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MINI-REVIEW

Relevance of peroxiredoxins in pathogenic microorganisms

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Abstract

The oxidative and nitrosative responses generated by animals and plants are important defenses against infection and establishment of pathogenic microorganisms such as bacteria, fungi, and protozoa. Among distinct oxidant species, hydroperoxides are a group of chemically diverse compounds that comprise small hydrophilic molecules, such as hydrogen peroxide and peroxynitrite, and bulky hydrophobic species, such as organic hydroperoxides. Peroxiredoxins (Prx) are ubiquitous enzymes that use a highly reactive cysteine residue to decompose hydroperoxides and can also perform other functions, like molecular chaperone and phospholipase activities, contributing to microbial protection against the host defenses. Prx are present in distinct cell compartments and, in some cases, they can be secreted to the extracellular environment. Despite their high abundance, Prx expression can be further increased in response to oxidative stress promoted by host defense systems, by treatment with hydroperoxides or by antibiotics. In consequence, some isoforms have been described as virulence factors, highlighting their importance in pathogenesis. Prx are very diverse and are classified into six different classes (Prx1-AhpC, BCP-PrxQ, Tpx, Prx5, Prx6, and AhpE) based on structural and biochemical features. Some groups are absent in hosts, while others present structural peculiarities that differentiate them from the host's isoforms. In this context, the intrinsic characteristics of these enzymes may aid the development of new drugs to combat pathogenic microorganisms. Additionally, since some isoforms are also found in the extracellular environment, Prx emerge as attractive targets for the production of diagnostic tests and vaccines.

Key points

- *Peroxiredoxins are front-line defenses against host oxidative and nitrosative stress.*
- *Functional and structural peculiarities differ pathogen and host enzymes.*
- *Peroxiredoxins are potential targets to microbicidal drugs.*

Keywords Peroxiredoxins · Oxidative stress · Antibiotic resistance · Hydroperoxides · Virulence · Structure

Introduction

Microbial pathogen infections trigger several host defense mechanisms (Medzhitov 2007; Nurnberger et al. 2004), such as the release of large amounts of reactive oxygen species (ROS) and nitrogen species (RNS). Among the ROS, hydrogen peroxide and superoxide are not powerful oxidants, but they can be converted to hydroxyl radical which is a highly reactive species (Halliwell and Gutteridge 2015). Furthermore, myeloperoxidase can use hydrogen peroxide to generate highly microbicidal species, such as hypochlorous acid (Winterbourn et al. 2016). Host organisms also produce nitric oxide radicals and derived oxidants (Prolo et al. 2014), such as peroxynitrite, a powerful oxidizing hydroperoxide (Radi 2018). Additionally, the oxidation of amino acids, nucleotides, and lipids generate high levels of organic

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hydroperoxides (OHPs) over the course of the host response. Noteworthy, some evidences indicate that microbicidal drugs can enhance superoxide and hydrogen peroxide production (Dwyer et al. 2014; Lam et al. 2020; Repolês et al. 2020). Therefore, pathogens must remove these oxidants for establishment in a host.

Pathogenic organisms express several antioxidant enzymes to counteract oxidative insults (Staerck et al. 2017). Among them, catalases (Cat) specifically decompose hydrogen peroxide and peroxynitrite, while glutathione peroxidases (Gpx) and peroxiredoxins (Prx) can decompose several kinds of hydroperoxides, including hydrogen peroxide, peroxynitrite, and OHPs (Staerck et al. 2017). Therefore, antioxidant enzymes gain importance with the emergence of microbial strains resistant to multiple drugs, a global health threat, and the search for novel biological targets is a worldwide concern (Fisher et al. 2017). Since that some evidence indicates that microbicidal drugs can enhance superoxide and hydrogen peroxide production (Dwyer et al. 2014; Lam et al. 2020; Repolês et al. 2020), the search for antioxidant enzyme inhibitors raises as a possible alternative approach. Prx members are important targets due to their diversity and structural differences between isoforms found in pathogenic microbial organisms and hosts. Here, we aim to review several aspects of Prx enzymes such as abundance, substrate diversity, and structural/functional peculiarities that place them as potential targets for novel strategies to combat microbial infections.

Abundance and distribution of peroxiredoxins in microbial cells

Prx are the main scavengers of hydroperoxides in several organisms (Condeles et al. 2020; Seaver and Imlay 2001; Winterbourn and Hampton 2008) and especially in some microbial pathogens that lack both catalase and Gpx (Mastronicola et al. 2014; Richard et al. 2011). The significance of Prx in bacteria is highlighted by the number of different isoforms expressed, ranging from three to ten enzyme isoforms, representing some of the most abundant proteins in several bacteria. Additionally, bacterial Prx are found in the cytosol, associated with the cell membrane or with DNA, in the periplasmic space and even in biofilms (Cha et al. 1995; Enany et al. 2014; Hicks et al. 2010; Murphy et al. 2005; O'Riordan et al. 2012). It is important to mention that bacterial Prx are naturally abundant in basal conditions. Nonetheless, immune cells such as macrophages or neutrophils impose oxidative insults that can enhance Prx levels in *Salmonella typhimurium* and *Mycobacterium avium* (Francis et al. 1997; Zhu et al. 2008). Additionally, Prx are upregulated by distinct bactericidal drugs, such as amikacin, ciprofloxacin, kanamycin, tetracycline, vancomycin among others (Chen et al. 2013; Kumar et al. 2013; Li et al. 2018; Vranakis et al. 2012).

The number of Prx isoforms is also elevated in eukaryotic organisms, achieving up to six isoforms in fungi (Park et al. 2000; Rocha et al. 2018; Skrzypek et al. 2017) and three to five in protozoans (Richard et al. 2011). Several isoforms are distributed throughout diverse cellular compartments, such as the cytosol, mitochondria, nucleus, peroxisomes, protozoan glycosomes, and they are even exported outside cells (Park et al. 2000; Richard et al. 2011; Rocha et al. 2018; Urban et al. 2005; Vallejo et al. 2012). In fungi, extracellular Prx isoforms are also associated with the hypha/cell wall and biofilm (Choi et al. 2003). It is important to highlight that biofilm confers resistance to bacteria and fungi against host immune defenses and antimicrobial drugs (Lynch and Robertson 2008) and the extracellular location of some Prx in pathogenic microorganisms makes these enzymes promising targets for diagnostic tests and vaccines (Fereig et al. 2017; O'Riordan et al. 2012; Rodrigues et al. 2020).

Prx are also abundant in microbial eukaryotes, such as fungi and protozoans. *Saccharomyces cerevisiae*, a model yeast for genetic and biochemical studies, is an opportunistic pathogen in immunocompromised individuals (Souza Goebel et al. 2013). In this yeast, the abundance of Prx isoforms can attain ~ 1% of the total soluble proteins in the cell and are much more abundant than catalases and Gpx (Ghaemmaghami et al. 2003). Proteomic approaches of representative fungi and protozoans revealed a high amount of Prx in these microorganisms (de Godoy et al. 2012; Kaneva et al. 2018).

Similarly to observed in bacteria, Prx expression levels are enhanced in pathogenic fungi and protozoans in response to oxidative burst and to antimicrobial agents. In *Candida glabrata*, the expression of the Prx is strongly enhanced when insulted by the oxidative stress promoted by the host immune system (Gutierrez-Escobedo et al. 2020). In *Trypanosoma cruzi*, ectopic overexpression of Prx isoforms enhances the resistance of the pathogen against peroxynitrite and hydrogen peroxide produced by macrophages and pathogen metabolism (Piacenza et al. 2008). Concerning the antimicrobial drugs, it was observed an increased Prx expression for a wide range of antimicrobial drugs, such as amphotericin B, antimony, benznidazole, camphene thiosemicarbazide, caspofungin, fluconazole, fludioxonil, itraconazole, miltefosine, and others (Andrade et al. 2008; Das 2018; Gautam et al. 2016; Gautam et al. 2008; Shishodia et al. 2019; Silva et al. 2018; Vediyappan et al. 2010). Overall, the data presented in this section highlight the importance of Prx for microbial pathogen survival under oxidative stress conditions.

Catalytic mechanism of Prx

Prx are Cys-based peroxidases that efficiently decompose several kinds of hydroperoxides, achieving rate

constants up to 10^8 M^{-1} s^{-1} (Reyes et al. 2011; Tairum et al. 2016). The catalytic cysteine (named peroxidatic cysteine, C_P) reduces the hydroperoxide and is oxidized to sulfenic acid (C_P-SOH) (Hall et al. 2011). Thr (or Ser) and Arg are found with C_P in the active site of all Prx, composing a triad that is essential to the catalytic power of Prx enzymes (Fig. 1) (Hall et al. 2010; Poole and Nelson 2016). The catalytic triad Thr can be substituted by Ser in some Prx, with structural and functional consequences, but with no effect on reactivity under low concentrations of hydroperoxides (Tairum et al. 2016). Interestingly, catalytic Ser is more frequent in Bacteria than in Archaea or in Eukarya domains of life, but the evolutive reasons for this distribution are not clear to date (Tairum et al., 2021, in press).

C_P is very reactive to most hydroperoxides due to the active site microenvironment (Hall et al. 2010). Thr/Ser and Arg of the catalytic triad activate C_P and orientate the substrate in the active site for optimal reactivity (Fig. 1) through a S_N2 mechanism (Hall et al. 2010). The oxidation of C_P by hydroperoxide is common to all Prx, while the subsequent steps define two groups. Some Prx have only one catalytic cysteine (1-Cys Prx), while a second cysteine residue (named resolving cysteine, C_R) is involved in the catalysis of another group (2-Cys Prx) by forming a disulfide bond (C_P-S-S-C_R). 2-Cys Prx can be further divided into atypical, in which both cysteines are in the same subunit; and typical, that have a homodimer as minimal catalytic unit due to C_P and C_R are in different chains (Perkins et al. 2015).

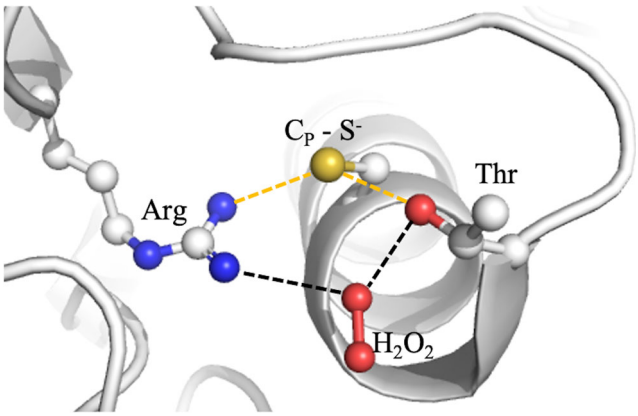

Fig. 1 Catalytic triad of Prx. Polar interactions among Arg, Thr/Ser, and C_P (yellow lines) stabilize the S^γ in the deprotonated (thiolate) form. Polar interaction among Arg, Thr/Ser, and substrate (black lines) orientate the hydroperoxide towards the thiolate of C_P. The crystallographic structure of yeast Prx (PDB = 3SBC) is represented as cartoon (light gray), highlighted amino acids are represented as balls and sticks and colored as follows: carbon = light gray, oxygen = red, nitrogen = blue, and sulfur = yellow

Common aspects, structural variability, and alternative functions of Prx

All Prx enzymes display the thioredoxin-fold (Trx-fold) that is composed of four β-sheets surrounded by three α-helices, a structure that is shared with several other redox proteins from the thioredoxin super-family (Hall et al. 2011). Prx enzymes evolved from a common Trx ancestor, with the addition of secondary structural elements (Copley et al. 2004). They are subdivided into six classes: AhpC-Prx1, BCP-PrxQ, Tpx, Prx5, Prx6, and AhpE (Fig. 2a–f) based on amino acid residues in the active site and structure (Nelson et al. 2011). The AhpC-Prx1 class is mostly composed of the typical 2-Cys Prx, while the atypical 2-Cys Prx are distributed in three classes: BCP-PrxQ, Prx5, and Tpx. Proteins displaying the 1-Cys Prx mechanism are mainly present in the Prx6 group, but there are also 1-Cys Prx in the BCP-PrxQ, Prx5, and AhpE classes (Nelson et al. 2011).

The oligomeric states of these enzymes are also very diverse: monomers, dimers, decamers, and other quaternary species (Fig. 3) (Hall et al. 2011; Jang et al. 2004; Nelson et al. 2011; Tairum et al. 2016). The Prx dimers can assemble in two different ways: A-type (Fig. 3a), presenting unique

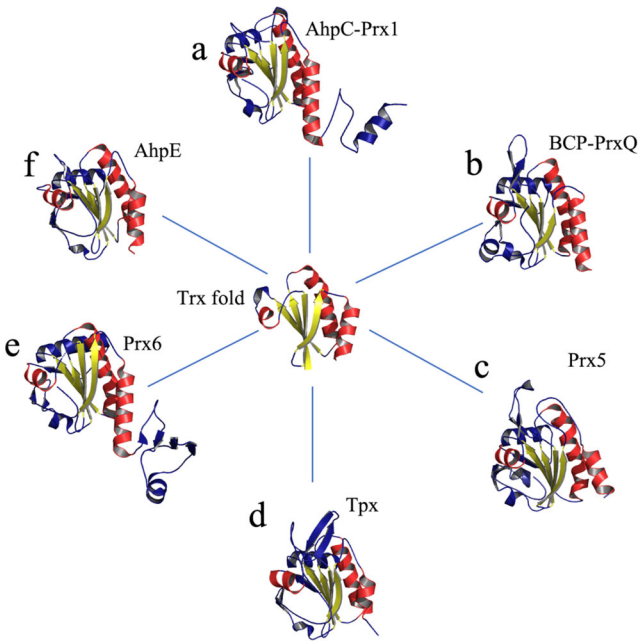

Fig. 2 The common Trx-fold and structural variations among the six Prx classes. Prx from different organisms as representatives of the six classes are derived from a common Trx-fold (PDB = 2J23) (center of image). (**a**) AhpC-Prx1, yeast Tsa1 (PDB = 3SBC); (**b**) BCP-PrxQ, *Xylella fastidiosa* BCP (PDB = 3IXR); (**c**) Prx5, *P. falciparum* AOP (PDB = 1XIY); (**d**) Tpx, *E. coli* Tpx (PDB = 3HVV); (**e**) Prx6, *P. aeruginosa* LsfA (PDB = 6P0W); (**f**) AhpE, *M. tuberculosis* AhpE (PDB = 4X0X). The structures are represented as cartoon, in which the α-helixes that compose the Trx-fold are represented in red and the β-sheets are colored in yellow. Additional elements specific to each class are shown in blue. The structures are represented as monomers for clarity

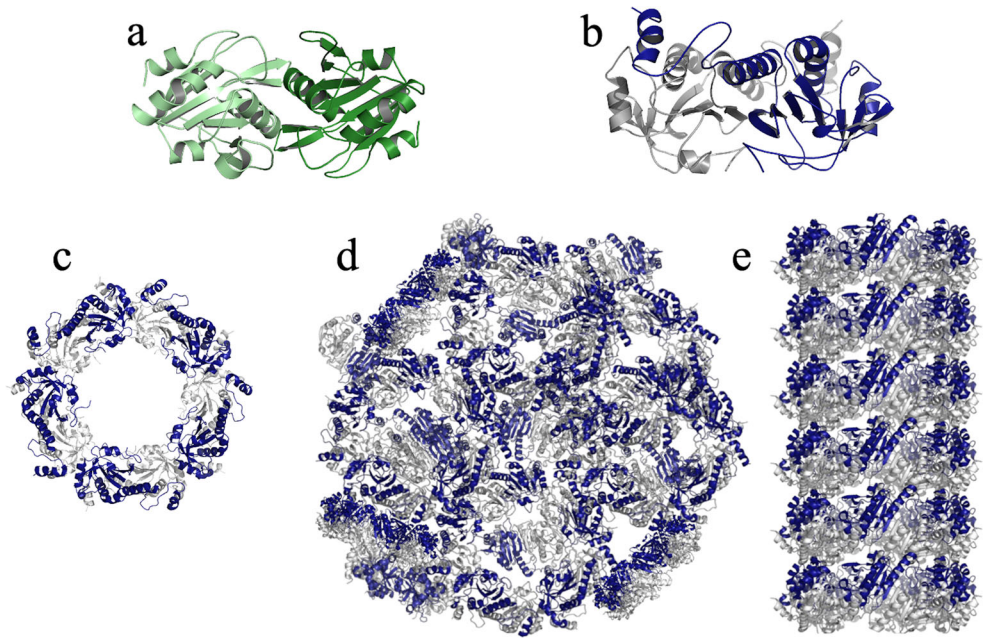

Fig. 3 Representation of the two types of Prx dimers and the quaternary structures diversity of peroxiredoxins. Structures are represented as cartoons, and each monomer is represented by a different color. (**a**) A-type dimers present in the BCP-PrxQ, Tpx, Prx5, and AhpE classes. The A-type is represented by yeast Ahp1 (PDB = 4OWY), and the monomers are colored in light green and green. (**b**) B-type dimers are found in the classes AhpC-Prx1 and Prx6 (light gray and dark blue) (PDB = 3SBC). Some dimeric Prx from the AhpC-Prx1 and Prx6 classes can assemble into toroidal structures formed by pentamers of dimers (decamers) (PDB = 3SBC). (**c**) Under oxidative or heat stresses, some Prx can organize in high molecular weight (HMW) species as spherical (**d**) or filamentous multimers (**e**). The HMW complexes are illustrative and were constructed using the yeast Prx coordinates (PDB = 3SBC). The monomers of the dimers are represented in dark blue and light gray for clarity

globular domain, and B-type (Fig. 3b), in which the central β-sheets of both monomers are aligned (Poole and Nelson 2016). Members of the BCP-PrxQ, Prx5, Tpx, and AhpE classes can form A-type dimers, but there is a wide variation at this organization level. Most proteins of the BCP-PrxQ class are monomers, with a few of them as A-type dimers. Representatives of the Prx5 group are detected as monomers and dimers, and some bacterial members possess Prx5 fused to a glutaredoxin molecule and can form tetramers (Kim et al. 2003; Nelson et al. 2011). The Tpx members are found only as A-type dimers. Finally, the AhpE members assemble as A-type dimers that can further associate as octamers (tetramers of dimers) (Hall et al. 2011).

The B-type dimer is present in members of the AhpC-Prx1 and Prx6 classes, representing the minimum catalytic unit of AhpC-Prx1, since C_P and C_R are present in different monomers. Interestingly, AhpC-Prx1 and Prx6 enzymes can further assemble into tetramers, octamers, decamers, dodecamers, or high molecular weight species (Poole et al. 2011; Poole and Nelson 2016). Additionally, AhpC-Prx1 enzymes with Thr in the catalytic triad possess the particularity of switching between oligomeric states in a redox-dependent manner: decamers in the reduced form (Fig. 3c) and dimers in the disulfide state (Tairum et al. 2016).

The diverse structural features among Prx classes might represent an opportunity for the characterization of inhibitors used as drugs in the combat of pathogens. Part of the diversity of proteins of the six Prx classes resides in the amino acid composition of the active sites (Hall et al. 2011). Tpx and AhpE members are found almost exclusively in prokaryotes and BCP-PrxQ is absent in animals (Poole and Nelson 2016). For the other three classes, specific features can be taken into account to design molecules that specifically target enzymes from pathogens and not from the hosts.

The amino acid sequences of microbial Prx isoforms (bacteria, fungi, and protozoans) differ considerably from host enzymes (mammals and plants), ranging from 35 to 60% of identity (data not shown). Some of these different residues are found in the active site. These differences can be explored for obtaining specific inhibitors. To illustrate this variation, the structure of representative proteins from pathogens and hosts of the subclasses AhpC-Prx1, BCP-PrxQ, Prx5, and Prx6 were overlapped (Fig. 4). Notably, some of the differences between host and pathogen protein surfaces are close to C_p (Fig. 4a–d). AhpC-Prx1 from eukaryotes possesses a C-terminal α-helix and other specific features involved in the increased susceptibility of C_P to hyperoxidation that are absent in most prokaryotic proteins (Wood et al. 2003) (Fig. 4a). The catalytic triad Thr residue is replaced by a Ser residue in some pathogenic bacteria (*Staphylococcus* sp. and *Bacillus* sp., among others), fungi (Saccharomycetales), and protozoans (*Leishmania* sp.), but is almost absent in hosts (unpublished data). This single substitution confers considerable structural and functional differences between Prx containing Thr or Ser

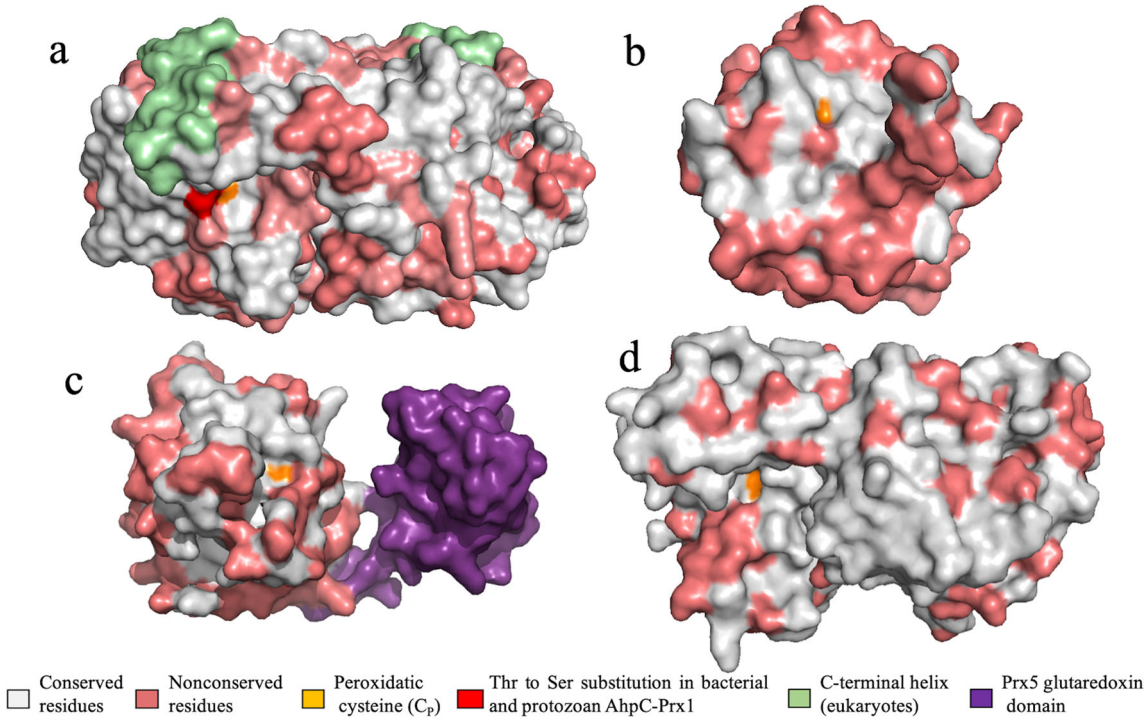

Fig. 4 Conservation of surface residues among Prx from the host and pathogen. Molecular surfaces of Prx enzymes, depicting the common amino acids between host and pathogen (white), the different ones (pink), and the active site catalytic C_P (orange). Conserved residues were considered the same amino acid or amino acids presenting similar physicochemical properties. (**a**) Molecular surface of human AhpC-Prx1 (Prx2; PDB: 1QMV) was used as template and compared to the homologue isoform from *S. typhimurium* (UniProt ID: P0A251). C-terminal α-helix that are absent in most prokaryotes is colored in light green. Position of Thr/Ser in the active site is highlighted in red. (**b**) BCP-PrxQ from *X. fastidiosa* (PDB: 3IXR) compared with the plant *Citrus sinensis* (NCBI ID: XP_006474598.1). (**c**) The structure of Prx5 from *H. influenzae* (PDB: 1NM3) and human Prx5 (UniProt ID: P30044). The additional Grx domain present in some pathogenic bacteria is colored in purple. (**d**) Human Prx6 (PDB: 1PRX) compared with its bacterial counterpart from *P. aeruginosa* (UniProt ID: A0A0H2ZEH5)

(Tairum et al. 2016). The Thr/Ser substitution may also provide a different microenvironment to ligands targeted to Prx from pathogens (Fig. 4a). For some pathogenic bacteria, such as *Haemophilus influenzae*, *Neisseria meningitidis*, and *Vibrio cholerae*, the differences among the Prx5 isoforms are accentuated as a consequence of a glutaredoxin domain fused to the C-terminal region (Fig. 4c), a feature that is not observed in animal and plant isoforms (Kim et al. 2003).

Besides the peroxidase activity, some peroxiredoxins present additional functions. At high hydroperoxide concentrations, C_P is hyperoxidized to sulfinic acid (C_P-SO_2H), resulting in loss of peroxidase activity and concomitant acquisition of chaperone (holdase) function. In parallel, these 2-Cys Prxs undergo structural rearrangements to form high molecular weight species (HMW), presenting a spherical or filamentous organization (Fig. 3 d and e) (Hall et al. 2009; Jang et al. 2004; Saccoccia et al. 2012; Tairum et al. 2016). A C-terminal α-helix, which is restricted to eukaryotic isoforms with rare exceptions (e.g., *Helicobacter pylori* AhpC), facilitates C_P hyperoxidation by impairing disulfide formation (Hall et al. 2009). Molecular chaperone activity has also been described in Prx from some microorganisms previously exposed to heat shock without the requirement of C_p hyperoxidation (Kamariah et al. 2018; Morais et al. 2017; Saccoccia et al. 2012; Teixeira et al. 2015). In addition, a BCP-PrxQ from *Deinococcus radiodurans* and a Prx6 from *Anabaena* sp. also present molecular chaperone activity (Cho et al. 2019; Mishra et al. 2017).

Another additional function displayed by some members of the Prx6 class is a calcium-independent phospholipase A_2 activity (PLA_2), which is unrelated to the peroxidase function (Bannitz-Fernandes et al. 2019). The PLA_2 activity of Prx6 depends on a second active site separated from the peroxidase center and composed of a catalytic Ser, a His and an Asp (Fig. 5). In pathogens, PLA_2 activity was described in Prx6 enzymes from *Pseudomonas aeruginosa* and from *Aspergillus fumigatus*, two respiratory airway pathogens. These phospholipase activities might be related to the metabolism of surfactants in the lungs during colonization by damaging phospholipids from the host cell membrane or nutrient acquisition (Bannitz-Fernandes et al. 2019). Besides the peroxidase function, these additional activities of some Prx groups may support the ideal condition for organism survival, especially microorganisms.

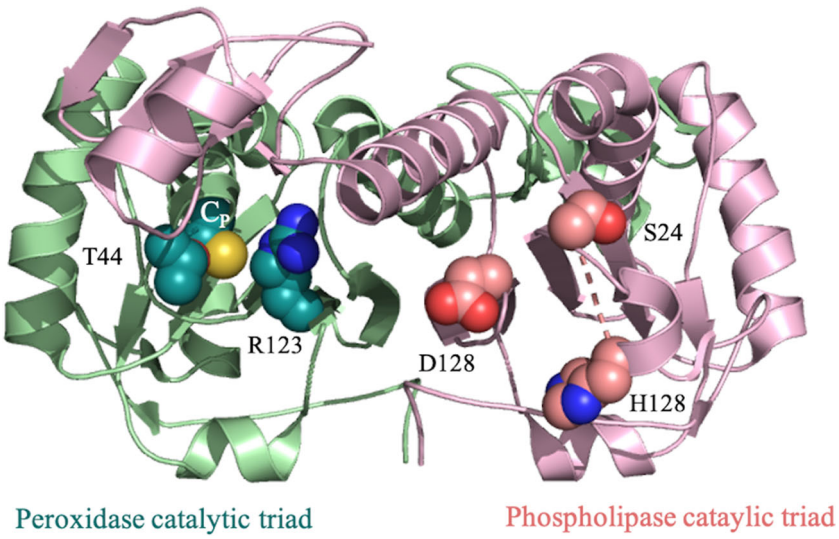

Fig. 5 Catalytic triads of peroxidase and PLA_2 activities of a representative Prx6 enzyme. The active sites of the two functions performed by members of the Prx6 class are independent. The LsfA structure (PDB = 6P0W) is represented as cartoon and each monomer present a different color (pale green and light pink). Corresponding residues for each catalytic triad are represented as spheres and colored as follows: C = green or pink (peroxidase or phospholipase catalytic triad, respectively), N = blue, O = red, and S = light orange

Peroxiredoxin reductants

To perform catalysis efficiently, