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Review article

Plant glutathione peroxidases: Emerging role of the antioxidant enzymes in plant development and stress responses

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ABSTRACT

The plant glutathione peroxidase (GPX) family consists of multiple isoenzymes with distinct subcellular locations which exhibit different tissue-specific expression patterns and environmental stress responses. Contrary to most of their counterparts in animal cells, plant GPXs contain cysteine instead of selenocysteine in their active site and while some of them have both glutathione peroxidase and thioredoxin peroxidase functions, the thioredoxin regenerating system is much more efficient *in vitro* than the glutathione system. At present, the function of these enzymes in plants is not completely understood. The occurrence of thiol-dependent activities of plant GPX isoenzymes suggests that – besides detoxification of H_2O_2 and organic hydroperoxides – they may be involved in regulation of the cellular redox homeostasis by maintaining the thiol/disulfide or NADPH/$NADP^+$ balance. GPXs may represent a link existing between the glutathione- and the thioredoxin-based system. The various thiol buffers, including Trx, can affect a number of redox reactions in the cells most probably *via* modulation of thiol status. It is still required to identify the *in vivo* reductant for particular GPX isoenzymes and partners that GPXs interact with specifically. Recent evidence suggests that plant GPXs does not only protect cells from stress induced oxidative damage but they can be implicated in plant growth and development. Following a more general introduction, this study summarizes present knowledge on plant GPXs, highlighting the results on gene expression analysis, regulation and signaling of *Arabidopsis thaliana* GPXs and also suggests some perspectives for future research.

Contents

Abbreviations: ABA, abscisic acid; ABI, abscisic acid insensitive; APX, ascorbate peroxidase; AS, antisense; ASC, ascorbate; CAT, catalase; DHA, dehydroascorbic acid; GA, gibberellic acid; GPX, glutathione peroxidase; GPx4/PHGPX, phospholipid hydroperoxide glutathione peroxidase/animal GPx4 enzime; GR, glutathione reductase; GRX, glutaredoxin; GSH, reduced glutathione; GSSG, oxidized glutathione/glutathione disulfide; GST, glutathione transferase; IAA, indole-3-acetic acid; MeJA, methyl jasmonate; POD, guaiacol peroxidase; Prx, peroxiredoxin/thioredoxin peroxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; SA, salicylic acid; Trx, thioredoxin.

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The plant glutathione peroxidases are members of the thioredoxin-dependent peroxidase family

Peroxidases are known to be implicated in many physiological and developmental processes, including defenses against pathogen infection, wounding and other abiotic stresses. They control cell growth either by restriction or promotion of cell elongation; they have a role in auxin catabolism, destruction of flavonoids, biosynthesis of ethylene and secondary metabolites (Welinder et al., 2002; Liszkay et al., 2003; De Gara, 2004; Passardi et al., 2004; Cosio and Dunand, 2009; Csiszár et al., 2012).

Peroxidases oxidize various substrates utilizing H_2O_2 or organic hydroperoxides, thus they are involved in scavenging of reactive oxygen species (ROS). ROS are natural byproduct of the normal metabolism and have important roles in cell signaling and control of redox homeostasis, while unbalanced generation of these species induces detrimental oxidation of macromolecules including DNA, proteins, and lipids. To keep the ROS level tightly regulated and to minimize ROS-derived damage, different non-enzymatic and enzymatic antioxidant systems have been evolved in aerobic organisms, including the diverse super-family of peroxidase enzymes.

Peroxidases can contain a heme cofactor in their active site (such as ascorbate peroxidases or guaiacol peroxidases) or possess redox active cysteine or selenocysteine residues (non-heme peroxidases) (http://peroxibase.toulouse.inra.fr; Koua et al., 2009). The non-heme peroxidases comprise thiol peroxidases, such as thioredoxin peroxidases or peroxiredoxins (Prxs) and glutathione peroxidases (GPXs). A very conserved catalytic cysteine near the N-terminus of these proteins is called the peroxidatic cysteine (Cys_P-S^-) and is used to reduce hydroperoxides and peroxynitrites. This Cys residue is first transformed into a sulfenic acid (Cys_P-SOH) when exposed to peroxides. The main difference between the different classes is the mechanism of regeneration of the Cys_P-SOH, which can be reduced directly (1-Cys mechanism) or by involving a second, so-called resolving Cys residue (Cys_R-SH), which condenses with the sulfenic acid to form a disulfide (2-Cys catalytic cycle). The 2-Cys disulfide is reduced by thioredoxin – a low-molecular weight protein with two vicinal Cys residue – or by glutathione (reduced form GSH, γ-glu-cys-gly) (Toppo et al., 2009).

The plant thiol peroxidases can be classified into five subgroups which includes the 2-Cys Prx, 1-Cys Prx, type II Prx, Prx Q and GPX type peroxidases (Rouhier and Jacquot, 2005). In *Arabidopsis thaliana* 18 thiol peroxidases were identified: one 1-Cys Prx, two 2-Cys Prxs, six type II Prxs, one type Q Prx and eight GPXs (http://peroxibase.toulouse.inra.fr; Koua et al., 2009).

The mammalian glutathione peroxidases (GPXs)

The term glutathione peroxidase (EC 1.11.1.9.) was introduced by Mills who discovered the reaction with H_2O_2 in enzyme preparations from mammalian red blood cells (Mills, 1957); the generaly accepted abbreviation of them is GPxs. They are central components of animal antioxidant metabolism and participate largely in the repair of biomembranes (Imai and Nakagawa, 2003). While GPx1–3, 5 and 6 function as homotetramers, GPx4, 7, and 8 are monomers. The selenium-containing mammalian GPxs (GPx1–4 and, in human only, GPx6) as well as the cysteine-containing GPx-isoforms (GPx5, 7 and 8) were shown to be key players in important biological processes far beyond the detoxification of hydroperoxides (reviewed by Margis et al., 2008; Brigelius-Flohé and Maiorino, 2013). GPxs are involved in balancing the H_2O_2 homeostasis in signaling cascades, *e.g.* in the insulin signaling pathway by GPx1 (Loh et al., 2009; Lubos et al., 2011; Brigelius-Flohé and Maiorino, 2013). GPx1 was shown to prevent oxidative DNA damage and reduce the initiation of carcinogenesis (Baliga et al., 2007; Brigelius-Flohé and Kipp, 2009). The GPx2 has anti-inflammatory function and plays a dual role in carcinogenesis depending on the mode of initiation and cancer stage (Dittrich et al., 2010; Brigelius-Flohé and Kipp, 2012). The GPx3 is membrane associated and its reduced expression or activity was also connected to many types of inflammation and cancer, even to obesity, which might be associated with oxidative stress (Lee et al., 2005, 2008; Burk et al., 2011). GPx4 enzymes can directly interfere with hydroperoxidized phospholipids in biomembranes (they are also called phospholipid hydroperoxide glutathione peroxidases, PHGPXs). Moreover, they have been reported to have a role in the regulation of apoptosis and, together with GPx5, in male fertility (Conrad et al., 2005; Seiler et al., 2008). Functions of GPx6–8 are largely unknown, although GPx7 and GPx8 were suggested to be involved in the reoxidation of protein disulfide isomerases (PDIs) during folding of proteins in the endoplasmic reticulum (Brigelius-Flohé and Maiorino, 2013). GPx7 was recently identified as an oxidative stress sensor/transducer that senses and transmits cellular ROS signals to downstream mediators to reduce ROS accumulation (Chang et al., 2013).

The plant glutathione peroxidases

The plant glutathione peroxidases (their more often used abbreviation is GPXs) are ubiquitous enzymes which have been shown to be present in different plant tissues, compartments and developmental stages (Mullineaux et al., 1998; Yang et al., 2005, 2006). The *Arabidopsis* genome contains eight *GPX* genes (Table 1) whose expression can be induced by multiple signals (Sugimoto and Sakamoto, 1997; Chang et al., 2009; Gaber et al., 2012; Passaia et al., 2014). An alignment of different plant GPX proteins showing conserved amino acid motifs and Cys residues is shown in Supplementary Fig. S1.

In plants, the glutathione-dependent peroxidase activity can be associated with glutathione transferase (GST) isoenzymes. Their role in detoxifying lipid hydroperoxides and other reactive molecules has been shown in different species and under several stress conditions (Roxas et al., 1997; Csiszár et al., 2004; Kilili et al., 2004; Basantani and Srivastava, 2007; Dixon et al., 2009; Edwards and Dixon, 2009). Plant *GPX* genes with significant sequence homology to the animal phospholipid hydroperoxide glutathione peroxidases (GPx4/PHGPX enzymes) have also been isolated from several plants. All the plant GPXs characterized so far are in monomeric form (Navrot et al., 2006) except for the poplar GPX5, which showed an unique dimerization pattern mainly depending on hydrophobic contacts and was able to interact with