Peroxiredoxins: Types, Characteristics and Functions in Higher Plants

José Rafael Pedrajas and José Antonio Bárcena

Abstract Peroxiredoxins (PRXs) are a class of peroxidases present in all organisms with thiol-based catalytic activity with a variety of peroxide substrates. Cells usually contain several PRX isoenzymes specifically distributed in organelles. PRXs can be differentiated into two categories: 1-Cys and 2-Cys, depending on the number of cysteine residues that participate in the catalytic mechanism. An additional classification can be made within 2-CysPRXs: typical and atypical. PRXs can also be structurally differentiated into six subfamilies that are named after a canonical member: AhpC/Prx1, Prx5, Prx6, Bcp, AhpE and Tpx. The first four subfamilies are present in plants. In this chapter we will discuss the general characteristics of these four subfamilies of PRXs, giving specific attention to their functions in plants, where they show an important role in the defense against oxidative stress and adverse environmental conditions. In addition, we will focus on tissue specific and developmental distribution of plant PRXs.

Keywords Peroxidase · Peroxiredoxin · Thioredoxin · Glutaredoxin
Glutathione · Reactive oxygen species · Antioxidants

1 Introduction

Peroxides are compounds with a peroxyl motif (–O–O–) that exert relevant actions on living beings. Hydrogen peroxide (H_2O_2) is a reactive oxygen species (ROS) with a relatively low oxidative power but its reduction via the Fenton

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reaction generates the very reactive hydroxyl radical ($^•OH$), which is a strong oxidant for most of biomolecules including lipids, proteins and DNA (Sies 1986). H_2O_2 is mainly produced in cells as a product of the dismutation of the superoxide anion ($O_2^{•-}$), catalyzed by superoxide dismutases. It is metabolically produced in many processes; for example, as a byproduct of cellular respiration and photosynthesis, β-oxidation, NADPH oxidases and other oxidases (Cadenas et al. 1977; Heber 2002; Foreman et al. 2003; Geiszt and Leto 2004; Corpas 2015). H_2O_2 can also be generated by abiotic factors like redox-cycling xenobiotics, metals or high-energy radiations. High H_2O_2 concentrations are potentially deleterious for cells for the reason described above; however, at low levels, hydrogen peroxide acts as an intramolecular messenger in cellular signalling (Neill et al. 2002; Vivancos et al. 2005; Stone and Yang 2006; Veal et al. 2007). The radical mediated oxidation of unsaturated fatty acids known as lipid peroxidation leads to the propagation of alkyl hydroperoxides and other degradation products that can form adducts with macromolecules, altering their functions (Pedrajas et al. 1998). Peroxynitrite (ONOOH) is generated in cells by the spontaneous reaction of nitric oxide ($^•NO$) with the superoxide anion and can mediate nitration of tyrosine residues in proteins and fatty acids, causing cellular dysfunctions (Radi 2004; Chaki et al. 2015; Mata-Pérez et al. 2016). Cells defend against the damage caused by peroxides using antioxidant enzymes with peroxidase activity and non-enzymatic biomolecules such as tocopherols, carotenoids or ascorbic acid.

2 Common Characteristics of Peroxiredoxins

Peroxiredoxins (PRX; E.C. 1.11.1.15) are simple proteins with peroxidase activity on a variety of peroxide substrates, such as hydrogen peroxide (H_2O_2), alkyl hydroperoxides (ROOH) and peroxynitrite (ONOOH). They exist in virtually all living beings and cells usually contain several isoforms specifically distributed in organelles such as cytosol, mitochondria, peroxisomes, nucleus and chloroplasts, and even in the extracellular space. All peroxiredoxins contain a 'peroxidatic' cysteine (C_P) at the active site, which is oxidized to cysteine sulfenic acid (C_P-SOH) by the peroxide substrate, resulting in the peroxide being reduced to the corresponding hydroxylated compound. This reaction occurs with a second order rate constant ranging from 10^{-5} to 10^{-8} M^{-1} s^{-1} and with K_m of micromolar magnitude (Winterbourn and Peskin 2016). The C_P-SOH can be reduced to C_P-SH with non-physiological thiol reducers, such as dithiothreitol or β-mercaptoethanol, but physiologically the sulfenic group condensates with another cysteine of the same protein, the 'resolving' cysteine (C_R), forming a disulfide bond. Then, the disulfide is reduced by an enzymatic thiol-based system, generally a thioredoxin system, composed of thioredoxin (TRX) and thioredoxin reductase (TRR); for this reason, the peroxiredoxins have been also named thioredoxin peroxidases (Chae et al. 1994; Jeong et al. 1999, 2000). In some cases, the tripeptide glutathione (GSH) provides the resolving cysteine to the peroxiredoxin, forming a mixed

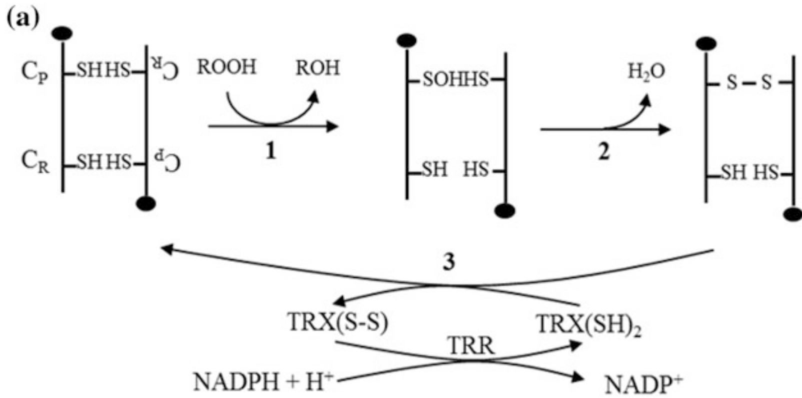
disulfide that is reduced by a glutaredoxin system, composed of glutaredoxin (GRX), GSH and glutathione reductase (GR) (Rouhier et al. 2002b; Pedrajas et al. 2010, 2016). Particularly, the resolving cysteine of *Mycobacterium tuberculosis* AhpE peroxiredoxin is provided by mycothiol, a disaccharide conjugated with cysteine (Hugo et al. 2014; Kumar et al. 2016). In all cases, NADPH is the source of reducing equivalents for all peroxiredoxins. Therefore, the catalytic mechanism of peroxiredoxins consists of three stages: peroxidation, resolution and recycling (Fig. 1).

The structure of the peroxiredoxin protein contains a typical TRX fold, with a core of seven β-strands surrounded by five α-helices (Copley et al. 2004). The C_P is located at the first turn of the α_2-helix, included in a conserved motif (PXXX[T/S]XXC). A conserved arginine residue at the β_6 strand near the C_P in the folded protein contributes to stabilizing the deprotonated thiolate form of the C_P, thus conferring a high reactivity toward peroxides (Hall et al. 2011; Nelson et al. 2011).

