrated that 1-Cys PRDXs are reduced by ascorbate (Fig. 2).

Members of the Prx1/PRDX1 and Prx6/PRDX6 subfamilies dimerize using the 'B interface' (denoting the β-strand interactions) to form an extended 10 to 14-strand β-sheet (29) (Fig. 3), whereas members of the Prx5/PRDX5 subfamily

Table I. PRDXs are functionally conserved in all three phylogenetic domains.[a]

Species	Gene symbol	Identity (%)	
		Protein	DNA
H. sapiens PRDX1			
vs. *P. troglodytes*	PRDX1	100.0	99.7
vs. *M. mulatta*	PRDX1	99.5	98.5
vs. *C. lupus*	PRDX1	99.0	93.3
vs. *B. taurus*	PRDX1	96.5	93.6
vs. *M. musculus*	Prdx1	95.5	90.8
vs. *R. norvegicus*	Prdx1	97.5	91.3
vs. *R. norvegicus*	Prdx1l1	97.0	91.3
vs. *G. gallus*	PRDX1	88.4	78.7
vs. *X. tropicalis*	LOC101731384	84.9	76.2
vs. *X. tropicalis*	Prdx1	84.9	76.0
vs. *D. rerio*	Prdx1	81.3	73.9
H. sapiens PRDX2			
vs. *P. troglodytes*	PRDX2	100.0	99.8
vs. *M. mulatta*	PRDX2	100.0	98.1
vs. *C. lupus*	PRDX2	93.4	88.2
vs. *B. taurus*	PRDX2	91.2	87.4
vs. *M. musculus*	prdx2	93.4	88.2
vs. *R. norvegicus*	prdx2	93.4	87.0
vs. *X. tropicalis*	prdx3	79.6	70.7
vs. *X. tropicalis*	prdx2	77.5	72.4
vs. *D. rerio*	prdx2	76.6	72.8
vs. *D. melanogaster*	Jafrac1	71.3	67.4
vs. *A. gambiae*	TPX2	68.1	66.0
vs. *C. elegans*	prdx2	73.2	66.7
vs. *S. cerevisiae*	TSA1	66.8	61.1
vs. *S. pombe*	tpx1	68.8	60.8
vs. *A. thaliana*	2Cys Prx B	63.8	61.2
vs. *A. thaliana*	AT3G11630	64.4	61.3
vs. *O. sativa*	Os02g0537700	62.2	61.5
H. sapiens PRDX3			
vs. *P. troglodytes*	PRDX3	100.0	99.6
vs. *M. mulatta*	PRDX3	97.7	97.5
vs. *C. lupus*	PRDX3	91.4	88.2
vs. *B. taurus*	PRDX3	89.1	88.8
vs. *M. musculus*	Prdx3	86.3	84.2
vs. *R. norvegicus*	Prdx3	85.2	83.2
vs. *G. gallus*	PRDX3	79.2	71.7
vs. *M. mulatta*	LOC719764	99.2	97.8
vs. *D. rerio*	prdx3	75.4	66.8
vs. *D. melanogaster*	Prx3	64.5	61.7
vs. *A. gambiae*	TPX1	63.9	58.6
vs. *C. elegans*	prdx3	66.8	60.4
vs. *S. cerevisiae*	TSA2	57.3	57.1
vs. *K. lactis*	KLLA0B01628g	56.8	58.7
vs. *E. gossypii*	AGOS_AER312W	57.8	59.5
H. sapiens PRDX4			
vs. *M. mulatta*	PRDX4	98.5	98.4
vs. *C. lupus*	PRDX4	93.0	89.2
vs. *B. taurus*	PRDX4	93.8	90.8
vs. *M. musculus*	Prdx4	95.0	89.1
vs. *R. norvegicus*	Prdx4	94.5	90.3
vs. *G. gallus*	PRDX4	91.9	81.6
vs. *X. tropicalis*	prdx4	93.6	81.1
vs. *D. rerio*	prdx4	88.7	74.8
vs. *D. melanogaster*	Jafrac2	71.0	64.4
vs. *A. gambiae*	TPX3	74.7	65.9
H. sapiens PRDX5			
vs. *P. troglodytes*	PRDX5	99.5	99.7
vs. *B. taurus*	PRDX6	95.1	92.9
vs. *C. lupus*	PRDX5	85.5	84.9
vs. *B. taurus*	PRDX5	81.9	83.8
vs. *M. musculus*	Prdx5	87.2	86.1
vs. *R. norvegicus*	Prdx5	88.1	85.3
vs. *X. tropicalis*	prdx5	67.3	65.2
vs. *D. rerio*	prdx5	61.3	64.0
vs. *D. melanogaster*	Prdx5	59.5	62.4
vs. *A. gambiae*	AgaP_AGAP 001325	60.0	60.9
vs. *K. lactis*	KLLA0A07271g	39.3	46.8
vs. *E. gossypii*	AGOS_ADL154C	40.5	48.4
vs. *S. pombe*	SPCC330.06c	35.3	42.7
vs. *M. oryzae*	MGG_00860	44.4	53.0
vs. *N. crassa*	NCU06880	44.1	52.8
vs. *A. thaliana*	AT1G60740	42.7	49.7
vs. *A. thaliana*	TPX1	43.9	50.5
vs. *A. thaliana*	TPX2	42.7	49.7
vs. *O. sativa*	Os01g0675100	44.0	49.9
H. sapiens PRDX6			
vs. *P. troglodytes*	PRDX6	100.0	99.7
vs. *M. mulatta*	PRDX6	98.7	98.4
vs. *C. lupus*	PRDX6	92.9	91.5
vs. *M. musculus*	Prdx6	89.7	87.4
vs. *R. norvegicus*	Prdx6	91.5	88.8
vs. *G. gallus*	PRDX6	86.4	78.0
vs. *X. tropicalis*	prdx6	76.9	71.0
vs. *D. rerio*	prdx6	73.6	67.3
vs. *D. melanogaster*	Prx6005	61.0	58.9
vs. *A. gambiae*	TPX5	60.2	59.7
vs. *C. elegans*	prdx6	52.4	55.6
vs. *S. cerevisiae*	PRX1	51.0	54.8
vs. *K. lactis*	KLLA0E20285g	48.6	54.6
vs. *E. gossypii*	AGOS_AGR368W	50.5	55.4
vs. *M. oryzae*	MGG_08256	53.5	58.1
vs. *N. crassa*	NCU06031	53.3	58.7
vs. *A. thaliana*	PER1	52.6	55.8
vs. *O. sativa*	Os07g0638300	53.5	59.3
vs. *O. sativa*	Os07g0638400	53.9	56.5

[a]Homologs of the PRDX genes are listed in the Table. In the figure the Pairwise Alignment Scores and evolutionary distances have been reported (http://www.ncbi.nlm.nih.gov/gene/). PRDX, peroxiredoxin; TPX, thiol peroxidase.

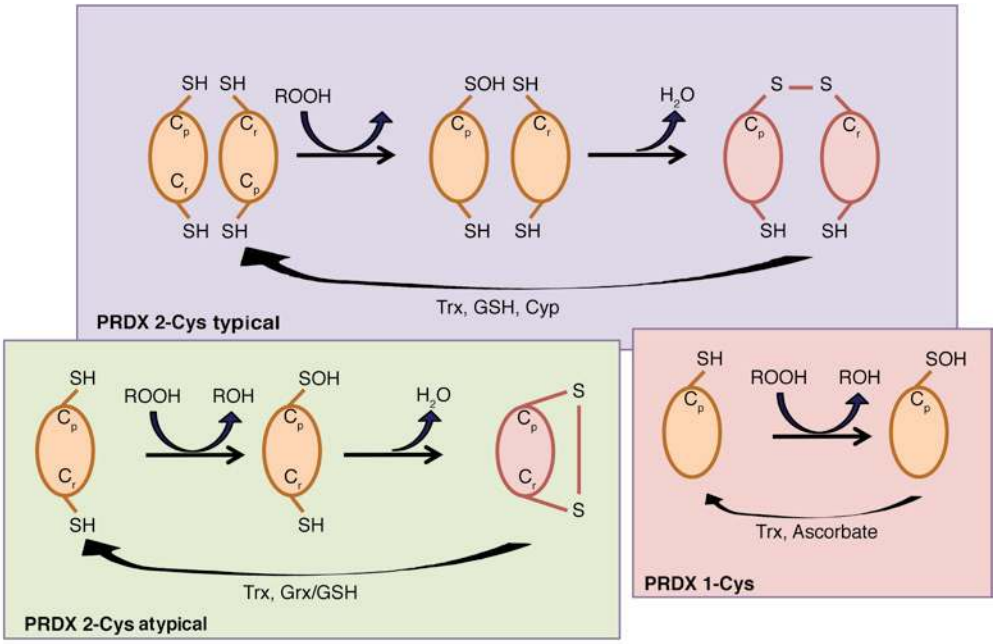

Figure 2. Mechanisms of the three PRDX subtypes. In typical 2-Cys PRDXs, the main cysteine residue (C_p) reacts with the residue C_r on the second subunit of the dimer. In atypical 2-Cys PRDXs, the oxidized C_p reacts with the C_r residue located in the same molecule. In 1-Cys PRDXs, the C_p residue generates sulfenic acid and is regenerated directly through donation of an electron to the thiol form in presence of ascorbate. Cyp, cyclophilin; Grx, glutaredoxin; GSH, reduced glutathione; ROOH, peroxide; C_p, peroxidatic Cys; C_r, resolving cysteine; Trx, thioredoxin.

typically dimerize and associate across the 'A interface' (denoting either 'alternate' or 'ancestral'). In addition, a large number of PRDXs that form dimers across their B interface can show a further redox-sensitive dependent oligomerization to form octamers, decamers or dodecamers across their A interface (19).

Typical 2-Cys PRDXs (PRDX1-4) form decamers or dodecamers in the reduced or hyperoxidized state, acquiring the ability to exercise other functions as chaperones, binding partners, enzyme activators and/or redox sensors, while the oxidized form is preferentially present as dimers (30) (Fig. 3). Atypical 2-Cys PRDXs are able to undergo protein-protein interactions with functional implications, although their level of polymerization is less compared with that of typical 2-Cys PRDXs.

By contrast, 1-Cys PRDXs are not able to form decamers, and this is probably the reason why they serve mainly an antioxidant function rather than a molecular chaperone function, despite their enzymatic mechanism being very similar to that of 2-Cys PRDXs (31). Concerning the catalytic function, PRDXs tune the sensitivity to hyperoxidation switching from a fully folded (FF) conformation, in which C_p can react with the peroxide, to a locally unfolded (LU) conformation, in which the C_p is exposed and can form a disulfide bridge with the C_r (Fig. 4).

PRDXs are highly involved in the control of cellular physiological functions, including growth, differentiation, apoptosis, embryonic development, lipid metabolism, the immune response, as well in the maintenance of cellular homeostasis (32) (Fig. 5). Over the course of the last few years, a large body of evidence has suggested their involvement in carcinogenesis and in the development of drug resistance. This review focuses on the complex relationships between oxidant balance and cancer, and it provides a brief account of the involvement of PRDXs in tumorigenesis and in the development of chemoresistance.

3. ROS stress in cancer cells

ROS, such as the superoxide radical, the hydroxyl radical and H_2O_2 or RNS, such as peroxynitrites and nitrogen oxides, are toxic metabolic secondary products that pose a significant threat by damaging DNA, lipids, proteins and other macromolecules (33). Controlling their cellular levels is essential for proper function. Nanomolar amounts of ROS are able to act as potent mitogens, regulating cell growth and angiogenesis. High levels of ROS may be harmful, causing damage and driving signaling pathways involved in proliferation arrest, or even in cell death (34). Several studies have implicated an increase of ROS in carcinogenesis due to a loss of proper redox control (35-39). Aberrant ROS levels are able to drive cancer initiation and progression. In general, the activity of ROS on carcinogenesis depends on their mutagenic potential. Their contribution to cancer progression and metastases is mainly due to their ability to affecting anchorage-independent cell growth (40,41), the epithelial-to-mesenchymal transition (EMT) (42), *de novo* angiogenesis (43,44) and apoptosis through the modulation of the phosphoinositide 3-kinase (PI3-kinase)/Akt pathway (41).

Moreover, the tendency of cancer cells to undergo profound changes in their own intrinsic metabolism (Warburg metabolic reprogramming), characterized by increased activity in aerobic glycolysis and by lipid metabolism deregulation, is also largely modulated by oxidative stress. Therefore, ROS may promote numerous aspects of tumor onset and progression towards a malignant phenotype (45-47). Nevertheless, it should not be overlook that high levels of ROS can be lethal for the cancer cells. This could be one of the reasons why cancer cells, in

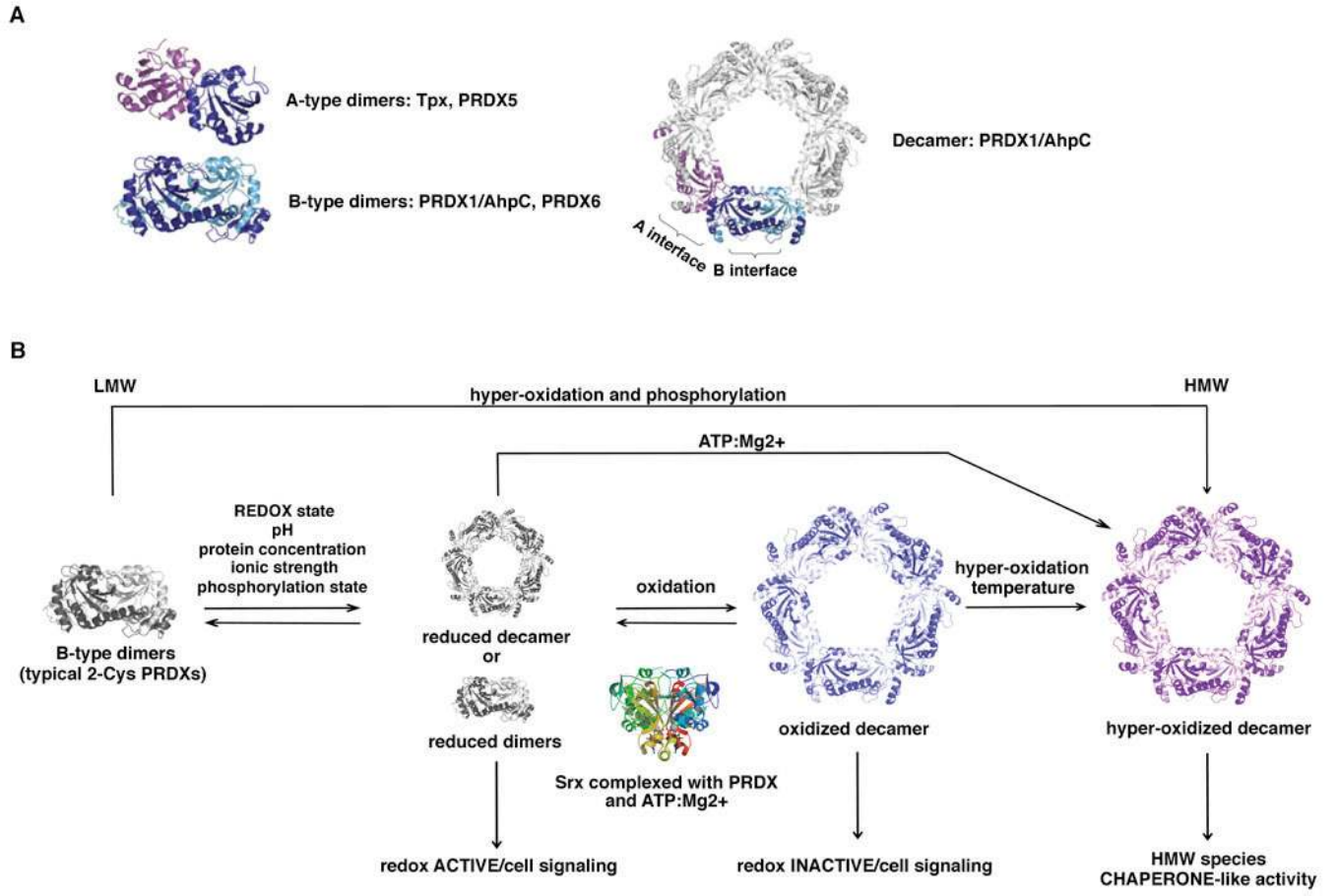

Figure 3. Quaternary structure of PRDXs. (A) A-type dimers or B-type dimers. Certain components of the PRDX1 and PRDX6 subfamilies form a decameric structure through the interaction of five B-type dimers via the A-type dimer interface (A-type dimer colored in purple/blue; B-type dimer colored in blue/light blue). (B) The model of typical 2-Cys PRDX oligomerization and function: Different factors induce oligomerization of the dimers to hexa-, octa-, decamers or higher-order aggregates that are able to function as a peroxidase. Oxidation leads to the breakdown of the decamers, whereas hyperoxidation stabilizes the oligomer. Oxidized decamers can be reversed by sulfiredoxin (Srx) reduction (167). Hyperoxidized decamers are stable HMW complexes with chaperone-like activity. LMW, low molecular weight; HMW, high-molecular-weight; PRDX, peroxiredoxin.

order to defend themselves, potentiate their antioxidant capacity (48,49).

4. PRDXs in tumorigenesis

Cells are endowed with several overlapping peroxide-degrading systems, the relative importance of which is a matter of debate. PRDXs are a fascinating group of thiol-dependent peroxidases that, under physiological conditions, are responsible for divergent functions, such as protecting cells against oxidative DNA damage and genomic instability, regulating cell signaling associated with H_2O_2, and influencing cell differentiation and proliferation, immune responses and apoptosis (50) (Fig. 6). A number of studies have demonstrated that cancer cells exhibit an increased production of ROS, in part caused by a loss in proper redox control (35,36-39). Therefore, over the course of the last few years, much attention has been paid to exploring the role of PRDXs in cancerogenesis. Increased or decreased levels of PRDXs have been demonstrated in many human cancers. Studies performed *in vitro* or *in vivo* models have demonstrated that overexpression of PRDXs may either inhibit cancer development or promote cancer growth (48), depending on the specific PRDX family member and on the cancer context.

In the following chapters, the most recent findings regarding the dual action of PRDXs in tumorigenesis are reviewed and discussed. Table II summarizes different types of cancer in which the expression of an individual member of the PRDX family is altered.

PRDX1: Dual effect in cancerogenesis. Amongst the PRDX family members, PRDX1 possess the widest cellular distribution and show the highest abundance in various tissues (51). Its cellular expression is controlled at the transcriptional level by nuclear factor (erythroid-derived 2)-related factor 2 (NRF2) (52), and at the post-transcriptional level, through degradation and deadenylation/polyadenylation processes (53).

PRDX1 as a tumor suppressor. A tumor suppressor function of PRDX1 was first demonstrated in a knockout-mouse model, where its deficiency generated mice suffering from hemolytic anemia and multiple tumors, including mammary carcinomas (54-56). These studies suggested that the tumor suppressive effects of PRDX1 were mediated by a reduction of c-Myc transcriptional activity (55) or of phosphatase and tensin homolog (PTEN/AKT) activity (56). In particular, PRDX1 exerts its protective effect by oxidation of the Cys

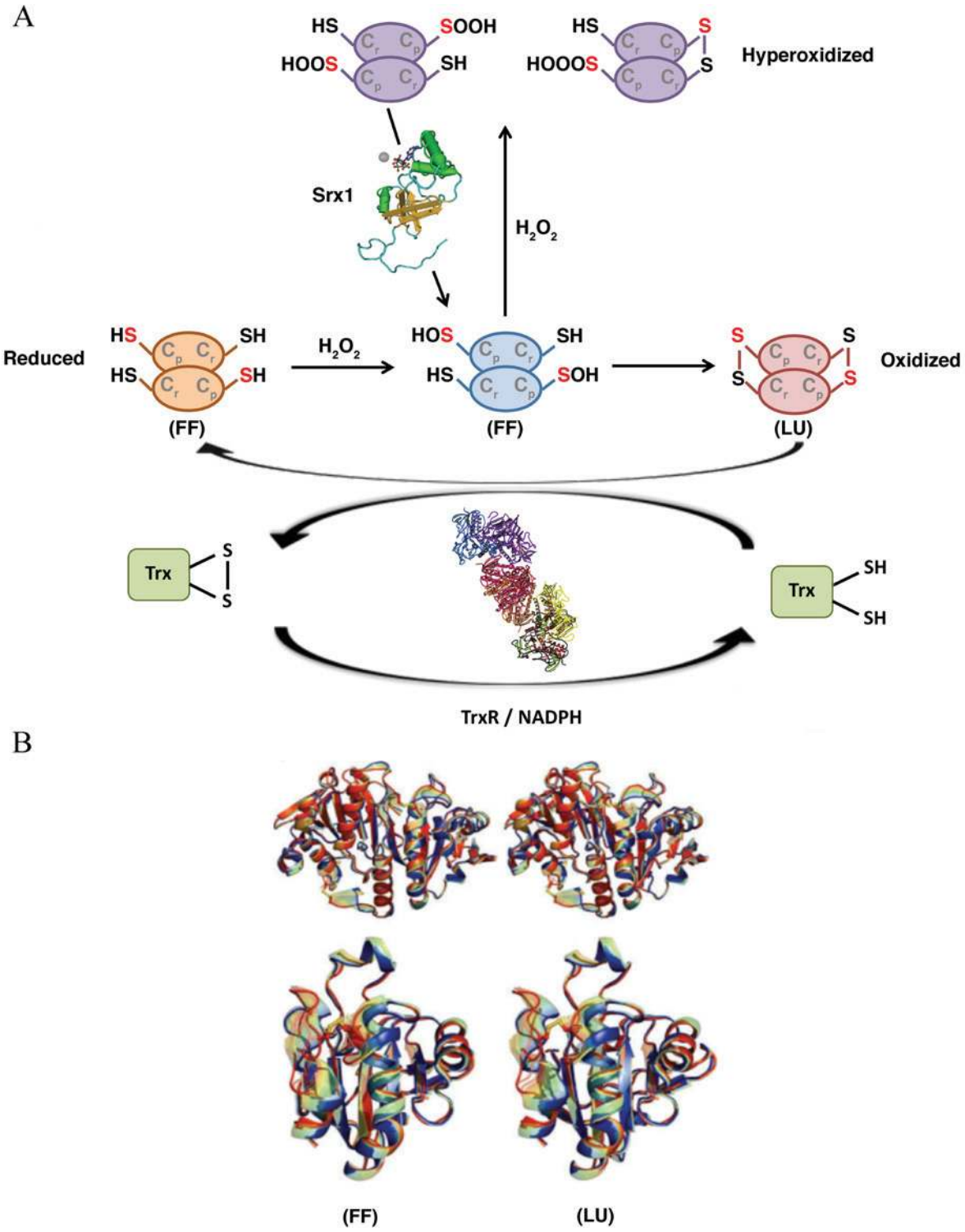

Figure 4. Catalytic mechanism of typical 2-Cys PRDXa. (A) PRDXs switch from an FF conformation, in which C_p reacts with the peroxide, to an LU conformation, in which the C_p is exposed and forms a disulfide bridge with the C_r residue. The thiol groups are converted into sulfenic acid (-S-OH) and form disulfide bonds with other thiol groups (-SS-) (oxidized status-LU conformation). At high peroxide concentrations, the sulfenic acid intermediate is overoxidized to sulfinic acid (-SOOH) or even sulfonic acid (-SOOOH), causing the inactivation of the enzyme (hyperoxidized status). (B) Stereo-view of the interpolated structural changes shown in rainbow colors between the FF (blue) and LU (red) conformations for a representative of Prx1 subfamily (upper) and Prx5 subfamily (lower). PRDX, peroxiredoxin; Srx1 sulfiredoxin 1, Trx, thioredoxin; TrxR, thioredoxin reductase; FF, fully folded; LU, locally unfolded.

residue located within the active site of PTEN phosphatase, thereby reducing the predisposition of PRDX1-deficient mice to develop Ras-induced mammary tumors (56).

In breast cancer (estrogen-receptor-positive cases), PRDX1 prevents oxidative stress-mediated estrogen receptor α reduction. Its overexpression in these cancer tissues may be considered as a biomarker of favorable prognosis (57). In lung cancer, the tumor suppressant effect is mediated by the modulation of the ROS-mediated activation of the K-Ras/extracellular signal-regulated kinase (ERK) pathway (58). Similarly, in

Figure 5. WordCloud for PRDXs. The WordCloud representation shows the majority information about the PRDX family (see http://www.maayanlab.net/G2W/help.php). PRDX, peroxiredoxin.

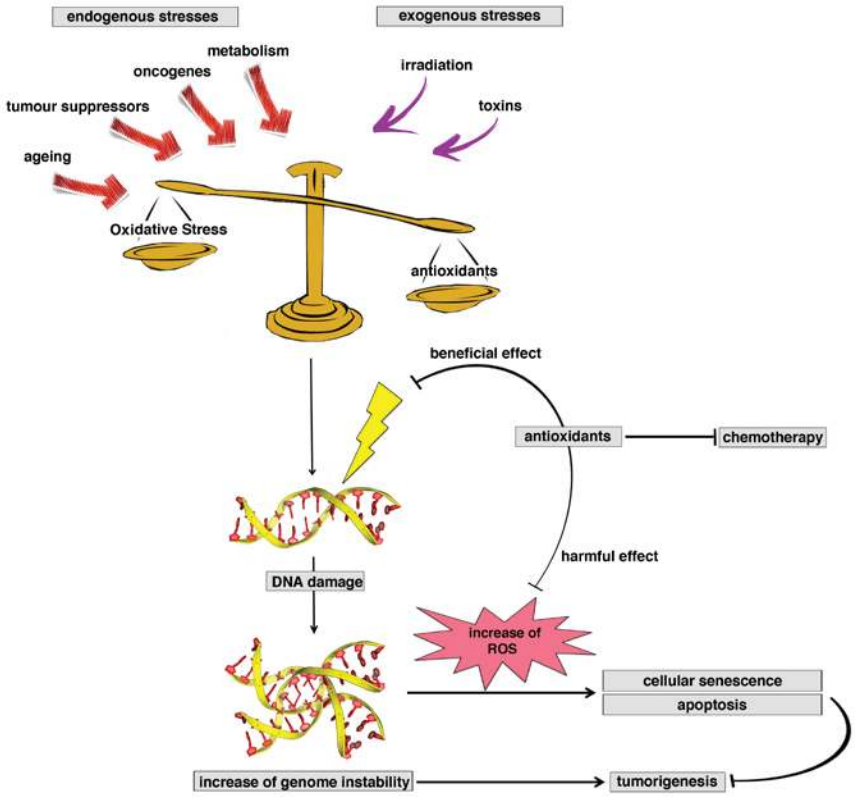

Figure 6. Antioxidants: a 'double-edged sword' in tumorigenesis. Antioxidants are a double-edged sword in tumorigenesis, and may be involved in reduction of the levels or reactive oxygen species (beneficial effect) or in accelerating tumor formation, inhibiting senescence or apoptotic processes (harmful effects).

human acute myeloid leukemia (AML), PRDX1 promotes the reactivation of the protein tyrosine phosphatase DEP-1, a tumor suppressor that counteracts the action of the transforming kinase, FLT3 ITD (59).

PRDX1 as a tumor promoter. The tumor-promoting function of PRDX1 has been demonstrated in numerous types of human cancer, and appears to be mediated through its interaction with several cancer-associated signal pathways. An increased level of PRDX1 has been described in lung cancer (60), in bladder cancer (61), in ovarian carcinoma (62), in aggressive esophageal squamous carcinomas (63), in hilar cholangiocarcinoma (64), in liver cancer (65), in pancreatic cancer (66), in mesothelioma (67) and in glioblastoma (68). In prostate cancer, PRDX1 overexpression induces tumor growth and tumor progression through the Toll-like receptor 4 (TLR4)-dependent regulation

Table II. Differential expression of PRDX family members in tumor types.[a]

PRDX family member	Expression levels in different tumor types	Refs.
PRDX1	Increased in: Lung cancer, bladder cancer, ovarian carcinoma, aggressive esophageal squamous carcinomas, mesothelioma, glioblastoma, hilar cholangiocarcinoma, esophageal squamous cell carcinoma, liver cancer and pancreatic cancer	(60-67,142)
	Decreased in: Thyroid tumors (PTCs)	(74,75)
PRDX2	Increased in: Colorectal cancers, B cell-derived primary lymphoma cells, vaginal carcinoma, cervical cancer, ovarian cancer, prostate cancer, esophageal cancer and B-cell-derived primary lymphoma cells	(87-92,94)
	Decreased in: Melanoma	(85)
PRDX3	Increased in: Hepatocellular carcinomas, malignant mesothelioma, breast carcinoma, prostate cancer, cervical carcinoma and lung cancer	(67,102-106)
PRDX4	Increased in: Pancreatic cancer, prostate cancer, oral cavity squamous cell carcinoma, colorectal cancer, breast cancer, ovarian cancer and lung cancer	(70,90,114,116-119)
	Decreased in: Pancreatic cancer and acute promyelocytic leukemia	(113,121)
PRDX5	Increased in: Aggressive Hodgkin lymphomas, malignant mesothelioma, breast carcinoma, ovarian carcinoma and thyroid cancer	(67,87,103,127,128)
	Decreased in: Adrenocortical carcinoma	(129)
PRDX6	Increased in: Breast cancer, malignant mesothelioma, bladder cancer, esophageal cancer, lung cancer, ovarian cancer, pancreatic cancer, cancer of the gingivo-buccal area and lymphoma	(61,67,87,141-146)
	Decreased in: Thyroid tumors	(75,149)

[a]A summary is provided of the different types of cancer in which the expression of individual members of the PRDX family is up or downregulated. PRDX, peroxiredoxin; PTCs, papillary thyroid carcinomas.

of tumor vasculature, increasing the expression of the vascular endothelial growth factor (VEGF) (69). In certain lung cancer cellular models, it has become well established that the pro-oncogenic role of PRDX1 is mediated by the activation of c-Jun and AP-1 (70), and that the transforming growth factor β1 (TGFβ1)-induced EMT is caused by direct inhibition of E-cadherin expression (71). In addition, PRDX1 may exerts its tumor-promoting function by affecting intracellular signaling pathways that affect apoptosis. In thyroid cancer cells, it inhibits apoptosis through the inhibition of apoptosis signal-regulating kinase 1 (ASK1) activity (72), whereas in human hepatoma it suppresses the redox-dependent activation of caspases, inducing tumor necrosis factor-α (TNFα)-related apoptosis-inducing ligand (TRAIL) resistance (73).

Decreased PRDX1 levels in papillary thyroid carcinomas (PTCs) (74) correlate with the presence of the BRAF V600E mutation and of lymph node metastasis, suggesting that PRDX1 reduction may be caused by mutated BRAF, and this is associated with a more aggressive clinical outcome of PTCs (75).

PRDX2: Dual effect in cancerogenesis. PRDX2 is another member of the typical 2-Cys subgroup, and it is mainly present in the cytosol (76). In red blood cells (RBCs), the oxidation-reduction cycle of PRDX2 correlates with a robust temperature-entrainable and temperature-compensated circadian rhythm, the oscillations of which result in circadian rhythm-dependent oligomerization of PRDX2 (77). Notably, the fluctuations in levels of hyperoxidized PRDX2 are not affected at the transcriptional level, considering the absence of a nucleus in the RBCs (77); neither are they controlled by sulfiredoxin (Srx), but are rather controlled by hemoglobin autoxidation and the 20S proteasome (78). Circadian rhythms are highly conserved time-tracking systems regulating important biological processes at the systemic and the cellular level (76). Interestingly, it has been recently demonstrated that the nuclear levels of PRDX2 oscillate rhythmically over two entire 24-h long cycles in HaCaT keratinocytes, contributing to the regulation of the redox balance of human keratinocytes. These findings open new perspectives for an understanding of circadian-pathophysiological processes in the skin (79). It is not yet clear whether the PRDXs are essential for circadian rhythmicity, although it is evident that their deletion has generally deleterious cellular consequences (77).

PRDX2 is one of the most efficient intracellular H_2O_2 scavengers compared with the other antioxidants (80). Depending on its oxidized or hyperoxidized status, PRDX2 forms homodimers or oligomers, functioning as an H_2O_2 scavenger or as a chaperone, respectively (81). Its expression is regulated by ROS induction in a PTEN-dependent manner (82), and at the transcriptional level by Hand1/Hand2 factor (83) or by the extensive methylation of CpG islands in the promoter region (84).

PRDX2 as a tumor suppressor. Depending on the tumor type and the stage of tumor progression, PRDX2 may exhibit strong

tumor-suppressive or tumor-promoting functions. A decreased expression of PRDX2 has been demonstrated in only a few types of cancer, among which are the melanomas. The function of PRDX2 in melanoma cell growth and metastasis has not yet been fully elucidated. To date, it has been demonstrated, both *in vitro* in melanoma cell lines and *in vivo* in metastatic melanoma models, that a downregulation of PRDX2 correlates with increased proliferative and migratory activities, and with the acquisition of a metastatic potential. In particular, it appears that the PRX2-mediated signaling pathway for suppression of melanoma metastasis involves a synergistic collaboration of the processes of ERK-dependent E-cadherin expression and the Src-dependent retention of β-catenin in the adherens junctions (85). In a colorectal cancer (CRC) cellular model, PRDX2 inhibits TGFβ1-induced EMT, reducing the invasive phenotype through the modulation of the transcription factors, Twist1, Snail, ZEB1 and ZEB2 (86).

PRDX2 as a tumor promoter. Over the course of the last few years, a number of studies, instead, have revealed that PRDX2 is increased in various human malignancies, suggesting a possible role for PRDX2 as a tumor promoter. High levels of PRDX2 and 4 were observed in ovarian borderline cancer compared with the other benign ovarian lesions, allowing a hypothesis to be made for the potential use of these in determining a differential diagnosis between benign and borderline epithelial ovarian tumors (87). Elevated expression levels of PRDX2 have also been found in vaginal carcinoma (88), in cervical cancer (89), in prostate cancer (90), in esophageal cancer (91) and, more recently, in B cell-derived primary lymphoma cells (92). In breast cancer, PRDX2 works like a 'metabolic adaptor' driver protein that specifically induces the selective growth of metastatic cells in the lung by protecting them against oxidative stress (93). The dual action of PRDX2 in tumorigenesis has been demonstrated in a CRC model. Lu *et al* (94), in contrast with what was reported by Feng *et al* (86), demonstrated that PRDX2 overexpression in CRC tissues was strongly correlated with a more aggressive cancer behavior, tumor metastasis and the tumor-node-metastasis (TNM) stage, indicating a possible role for PRDX2 in CRC progression. Taken together, these data suggest that the mechanism by which PRDX2 exerts its oncogenic action is still poorly understood, and further studies are required.

PRDX3: Tumor-promoting effects. PRDX3 is a mitochondrial member of the antioxidant family of thioredoxin peroxidases that uses mitochondrial thioredoxin 2 (Trx2) as a source of reducing equivalents to scavenge hydrogen peroxide (95). Its specific localization to the mitochondria suggests that PRDX3, together with its mitochondrion-specific electron suppliers, Trx2 and Trx reductase 2 (TrxR2), may provide a primary line of defense against H_2O_2 produced by the mitochondrial respiratory chain (96). PRDX3 is highly sensitive to the oxidative state. The regulation of its expression involves sirtuin 1 (SIRT1), a class III histone deacetylase that is not cell-type-specific, in bovine aortic endothelial cells. SIRT1 positively controls PRDX3 expression by an enhancement of the formation of the PGC-1α/FoxO3a transcriptional complex (97). Depending on the cancer type, the regulation of PRDX3 expression may be mediated by different factors. In colon cancer stem cells (CSCs), the forkhead box protein 1, FOXM1, activates transcription of PRDX3 and the expression of CD133 (98). In medulloblastoma tumor tissue samples and cell lines, the level of the microRNA, miR-383, is a modulator of PRDX3 expression (99), whereas in human prostate cancer cells, miR-23b directly regulates PRDX3 expression under normal and hypoxic conditions (100). Finally, in von Hippel-Lindau (VHL)-deficient clear cell renal cell carcinoma (CCRCC), the transcription factor, hypoxia-inducible factor 1 (HIF-1), downregulates the level of PRDX3 (101).

A high level of PRDX3 expression has been reported in hepatocellular carcinomas (102), in malignant mesothelioma (67), in breast carcinoma (103), in prostate cancer (104), in lung cancer (105) and in cervical carcinoma (106). All these studies have demonstrated that PRDX3 overexpression in cancer cells correlates with a more aggressive phenotype.

PRDX4: Tumor-promoting effects. PRDX4 is another member of the typical 2-Cys PRDX family, homologous with other typical 2-Cys PRDXs, such as PRDX1 and PRDX2, which share the same catalytic mechanism. It is located predominantly in the endoplasmic reticulum (ER) and extracellular spaces, with the highest expression occurring in the pancreas, liver and heart, and lowest expression in blood leukocytes and the brain (107). A distinctive hydrophobic amino-terminus in PRDX4 functions as a signal sequence involved in the process of secretion from the cells (108). No solid evidence is available regarding the role of extracellular PRDX4 as a biomarker in certain types of disease (24). It has been suggested that the secretable form of PRDX4 may be involved in the interactions between carcinoma cells and the extracellular environment (109).

PRDX4 controls oxidative stress by reducing H_2O_2 to water in a thiol-dependent catalytic cycle. In addition, it has an important chaperone function, operating by means of a versatile mechanism that allows it to switch from redox-dependent and reversibly convertible, disulfide-linked homodimers to higher-order multimers, which enables the interaction with binding partners, including stress-responsive kinases, membrane proteins and immune modulators (110). As a chaperone protein, it cooperates with the protein disulfide isomerase (PDI), a key foldase and chaperone at the ER level, mediating the oxidative folding of various ER proteins (111). The PRDX4/PDI system was established to be a new oxidative folding pathway, working in parallel with the ER oxidoreductin 1 (ERO1)/PDI pathway (24).

As described above for the other PRDXs, modifications in PRDX4 levels have been associated with invasion, recurrence, prognosis, and other characteristics of cancer (112).

In pancreatic cancer, several reports have described the downregulation or upregulation of PRDX4 (113,114), although it is not yet clear whether the PRDX4 expression level may be considered to be a cause or an effect of pancreatic cancer. PRDX4 is overexpressed in prostate cancer (90), where it enhances the rate of cell proliferation (115). In other types of epithelial cancers, such as oral cavity squamous cell carcinoma (116), breast cancer (117), ovarian cancer (118), CRC (119) or lung cancer (70), overexpression of PRDX4 correlates with the metastatic potential. In particular, in lung cancer A549 cells, the Srx-PRDX4 complex significantly

contributes to the maintenance of anchorage-independent colony formation, cell migration and invasion (120). It is noteworthy that PRDX4 is overexpressed in the majority of cancers where Srx is also overexpressed (113), contributing to cell proliferation by the activation of the RAS-RAF-MEK signaling pathway (120). On the other hand, its marked down-regulation has been reported in acute promyelocytic leukemia (APL) (121).

PRDX5: Tumor-promoting effects. PRDX5 was the last member to be identified among the six mammalian PRDXs. It is the unique atypical 2-Cys PRDX in mammals, widely expressed in tissues at different levels, with a large subcellular distribution including the mitochondria, the peroxisomes, the cytosol and the nucleus (22). PRDX5 is a thioredoxin peroxidase that acts mainly by reducing alkyl hydroperoxides and peroxynitrite via cytosolic or mitochondrial thioredoxins. Its crystal structures highlight the unconventional enzymatic mechanism, involving two catalytic Cys residues that provide an opportunity for reaction with an additional molecule of H_2O_2, leading to overoxidation of C_p (122). PRDX5 is a cyto-protective antioxidant enzyme rather than a redox sensor, able to act against endogenous or exogenous peroxide attacks. Its overexpression in different subcellular compartments defends cells against death provoked by nitro-oxidative stresses, while its silencing makes the cells more susceptible to oxidative damage and apoptosis (122). It is constitutively expressed at a high level in different mammalian cell lines and normal tissues, but the specific transcription factors involved in the regulation of its expression have not yet been completely identified. It is known that transcription factors such as AP-1, nuclear factor-κB (NF-κB), antioxidant response element (ARE), insulin response element (InRE), glucocorticoid response element (GRE) (123), and also c-Myc (124), may directly modulate PRDX5 expression by interacting with putative responsive elements in the 5'-flanking region of the gene. Other transcription factors, such as nuclear respiratory factor 1 (NRF-1) and nuclear respiratory factor 2 (NRF-2; GABPA), involved in the response of mammalian cells to oxidative stress and in the biogenesis of mitochondria, are also able to modulate PRDX5 expression in an indirect way (123,125). c-Myc not only directly controls PRDX5 transcription, but also contributes in the maintenance of ROS homeostasis through its ability to selectively induce the transcription of specific PRDXs when the function of one of them is compromised (124). Up- or downregulation of PRDX5 has been reported in different types of cancer. An upregulation of transcriptional activity of PRDX5, mediated by E-twenty-six transcription factor 1 and 2 (Ets1/2) and high-mobility-group protein B1 (HMGB1), has been described in human prostate and epidermoid cancer cells exposed to H_2O_2 or hypoxia (126). Increased levels of PRDX5 have been reported in aggressive Hodgkin's lymphomas (127), in malignant mesothelioma (67), in breast carcinoma (103), in ovarian carcinoma (87) and in thyroid cancer (128). Reduced levels of PRDX5 expression have been described only in adrenocortical carcinoma (129).

PRDX6: Tumor-promoting effects. PRDX6 is the prototype and the only mammalian 1-Cys member of the PRDX family. Homologous 1-Cys proteins are widely distributed throughout all kingdoms, and they have been described in archaea, bacteria, parasites, yeast, insects, mollusks, amphibians, birds and other orders (130) (Table I). Although PRDX6 shares structural and functional properties with other members of the family, it has important and unique characteristics: It has a single conserved Cys residue causing a different catalytic cycle, and it uses glutathione (GSH) instead of thioredoxin as the physiological reductant. Furthermore, PRDX6 is able to bind and reduce phospholipid hydroperoxides, serving an important role in the repair of membrane damage caused by oxidative stress and, finally, it is a bifunctional enzyme with both phospholipase A2 (PLA2) activity and peroxidase function (130). Its catalytic Cys residue is buried at the base of a narrow pocket, differently from the other PRDXs, which renders PRDX6 unable to dimerize through disulfide formation in the native configuration, although it can homodimerize and multimerize through hydrophobic interactions (131).

PRDX6 has a widespread distribution in all organs, and essentially in all cell types (130). Its expression is regulated by the mainly redox-active regulators, such as Nrf2, Nrf3 (132,133), NF-κB (134), Sp1 (135), c-Jun, c-Myc (130) and HSF1 (136), which are able to interact with the ARE and the putative GRE localized in the PRDX6 gene promoter region. PRDX6 has been reported to be implicated in the development and progression of several human diseases, such as Alzheimer's disease (137), Parkinson's dementia (138), diabetes (139), cataractogenesis (140) and cancer. Concerning the neoplastic diseases, elevated levels of PRDX6 have been described in breast cancer (141), in malignant mesothelioma (67), in bladder cancer (61), in esophageal cancer (142), in lung (143), ovarian (87) and pancreas (144) cancer, in cancer of the gingivo-buccal area (145), and in lymphoma (146). Elevated expression levels of PRDX6 have been associated with a more invasive phenotype and metastatic potential of breast cancer (147), and with a worse prognosis of clinically localized prostate cancer following radical prostatectomy (148).

By contrast, studies performed using a thyroid proteomic approach have highlighted the reduction of PRDX6 in follicular adenomas (149), suggesting a possible role for this protein as a complementary marker to distinguish between different follicular neoplasms. More recently, a marked reduction in PRDX6 levels has been demonstrated in a cohort of PTCs (75). Taken together, all these studies have demonstrated that PRDX6 has a pro-tumorigenic function, promoting cell proliferation by its peroxidase activity, and facilitating invasiveness by means of its PLA2 activity (150).

To date, the association between PRDX6 single nucleotide polymorphisms (SNPs) and cancer has yet to be fully elucidated. In esophageal cancer, no association was identified between the risk of cancer and clinicopathological characteristics, including the tumor grade and stage, and the presence of SNPs (91). However, preliminary studies in breast cancer have demonstrated that the survival of carriers of the PRDX6 SNPs, rs4916362 and rs7314, was consistently less favorable (151).

5. PRDXs and chemoresistance

Cancer cells, compared with normal cells, have a high rate of ROS production as by-products of their metabolism (152), and to survive with this redox status, the levels of antioxidant

proteins, such as CAT, SOD, glutaredoxin and PRDXs, are increased (152-154). This unique capability of cancer cells may serve an important role also in the development of resistance to chemo- or radiotherapy, as these treatments are strongly dependent on ROS-induced cytotoxicity. A search of the literature demonstrates that increased levels of PRDXs are often associated with radioresistance or chemoresistance to numerous drugs. High levels of PRDX2 correlate with radioresistance in breast cancer and glioma cells (155), as well as with cisplatin chemoresistance in gastric cancer cell lines (156) and in human erythroleukemia K652 and human ovarian carcinoma SKOV-3 cells (157), since increased levels of this antioxidant inhibit apoptosis. Furthermore, in head-and-neck cancer and in gastric carcinoma cells, PRDX2-specific antisense vectors restore the induction of pro-apoptotic pathways following radiation or cisplatin treatment, confirming the important role of PRDX2 in the resistance process (158). Several other types of cancer, including erythroleukemia, breast carcinoma and human ovarian carcinoma, develop cisplatin resistance through a significant increase in the levels of PRDX1, PRDX3 and PRDX6 (157,159). In addition, the upregulation of PRDX2 is also involved in the development of gefitinib resistance in a non-small cell lung carcinoma model, where it is responsible for the induction of tumor cell growth via activation of phosphorylated c-Jun N-terminal kinase (JNK) and the suppression of apoptosis signaling (160). In breast cancer cell lines, increased PRDX3 levels correlate with resistance to the chemotherapeutic drug, doxorubicin (161). PRDX3 controls the apoptotic signaling pathway through the regulation of cytochrome *c* release from the mitochondria, as well as through interaction with the complex of leucine zipper-bearing kinase (LZK) and IKB kinase (IKK). Therefore, it is conceivable that drugs targeting PRDX3 and the mitochondrion-specific electron suppliers, Trx2, TrxR2 and Srx, could represent a good strategy for improving the response to various chemotherapeutic agents, including cisplatin, paclitaxel and etoposide (162,163). Finally, there is evidence that PRDX5 is also involved in the chemoresistance to adriamycin, bleomycin, vinblastine and dacarbazine in patients affected with aggressive Hodgkin's lymphomas (127) and *in vitro* in the lung carcinoma U1810 cell line (164), always by inhibiting chemotherapeutic-induced apoptosis.

Chemoresistance is a complex phenomenon caused by multiple and heterogeneous mechanisms of action, which are orchestrated not only by the tumor microenvironment, but also by the biology of the tumor itself. The modulation of endogenous antioxidant levels may be a determining factor for the sensitivity of certain tumors to various chemotherapeutic agents. In addition, it is important to highlight that the regulation of intracellular antioxidant concentration is a 'double-edged sword': On the one hand, enhanced antioxidant activity represents an advantageous protection of the cells from ROS, whereas, on the other hand, the depletion of antioxidants represents an important strategy to sensitize cancer cells to chemotherapy (chemosensitization) (50).

6. Conclusions

PRDXs serve a critical role in several physiological, as well as pathological, conditions involving redox signaling. Although their protective role in cardiovascular and neurological diseases is clear, their role in cancer remains controversial: Different PRDX isoforms may have a tumor-suppressor or an oncogenic role, depending on the cancer type. Considering the peroxidase-dependent and -independent secondary functions and the fine balance involved in the regulation of the oligomeric state and the function of the PRDX, more has been learnt about these antioxidants and their involvement in the control of cell growth and survival, particularly as a part of normal growth and development. To date, it remains to be clarified how the levels of peroxide and the peroxidases interplay, and how the regulatory behavior may change depending on the different developmental stages of the tissue, or on the disease states. Several studies have hypothesized that the ROS resistance of the cancer cells is sustained, at least in part, by overexpression of the PRDXs responsible for the antioxidant activity increase and/or the alteration in growth and activation of the death pathways (112,165). On the other hand, in certain cases PRDXs have been suggested to function as tumor preventers, rather than as tumor suppressors (166), in that, via detoxification of the ROS, they contribute to the maintenance of genomic integrity. In conclusion, in the future it will be crucial to clarify the exact role of PRDXs in cellular homeostasis, as well as in cancer development and drug resistance, in order to develop new target therapeutic strategies for cancer treatment or prevention.

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