3 Types of Peroxiredoxins

Peroxiredoxins can be differentiated into two categories, 1-Cys and 2-Cys peroxiredoxins, on the basis of which provides the resolving cysteine and how it participates in the resolution stage (Fig. 1). For 1-CysPRXs, a small thiolic molecule, generally GSH, provides the resolving cysteine and therefore a mixed disulfide is formed. Among 2-CysPRXs, an additional distinction can be made between typical and atypical. Typical 2-CysPRXs are obligated dimers so that the C_P-SOH of one monomer condensates with the C_R-SH of the other monomer forming an intermolecular disulfide, whereas the resolution of atypical 2-CysPRXs results in an intramolecular disulfide between the C_P and the C_R of one single polypeptide.

Another classification of peroxiredoxins is based on conserved sequences and structure profiles around the active site, resulting in six relevant subfamilies named after a canonical member: AhpC/prx1, prx5, prx6, Bcp, AhpE and Tpx (Soito et al. 2011; Nelson et al. 2011; Hall et al. 2011; Poole and Nelson 2016). The first four subfamilies are present in plants, and are summarized in Table 1. In this chapter, we will discuss the specific characteristics and functions of these four subfamilies of peroxiredoxins. Note that we will refer strictly to peroxiredoxins; plants also have a family of peroxidases referred to as glutathione peroxidases, which preferentially use thioredoxin instead of GSH as an electron donor, but its phylogenetic origin is different from that of peroxiredoxins (Rouhier and Jacquot 2005; Navrot et al. 2006) and will not be dealt with in this review.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TRX(SH)2
TRR
NADPH + H+
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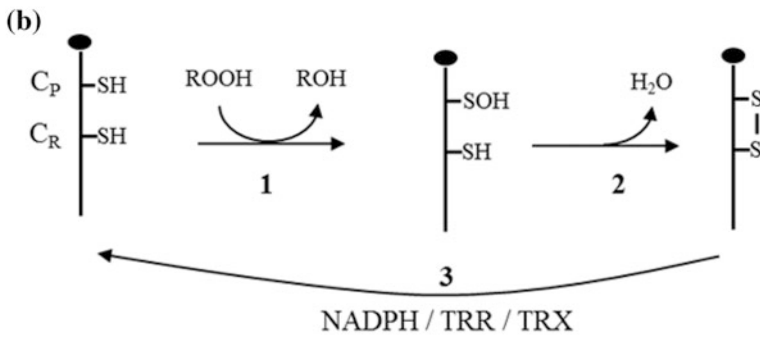
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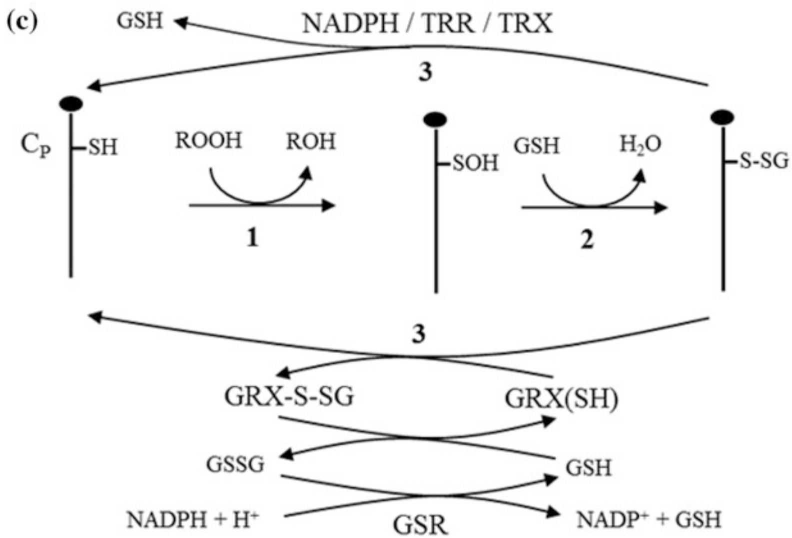
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GRX(SH)
GSSG
GSH
NADPH + H+
GSR
NADP+ + GSH

◂**Fig. 1** Catalytic cycle for typical 2-Cys peroxiredoxins (**a**), atypical 2-CysPRXs (**b**) and 1-CysPRXs (**c**), indicating the three stages of each peroxidase activity cycle: peroxidation (1), resolution (2) and recycling (3)

Table 1 Summary of PRX subfamily in higher plants

Subfamily	Representatives in *A. thaliana*	Localization (Specific for organ)	Catalytic mechanism	Distinctive features
AhpC/Prx1	2-CysPrxA, B	Chloroplast	Typical 2-Cys PRX	C_R at C-teminus B-type dimers Oligomerization to decamers Regenerated by sulfiredoxin
Prx6	*At*Per1	Nucleus and cytosol (seed)	Uncertain, without characterized C_R	B-type dimer Longer C-terminus
Prx5	*At*Prx IIB *At*Prx IIC, D *At*Prx IIE *At*Prx IIF*	Cytosol Cytosol (pollen) Chloroplast Mitochondria*	1-Cys PRX C_R provided by GSH	A-type dimers Heterocomplex with Trx-o* Regenerated by sulfiredoxin *
BCP	Prx Q	Chloroplast	Atypical 2-CysPrx	Monomeric C_PXXXXC_R motif

*Refers to specific features of AtPrx IIF protein

4 AhpC/prx1-Type Peroxiredoxins

The ahpC/prx1 subfamily of peroxiredoxins has representatives in all classes of prokaryotes and eukaryotes; characterized members include the bacterial AhpC protein (Jacobson et al. 1989; Parsonage et al. 2005), the tryparedoxin peroxidase of *Trypanosomatidae* (Flohé et al. 2002), the plant Bas1 protein (Baier and Dietz 1997), the *Saccharomyces cerevisiae* TSA proteins (Chae et al. 1994), and the human PrxI-IV proteins (Wood et al. 2003). The polypeptides have an average molecular weight of 25 kDa and, compared with the common core structure of the peroxiredoxins, a 40–50 residue extension at the C-terminus where the resolving cysteine is located. The basic structure is a B-type dimer in which the monomers are positioned oppositely, contacting along their β7 strands and, thus, their core strands together form an extended 10-strand sheet (Fig. 2a) (Hall et al. 2011). Both subunits are functionally complementary, possessing two active sites that develop a typical 2-Cys catalytic mechanism. To recycle the active site, the disulfide of resolution is reduced, usually by TRX, although other specific reductases with a Trx-like domain can perform the recycling step (Jönsson et al. 2007; Pérez-Ruiz et al. 2006; Pérez-Ruiz and Cejudo 2009). Structural studies show two

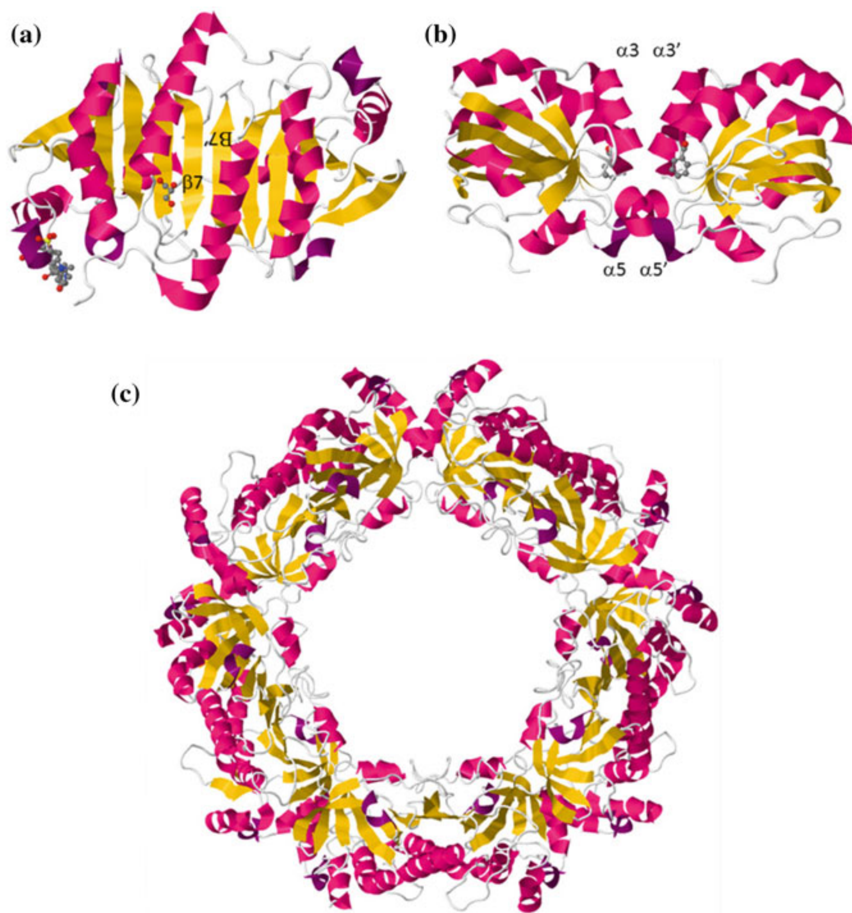

Fig. 2 Ribbon diagrams of **a** a B-type dimer formed by the peroxiredoxin HsPrxI, showing contact regions along β7 strands (PDB ID: 4XCS); **b** of the A-type dimer formed by HsPrxV (PDB ID: 2VL2), showing the association of the α3 helix of one monomer with the α5 helix of the other one; and **c** decamer formed by the peroxiredoxin HsPrxII (PDB ID: 1QMV)

conformations of the active site during the catalytic cycle, designated as FF (fully folded) and LU (locally unfolded) states (Wood 2003; Cao et al. 2011). At the FF state, the C_P is positioned at the first turn of the α2 helix 14 Å far from the complementary C_R, which is positioned in a β-strand at the C-terminus extension of the adjacent subunit. To form a disulfide bond, both motifs have to undergo a local unfolding in order for the cysteines to approach.

Two classes of peroxiredoxins can be distinguished in this subfamily according to their sensitivity to inactivation by overoxidation (Wood 2003). The robust peroxiredoxins, representatives of bacteria and some parasitic protozoan, maintain peroxidase activity at relatively high peroxide concentrations. The sensitive peroxiredoxins

are inactivated at high peroxide concentration because the peroxidatic cysteines are further oxidized to sulfinic (C_P-SO_2H) or sulfonic (C_P-SO_3H) acids. To be specific, we will refer to the robust peroxiredoxins as ahpC-type and to the sensitive peroxiredoxins as prx1-type. The sensitivity of the prx1-peroxiredoxins is related to two exclusive structural features: a conserved Gly-Gly-Leu-Gly sequence in a loop between α4 and β5 (the GGLG motif), and an additional helix (α7) at C-terminus with a conserved Tyr-Phe sequence (the YF motif). Both motifs pack next to the active site region hindering the approaching among C_P and C_R. Thus, C_P-SOH can be maintained momentarily without reacting with C_R-SH, favoring reaction with another peroxide molecule its over-oxidation by. This structural feature of the sensitive peroxiredoxins is considered an evolutionary resource related to cellular signaling processes in eukaryotes, since the inactivation may be part of a mechanism to increase the level of intracellular H_2O_2 sufficiently for it to act as messenger for signal transduction. Therefore, it has been proposed that prx1-peroxiredoxins act as floodgates that allow for local buildup of peroxide concentrations for signaling purposes (Neill et al. 2002; Wood 2003; Rhee et al. 2005; Veal et al. 2007; Karplus 2015).

If the hyperoxidation of the peroxiredoxins is a signaling mechanism, inactivation must not be permanent since controlled reversibility is a requirement for any mechanism to have physiological meaning. Sulfiredoxins (SRX) are small monomeric proteins that specifically reduce C_P-SO_2H to C_P-SOH in prx1-peroxiredoxins (Biteau et al. 2003; Woo et al. 2005). Sulfiredoxins transfer a phosphate group from ATP to the sulfinic moiety of the overoxidized C_P, leading to a phosphoryl sulfinic intermediate (PRX-SO-O-PO_3). Then, a catalytic cysteine of SRX attacks the phophoryl sulfinic ester bond to form a thiolsulfinate bond (PRX-SO-S-SRX). The resolution of the thiolsulfinate intermediate defines two types of sulfiredoxins. The 2-Cys sulfiredoxins use another cysteine residue of their own to attack the thiolsulfinate intermediate, generating an intramolecular disulfide bond in SRX that is finally reduced by TRX (Roussel et al. 2009). The second catalytic cysteine is absent in 1-Cys sulfiredoxins, so it is GSH that breaks the thiolsulfinate bond, resulting in a mixed disulfide (SRX-S-SG) that is finally dissociated by glutaredoxin (Boukhenouna et al. 2015). The outcome is a sulfenilated peroxiredoxin (PRX-S_POH) ready for peroxidase activity. Sulfiredoxins may also have activity as a deglutathionylating enzyme (Findlay et al. 2006). Prx1-peroxiredoxins can be glutathionylated at both catalytic and non-catalytic cysteines when exposed to an excess of oxidized glutathione (GSSG); sulfiredoxins can then reduce the resulting mixed disulfides (Park et al. 2009; Calderón et al. 2017).

Prx1-peroxiredoxins may also modulate peroxide signaling by consuming the reducing power accumulated in the cell in the form of thioredoxins, thus competing with other Trx-dependent signaling proteins (Brown et al. 2013). In addition, since they have a high affinity for peroxides, peroxiredoxins act as very effective transmitters of oxidative equivalents from peroxides to specific proteins with regulatory functions (Tachibana et al. 2009; Jarvis et al. 2012; Sobotta et al. 2014; Irokawa et al. 2016). On the other hand, the inactivation of peroxiredoxin by overoxidation allows thioredoxins to be targeted to other oxidative damage repair systems, improving cell survival under acute stress conditions (Day et al. 2012).

The ahpC/prx1-peroxiredoxins can reversibly assemble to constitute doughnut-shaped decamers or even higher-order oligomeric structures (Fig. 2c) (Schroder et al. 2000; Wood et al. 2002; Parsonage et al. 2005; Barranco-Medina et al. 2009). The active site conformation acts as a molecular switch that modulates the oligomeric state of these peroxiredoxins. The FF state favors the decameric structures and the disulfide-containing forms tend to remain as dimers. So, the peroxiredoxins in both reduced and overoxidized states, in which the FF conformation predominates, mainly form decamers. Decameric peroxiredoxins show higher catalytic efficiency than dimers (Kitano et al. 1999; Chauhan and Mande 2001; Parsonage et al. 2005). The α3 helix of the peroxiredoxin is the contact surface between adjacent dimers forming decamers. Specific cyclin-dependent kinases phosphorylate a Thr residue at the α3 helix of the mammalian prx1-type peroxiredoxins, which leads to the attenuation of peroxidase activity probably by destabilization of the decamers (Chang et al. 2002; Wood et al. 2003; Jang et al. 2006). The oligomerization confers other relevant functions to these peroxiredoxins as chaperones that protect proteins from denaturalization when they are exposed to heat and oxidative shocks (Jang et al. 2004; Moon et al. 2005). As the overoxidation of C_P favors the oligomerization of the ahpC/prx1-peroxiredoxins, the chaperone activity seems to be redox sensitive and potentiated under stress conditions.

Glutathionylated PrxI and II have been detected in mammalian tissues (Sullivan et al. 2000; Fratelli et al. 2002; Salzano et al. 2014; Checconi et al. 2015). Recently, it has been proved that human PrxII can be glutathionylated in both peroxidatic and resolving cysteines at physiological concentrations of GSH, the mixed disulfide being dissociated by glutaredoxin (Peskin et al. 2016). This study raises the question of whether most of the ahpC/prx1-peroxiredoxins can be physiologically glutathionylated at their active sites and therefore can be recycled by a dual mechanism using both thioredoxins and glutaredoxins. In addition, the glutathionylation of the active site cysteines could probably mediate the oligomerization state and the chaperone activity (Park et al. 2011).

4.1 The Plant Prx1-Peroxiredoxins

The prx1-type peroxiredoxins of plants are located in plastids, which are among the most abundant proteins in stroma. *Arabidopsis thaliana* genome expresses two chloroplast peroxiredoxins, 2-CysPrxA (2CpA) and 2-CysPrxB (2CpB), which share 85% homology (Baier and Dietz 1997; Dietz et al. 2002; Horling et al. 2003). Plastids contain a large set of thioredoxins and Trx-like reductases that can provide reducing equivalents to the 2-CysPrxs, but two of them in particular—Trx-x and, even more efficiently, NTRC (NADPH Thioredoxin Reductase C)—seem to be the most physiologically involved: (Broin et al. 2002; Collin et al. 2003; Pérez-Ruiz et al. 2006; Moon et al. 2006; Bernal-Bayard et al. 2014). NTRC is a fusion-like protein formed by an FAD-containing TRR domain and a TRX domain at the C terminus, and

constitutes a complete thioredoxin system by itself (Pérez-Ruiz and Cejudo 2009). The chloroplast thioredoxins, including Trx-x, get their reducing power from ferredoxin (Fd) catalyzed by the ferredoxin thioredoxin reductase (FTR). So, the reducing power obtained by chloroplast peroxiredoxins through thioredoxins ultimately comes from the electronic photosynthetic transport chain and, therefore from light. On the contrary, NTRC takes reducing power from NADPH, which is produced not only by ferredoxin reductase (FR) via the photosynthetic system, but also by other metabolic pathways such as the pentose phosphate pathway (Spínola et al. 2008). Therefore, NTRC supports the antioxidant activity of the 2-CysPrxs in darkness. In fact, the lack of NTRC in *Arabidopsis* reveals a hypersensitive phenotype related to oxidative stress in plants submitted to prolonged darkness (Pérez-Ruiz et al. 2006).

As a general feature of prx1-peroxirredoxins, plastidial 2-CysPrxs may also adopt oligomeric structures favored by the FF conformation of the active sites—that is, the reduced and the over oxidized states. Attachment of the oligomerized 2-CysPrxs to the thylakoid membrane has been observed (König et al. 2002, 2003), and for this reason it has been postulated that, under environmental constraints, plastidial peroxiredoxins are over oxidized, oligomerized and attached to thylakoids, conferring protection to the photosynthetic apparatus as chaperones (Kim et al. 2009; Muthuramalingam et al. 2009). Recently, this hypothesis has been questioned by evidence showing that the peroxiredoxins do not attach to thylakoid membranes and that the environmental constraints do not substantially change the over-oxidation and oligomerization status of 2-CysPrxs (Cerveau et al. 2016). Nevertheless, the levels of over-oxidized forms vary during the daytime, being highest after the dark–light transition. In addition, the absence of the sulfiredoxin does not affect the over-oxidation levels under normal environmental conditions (Cerveau et al. 2016).

2-CysPrxs are basically present in all plant organs (Cerveau et al. 2016). A moderate up-expression is observed at high light conditions and, conversely, they are notoriously downregulated at low light (Horling et al. 2003). Foliar exposure to oxidative compounds hardly modifies their gene expression; however, exposure to reductants like ascorbate or GSH causes acute repression (Horling et al. 2003). Plants with suppressed 2-CysPrx expression show symptoms of oxidative damage (Pulido et al. 2010; Awad et al. 2015). Plants null for both 2-CysPrxs show growth retardation, reduced chlorophyll content, bleached leaves, photosystem inhibition, reduced CO_2 fixation, higher levels of oxygen reactive species, lipid peroxidation and protein carbonylation, and H_2O_2-related repression of the anthocyanin biosynthesis (Awad et al. 2015). Chloroplast 2-CysPrxs seem to protect the photosynthetic apparatus with a water-water cycle much more efficiently than the characterized Mehler-ascorbate peroxidase pathway (Forti and Elli 1995; Kangasjärvi et al. 2008). The photosynthetic electron chain can become over-reduced by high light conditions. The electron pressure can be relieved by transfer of electrons to O_2, leading to the formation of $O_2^{\cdot-}$, which is subsequently dismutated to O_2 and H_2O_2 by the chloroplast SOD, what constitutes the Mehler reaction. Then, the ascorbate peroxidase (APX) reduces H_2O_2 to H_2O. Therefore, the photosynthetic apparatus is in this way protected from over-reduction. The

chloroplast 2-CysPrxs would not only reduce H_2O_2 generated by the Mehler reaction, but also they would use reducing equivalents generated from PSI via Fd-FTR-Trx, contributing to alleviate the electron pressure on the photosystems.

5 Prx6-Type Peroxiredoxins

Prx6-peroxiredoxins are present basically in all living beings. Members of this subfamily include the archaeal ApTPx (Jeon and Ishikawa 2003; Nakamura et al. 2006), the bacterial LsfA (Kaihami et al. 2014), the plant Per1 (Stacy et al. 1996; Haslekås et al. 1998), the yeast Prx1p (Pedrajas et al. 2000), and the mammalian PrxVI (Kang et al. 1998). Prx6-peroxiredoxins are structurally similar to the ahpC/prx1 ones, their basic structure is the B-type dimer and they have a longer C-terminal extension. However, they do not have the conserved resolving cysteine of the ahpC/prx1-peroxiredoxins. Some members of the prx6-peroxiredoxins behave as typical 2-Cys peroxiredoxins since they have a non-conserved C_R at the C-terminal that establishes an intermolecular disulfide with the C_P, which is reduced by TRX. Furthermore, they can form toroid-shaped decamers (Jeon and Ishikawa 2003; Mizohata et al. 2005; Nakamura et al. 2006). However, most prx6-peroxiredoxins do not have cysteine residues close enough to C_P to achieve the establishment of a disulfide that could be substrate for TRX. In fact, some prx6-peroxiredoxins have no more cysteine than the peroxidatic one (Kaihami et al. 2014; Pedrajas et al. 2016). Apart from those described before, prx6-peroxiredoxins do not form toroid-shaped decamers, probably due to steric hindrances (Smeets et al. 2008a, b).

Human PrxVI does not show Trx-dependent peroxidase activity in vitro although it can reduce peroxides with dithiothreitol (Kang et al. 1998). Some studies proposed the cyclophilin A as the physiological electron donor of PrxVI but this assumption has not been extensively corroborated (Lee et al. 2001). Other studies propose that Prx VI acts as a glutathione peroxidase mediated by πGST (Manevich et al. 2004; Ralat et al. 2006). PrxVI may form a heterodimer with the GSH-loaded πGST and thus oxidized C_P-SOH is glutathionylated. Then, the heterodimer is dissociated and other GSH molecule acts on the mixed disulfide regenerating the reduced peroxiredoxin and yielding GSSG. Moreover, mammalian PrxVI is a bifunctional enzyme with both peroxidase and phospholipase A_2 activities (Chen et al. 2000; Fisher 2011). The phospholipase activity is carried out in a different active site, specifically by a triad formed by Ser32, His26 and Asp140 in human PrxVI (Manevich et al. 2007). PrxVI is located in both cytosol and lysosomes (Akiba et al. 1998). The phospholipase activity is optimal at acid pH according to lysosomal location. However, the phosphorylation of PrxVI by specific kinases broadens the pH spectrum of activity, so it can develop a relevant phospholipase activity also in membranes surrounding cytosol (Wu et al. 2009). Therefore, PrxVI seems to perform a dual function as a specialized restorer of peroxidized lipids in membranes as well as a player in the catabolism of phospholipids (Fisher et al. 1999; Manevich et al. 2009; Fisher 2011).

Given that mammalian PrxIV is considered the prototype of 1-Cys peroxiredoxins, its inability to receive electrons from thioredoxin has been assumed for the rest of members of the group. However, prx6-peroxiredoxin from *S. cerevisiae*, named Prx1p, shows thioredoxin peroxidase activity in vitro (Pedrajas et al. 2000). The mature Prx1p is localized in the mitochondrial matrix and has no other cysteine residue apart from the peroxidatic residue. The peculiar thioredoxin peroxidase activity of Prx1p can be explained because the oxidized C_P-SOH of a subunit can react with the reduced C_P-SH of another subunit, forming a disulfide bridge between two C_P, which is a proper substrate for the mitochondrial Trx3p. In addition, the oxidized C_P-SOH of Prx1p can directly react with reduced glutathione at equivalent molecular ratios, forming a glutathionylated intermediate at the active site, which is resolved by Trx3p and GSH is recovered (Pedrajas et al. 2016). Therefore, characterization of *S. cerevisiae* Prx1p has revealed a novel antioxidant action of reduced glutathione, acting as a co-worker in the catalytic mechanism of a thioredoxin peroxidase without being oxidized in the process, unlike other peroxidases that depend on glutathione (Pedrajas et al. 2016). The mixed disulfide with glutathione formed at the peroxidatic cysteine is also resolved by the mitochondrial Grx2p throught a canonical mechanism with results in glutathione oxidation (Pedrajas et al. 2010). The formation of a disulfide between peroxidatic cysteines from two different subunits is an event that occurs in isolated Prx1p in vitro. Such a disulfide is physiologically unlikely and ephemeral in any case, due to the presence of the thioredoxin system and GSH, of which only micromolar traces are required (Pedrajas et al. 2016).

It has been also postulated that ascorbate is a reductant for the yeast 1-CysPRX (Monteiro et al. 2007). However, using the xylenol orange assay (FOX) that measures the H_2O_2 concentration (Lindahl and Cejudo 2013), we have not detected ascorbate dependent peroxide consumption by Prx1p (Pedrajas, unpublished results).

5.1 The Plant Prx6-Type Peroxiredoxins

Plants genomes have just one gene that codes for a prx6-peroxiredoxin, generally named Per1. *PER1* gene is expressed in seeds, specifically in the aleurone layer and embryo (Aalenf et al. 1994; Haslekås et al. 1998; Stacy et al. 1996). The expression level increases in late seed development, attenuates at the dehydration phase and is maintained in mature seeds during storage. Just before seed germination, *PER1* expression increases dramatically and then gradually disappears in seedlings (Haslekås et al. 1998; Chen et al. 2016). Per1 protein contains a putative C-terminal nuclear signal and therefore it localizes in the cell nucleus, although it can also be detected at cytosol (Stacy et al. 1999; Haslekås et al. 2003; Chen et al. 2016). The seed-specific expression pattern of *PER1* gene points to this peroxiredoxin contributing to the maintenance of seed dormancy (Aalenf et al. 1994; Stacy et al. 1996; Haslekås et al. 1998). In fact, *PER1* gene is strongly upregulated by the abscisic acid (ABA), a hormone that induces dormancy (Kim et al. 2011). However,

this assumption has been gradually ruled out in favor of an antioxidant function. Transgenic tobacco plants overexpressing the rice *PER1* showed higher resistance to ROS (Lee et al. 2000). Per1 prevented DNA cleavage in mixed function oxidation assays (Haslekås et al. 2003; Chen et al. 2016). Furthermore, the presence of Per1 proteins is not exclusive to seeds but it is also found in the nucleus of leaf cells in resurrection plants submitted to severe desiccation (Mowla et al. 2002). Both desiccation and resumption of respiration after rehydration produce high levels of reactive oxygen species (Leprince et al. 1994). Therefore, it seems likely that plant prx6-peroxiredoxin would have an antioxidant function protecting nuclear DNA from reactive oxygen species generated during the desiccation and rehydration of seeds and of certain specialized plants. In addition, the reduced or increased expression of *At*Per1 either anticipates or delays germination, respectively, under stressful conditions and for this reason it has been suggested that prx6-peroxiredoxin contributes to the perception of environmental conditions in seeds, preventing them from germinating under unfavorable conditions (Haslekås et al. 2003).

A study with *Ta*Per1 from wheat has revealed a novel electron donor for this type of peroxiredoxin: the NADPH-dependent thioredoxin reductase (NTR) (Pulido et al. 2009). NTR differs from the chloroplast NTRC referred to previously in that it does not carry a functional thioredoxin domain, so it is structurally and functionally similar to most of thioredoxin reductases. NTR and Trx-h constitute the main thioredoxin system in wheat seeds (Cazalis et al. 2006). However, in vitro assays demonstrated that NTR directly transfers the reducing power from NADPH to *Ta*Per1 and Trx-h has no influence on the peroxidase activity. *Ta*Per1 has four cysteine residues: the closest to the N-terminus is C_P; the following cysteine is conserved in the prx6-peroxiredoxins of plants; the third cysteine is conserved in monocotyledons; and the fourth appears to be common among grasses. *Ta*Prx1 variants without the second or third cysteine maintain some NTR-dependent peroxidase activity. However, the *Ta*Prx1 variant without the final cysteine has not been obtained, so its implication in the catalytic process is not known. This wheat peroxiredoxin oxidizes ascorbate in the presence of H_2O_2, as was also observed in the yeast prx6-peroxiredoxin (Monteiro et al. 2007; Pulido et al. 2009).

Finally, no investigation has yet been reported concerning the possible phospholipase activity of plants prx6-peroxiredoxin, although the putative catalytic triad His/Ser/Asp is present in many plant prx6-peroxiredoxins.

6 Prx5-Type Peroxiredoxins

The prx5-peroxirredoxins are present in all living beings except in archeaes. Prx5 polypeptides have an average molecular weight of 20 kDa and the native proteins form A-type dimers in which the α3 helix of one monomer comes into close contact with the α5 of the other monomer, and their respective core β-sheets are not aligned as in the B-type dimer (Fig. 2b) (Evrard et al. 2004; Echalier et al. 2005; Knoops

et al. 2011; Lian et al. 2012). The presence of the C_R is very variable among prx5-peroxiredoxins, so different catalytic mechanisms occur in this subfamily. For example, the human PrxV, whose C_R is in the loop preceding the α5 region, forms an intramolecular disulfide at the resolution stage and it is recycled by TRX, so PrxV displays an atypical 2-Cys pathway (Seo et al. 2000; Smeets et al. 2008a, b; Knoops et al. 2011). However, a cysteine adjacent to the α5 region is not present in the non-mammalian members of this subfamily. On the other hand, the prx5-peroxiredoxin from *S. cerevisiae* (Ahp1p), which contains three cysteine residues (C31, C_P62 and C120), displays a catalytic mechanism similar to that of the typical 2-Cys peroxiredoxins, forming an intermolecular disulfide bridge at the resolution stage that is reduced by TRX, even though the position of the resolving cysteine is different to that of the prx1-peroxiredoxins. The first studies pointed to C120 as the C_R of Ahp1p (Jeong et al. 1999); however, further studies showed that C31, which is located in an unfolded region between strands β1 and β2, is the catalytic partner for the C_P of the other monomer (Lian et al. 2012). C31 but not C120 is a conserved residue in prx5-peroxiredoxins of bacteria and fungi. Finally, some plants' prx5-peroxiredoxins display a 1-Cys catalytic mechanism (Rouhier et al. 2001, 2002b)—this aspect will be discussed later.

A group of pathogenic bacteria (*Haemophilus influenza*, *Neisseria meningitidis*, *Vibrio cholerae*, etc.) possess a particular hybrid protein, with a prx5-peroxiredoxin domain linked to a glutaredoxin domain (Kim et al. 2003). These hybrid proteins form tetramers so that the Grx redox cysteines of a protein are situated proximal to the C_P of the adjacent subunit. In fact, the glutathione molecule would fit tightly in the space between the active sites of the peroxiredoxin and the glutaredoxin. Therefore, these hybrid proteins constitute a functional set in which the peroxidase domains are assisted by the neighboring glutaredoxin domains. Apart from these hybrid peroxiredoxins, there is no evidence of oligomers greater than dimers in prx5-peroxiredoxins, except for the mitochondrial peroxiredoxin of plants, which will be discussed below.

6.1 The Plant Prx5-Type Peroxiredoxins

The first prx5-peroxiredoxin characterized in plants was that from *Brassica rapa*, which displayed peroxidase activity with the support of a yeast thioredoxin system (Choi et al. 1999). Thereafter, a homologous peroxiredoxin from poplar (*Pt*Prx II) was characterized that showed Trx-dependent peroxidase activity, but it was demonstrated that the peroxidase activity is also supported by the reducing power of a GSH/GRX system (Rouhier et al. 2001, 2002b). Thus, the 1-Cys catalytic mechanism of the peroxiredoxins was revealed for the first time. *Pt*Prx II has two cysteines, the peroxidatic C51 and C76. C76 is not absolutely conserved in plant prx5-peroxiredoxins and its substitution does not totally abolish the redoxin-assisted peroxidase activity, so it is not essential for the catalytic mechanism but it is structurally relevant. Prx-Grx heterodimers were initially observed,

and it was proposed that GRX would establish a transient disulfide with the oxidized Prx II. This disulfide would be undone by the same GRX and the resulting oxidized GRX would be finally regenerated by GSH (Rouhier et al. 2002b). It was later demonstrated that the sulfenilated C_P of *Pt*Prx II reacts directly with GSH to form a mixed disulfide, with the concomitant dimer dissociation. Therefore, the proposed catalytic mechanism was modified to the current 1-Cys pathway, in which *Pt*Prx II and GSH form a mixed disulfide for resolution and GRX recycles by deglutathionylation (Noguera-Mazon et al. 2006). In this sense, poplar prx5-peroxiredoxin resembles yeast prx6-peroxiredoxin (Prx1p) (Pedrajas et al. 2016). When yeast Prx1p is purified, the peroxidatic cysteines of two polypeptides are linked by a disulfide bridge, which is undone by TRX, thus explaining its Trx-peroxidase activity. Nonetheless, the sulfenilated Prx1p reacts easily with GSH with high affinity and the formed mixed disulfide is resolved by either TRX or GRX (Pedrajas et al. 2016). The work by Rouhier et al. (2002a, b) suggests that two *Pt*Prx II polypeptides might be linked by a disulfide bridge between peroxidatic cysteines, which would explain its Trx-peroxidase activity. Interestingly, a modified variant of *Pt*Prx II incorporating a cysteine residue at the same location where the mammalian PrxV has the C_R shows the molecular and functional characteristics of an atypical 2-CysPRX, since its electrophoretic mobility suggests the formation of an intramolecular disulfide bridge; its Grx-peroxidase activity disappears but the Trx-peroxidase activity does not (Rouhier et al. 2002b).

Prx5-peroxiredoxins are the most diverse and widely distributed peroxiredoxins in plants. For example, *A. thaliana* expresses three essentially identical cytosolic isoenzymes (*At*Prx IIB, C and D), one located in chloroplast stroma (*At*Prx IIE) and another located in the mitochondrial matrix (*At*Prx IIF) (Bréhélin et al. 2003). Particularly, the *A. thaliana* genome contains a sequence that might express a hybrid protein (*At*Prx IIA) with a prx domain and another similar to an F-box protein, but there is no evidence of its expression so it is considered a pseudogene. Nonetheless, inconclusive evidence by western blot of its possible expression have been observed in pea nodules (Groten et al. 2006). Unlike *Pt*Prx II, the cytosolic peroxiredoxins of *A. thaliana* are recycled only by the GSH/GRX system (Bréhélin et al. 2003; Rouhier et al. 2002a). *At*Prx IIB is expressed throughout the plant at low levels in roots and higher in tissues, related to the reproduction of buds, flowers, siliques and seeds, for example. *At*Prx IIC and D are expressed in pollen (Bréhélin et al. 2003). There is only one cytosolic peroxiredoxin in *Lottus japonicum* (*Lj*Prx IIB) that is notably expressed in pollen (Tovar-Mendez et al. 2011). The high expression of the cytosolic peroxiredoxins in pollen suggests the protective role of these antioxidant proteins against reactive oxygen species generated during desiccation. *At*Prx IIC expression is slightly induced by light changes, exposition to oxidants, saline stress and so on, while *At*Prx IIB and D do not (Horling et al. 2002, 2003). *At*Prx IID is markedly induced in plants growing in highly concentrated glucose solutions (Wang et al. 2013). The silencing of Prx IIB in *Nicotiana benthamiana* confers a withered appearance to the plant, which is enhanced under thermal stress, as well as a lower anthocyanin content (Vidigal et al. 2015).

The Prx IIF is recycled by the mitochondrial thioredoxin system Trx-o and NTRA; however, the mitochondrial Trx-h is not an efficient reductant of this peroxiredoxin. Glutathione and the mitochondrial monothiolic glutaredoxin also regenerate the oxidized Prx IIF (Finkemeier et al. 2005; Rouhier et al. 2005; Gama et al. 2007). Isolated Prx IIF can oligomerize in hexamers (Barranco-Medina et al. 2008), in common with the mitochondrial Prx1p of yeast (Pedrajas et al. 2010, 2016). For both peroxiredoxins, the formation of hexamers is inherent to the establishment of disulfide bridges between peroxidatic cysteines. Both GSH and TRX break the disulfides C_P-S-S-C_P in Prx1p and the hexamers dissociate to dimers. The presence of both TRX and GSH in mitochondria explains why the hexamers are not detected in yeast cells. The formation of hexamer Prx IIF in plants has not been conclusively demonstrated. However, Prx IIF and Trx-o bind to each other with high affinity and specificity, both in vitro and in vivo, creating a heterocomplex that enhances peroxidase activity (Barranco-Medina et al. 2008). There is no detailed information yet on the structure of this 95 kDa heterocomplex. Another relevant aspect of Prx IIF is that the over-oxidation of C_P to sulfinic acid can be reverted to sulfenic acid by the plant sulfiredoxin. Plant sulfiredoxin is located in both chloroplast and mitochondria because its signal peptide is recognized by the translocation systems of both organelles. This case reveals that sulfiredoxins do not act exclusively on prx1-peroxiredoxins, although the plant sulfiredoxin seems to be specific for Prx IIF because it does not reduce the over-oxidized cytosolic homologous Prx IIC (Iglesias-Baena et al. 2011). PRX IIF gene expression is generalized and does not vary substantially when the cells are exposed to diverse stresses (Horling et al. 2002, 2003; Gama et al. 2007).

The peroxidase activity of the stromal Prx IIE is assisted by GSH and the monothiolic Grx S12, but not by the other plastidial motothiolic Grxs (S14 and S16), probably due to the different composition of their active sites. It has not been verified whether the dithiolic Grx C5 of chloroplast acts on Prx IIE, but the cytosolic Grx C4 does act on Prx IIE (Gama et al. 2008). NTRC—that is, the electron donor of the plastidial 2-Cys Prxs—does not act on Prx IIE (Moon et al. 2006). It has not yet been evaluated whether any plastidial TRX is an electron donor for Prx IIE, but the cytosolic Trx-h is not (Gama et al. 2008). PRX IIE gene expression is also generalized and does not vary substantially under different stress conditions (Horling et al. 2003; Gama et al. 2008; Tovar-Méndez et al. 2011).

S-nitrosylation consists in the union of a nitrous group (–NO) to the sulfur of cysteines in proteins. S-nitrosylation is exerted by reactive nitrogen species derived from nitric oxide (NO) or by the transference of –NO from small molecules, like nitrosoglutathione (GSNO). S-nitrosylation usually produces a change of function in the proteins and, as it is reversible, it may act as a mechanism for cellular signaling (Romero-Puertas et al. 2013). In this sense, Prx IIF and E are susceptible to transnitrosylation from GSNO, leading to inactivation (Romero-Puertas et al. 2007; Camejo et al. 2015). Nitrosylated Prx IIF has also been detected in plants submitted to saline stress (Camejo et al. 2015).

7 Bcp-Type Peroxiredoxins

Bcp-type peroxiredoxins form a very heterogeneous group of proteins. They seem to conserve many features of the ancestral peroxiredoxins, so they are situated at the threshold of divergence in the evolution of peroxiredoxins (Nelson et al. 2011). Bcp-peroxiredoxins are present in archaea, bacteria, yeast and plants (D'Ambrosio et al. 2009; Jeong et al. 2000; Cha et al. 2003; Kong et al. 2000). Evidence of these proteins first arose by characterizing an *E. coli* protein with a similar electrophoretic mobility to bacterioferritin, hence the name of the subfamily (BCP: bacterioferritin co-migratory protein) (Andrews et al. 1991). Most of the members are monomeric proteins of about 17-kDa molecular weight, but some form A-type dimers (Liao et al. 2009; Limauro et al. 2010; Perkins et al. 2012). Roughly half the members contain the C_R in the α2 helix five residues beyond the C_P (CXXXXC active site), another group (10% approximately) contains the C_R in the α3 helix and the rest have no C_R (Hall et al. 2011). Both α2-C_R and α3-C_R are situated about 15 Å apart from the C_P, so the disulfide formation requires a local unfolding of the active site (Liao et al. 2009; Perkins et al. 2012). Those members containing C_R show an atypical 2-Cys catalytic mechanism, forming an intramolecular disulfide at the resolution stage that is reduced by TRX (Jeong et al. 2000; Kong et al. 2000; Latifi et al. 2007; Cha et al. 2007; Horta et al. 2010). Members without C_R show a 1-Cys pathway, forming a mixed disulfide with glutathione at the resolution stage that is recycled with GRX (Clarke et al. 2010). Interestingly, the Bcp-peroxiredoxin of *E. coli* (atypical 2-CysPRX) behaves like 1-CysPRX when the α2-C_R is substituted, whereas the Bcp-peroxiredoxin of *B. cenocepacea* (1-CysPRX) behaves like atypical 2-CysPRX when the α2-C_R is incorporated (Clarke et al. 2010). To an even greater extent, some 2-Cys BCP-peroxiredoxins whose C_R has been substituted display Trx-peroxidase activity (Jeong et al. 2000; Clarke et al. 2009; Horta et al. 2010).

7.1 The Plant Bcp-Type Peroxiredoxins

The plant Bcp-peroxiredoxins are specifically named Prx Q. The first Prx Q to be characterized was that of *Sedum lineare* (Kong et al. 2000). *Sl*Prx Q contains a CXXXXC active site and both cysteine residues are essential for the thioredoxin peroxidase activity, which was evaluated using a thioredoxin system from *E. coli*. Subsequently, spinach Prx Q was trapped from chloroplast lysates using an immobilized variant of Trx-m without the internal Cys at the active site, and the recombinant Prx Q of *A. thaliana* was demonstrated to display thioredoxin peroxidase activity with the chloroplast Trx-m (Motohashi et al. 2001), although the most efficient electron donors were Trx-x and Trx-y from chloroplast (Collin et al. 2004). Contrary to the *Sl*Prx Q, a variant of poplar Prx Q with only the peroxidatic cysteine also displays Trx-dependent peroxidase activity seemingly as efficiently as

the wild-type protein and forms homodimers linked by a disulfide bridge between peroxidatic cysteines (Rouhier et al. 2004). The intermolecular disulfide was reduced by TRX, thus explaining the Trx-dependent activity, similar to the yeast 1-CysPRX (Pedrajas et al. 2016). Structural studies have demonstrated that plant Prx Q is functionally an atypical 2-CysPRX, with the reaction cycle involving an extensive structural rearrangement where the catalytic segment switches from an α-helical to a β-sheet conformation to form an intramolecular disulfide (Ådén et al. 2011).

Plant Prx Q is synthesized with a long 60–70 kDa N-terminal extension, which drives its translocation into chloroplast. It is estimated that Prx Q accounts for about 0.3% of chloroplast proteins (Rouhier et al. 2004). Prx Q attaches to the thylakoid membrane specifically associated to PSII (Rouhier et al. 2004; Lamkemeyer et al. 2006; Petersson et al. 2006); however, the precise position of Prx Q at the thylakoid is unclear since one study assigns it to the lumenal side of the membrane (Petersson et al. 2006), whereas another study showed orientation toward the stromal side (Lamkemeyer et al. 2006). If Prx Q were situated at the lumenal side, then its physiological reductants would have to be brought into question since neither TRX nor GRX occupy the thylakoid lumen (Schubert et al. 2002).

Prx Q has been immunologically detected in most plant organs in *A. thaliana* except in roots (Lamkemeyer et al. 2006); however, it has been only detected in leaves in other species such as poplar or *Lotus japonicus* (Rouhier et al. 2004; Tovar-Méndez et al. 2011). PRX Q gene expression varies with light intensity, being upregulated when the plant is exposed to high light and downregulated until suppression at low light conditions. In addition PRX Q expression increases in leaf tissues soaked in oxidant compound solutions and decreases in ascorbate solutions (Horling et al. 2003). PRX Q is notably overexpressed in leaves infected with a virulent pathogen fungus (incompatible reaction) and, to the contrary, when infected with an avirulent strain (compatible reaction) (Rouhier et al. 2004). The plants defend themselves only in the incompatible reaction producing an oxidative burst to kill the pathogen but not in the compatible reaction. On the other hand, curiously, a Prx Q protein seems to possess antifungal properties per se (Kiba et al. 2005). Finally, Prx Q-deficient plants exhibit no phenotypic difference compared with wild-type plants and even seem to show a slightly better performance in stressing conditions (Lamkemeyer et al. 2006). This contradictory improvement could be explained by the fact that other proteins involved in redox homeostasis are overexpressed in Prx Q-null plants. All data together indicate that Prx Q fulfills an antioxidant function in plants.

8 Conclusions

Peroxiredoxins are thiol-dependent peroxidases acting on several peroxides and are present in every living being. They are classified into six families depending on their sequence characteristics. Plants possess two organelles specialized in

processes involving oxygen and the production of reactive oxygen species, the chloroplast and the mitochondria. It would be expected that they would be particularly well supplied with antioxidant defenses to cope with this double threat. This holds true for thioredoxins and glutaredoxins; plants possess remarkably large sets of both redoxins. However, only four families of Prx are represented in plants (see Table 1), although they are present at high concentrations. They are located in the cytosol, nucleus, mitochondria, chloroplast stroma and thylakoid, but, in contrast to the majority of eukaryotic organisms, no PRX have been identified in the peroxisome of plants to date, although some evidence points to the presence of PRX in this organelle (Corpas et al. 2017).

Not surprisingly, the supply of reducing power for plastid Prx comes from light via ferredoxin/Trx, but also from NADPH via NTRC, a fusion-like protein formed by a TrxR domain and a Trx domain, which plays a critical role when the plant is in the dark.

The chaperone function of Prx has been observed to occur in plants and, more precisely, in the thylakoids to protect the photosynthetic apparatus.

Only one member of the Prx6 family, Per1, is present in plants, which has been localized in seeds, probably playing critical antioxidant roles at rehydration and germination. Its electron donor seems to be a thioredoxin reductase, NTR. The catalytic triad His/Ser/Asp responsible for the phospholipase activity present in prx6-peroxiredoxins is also present in plant Per1, but its functionality remains to be demonstrated in seeds.

Prx5-peroxiredoxins are the most diverse and widely distributed peroxiredoxins in plants where they are named Prx IIA-F. They are mostly reduced by the Grx/GSH system and, in this respect, their catalytic mechanism resembles that of Prx1p from yeast, a PRX belonging to the Prx6 family. Prx II F and E are susceptible to transnitrosylation from GSNO leading to inactivation; the consequences of it are worth of study in the context of protein regulatory mechanisms by NO in plants, a promising area open to further research.

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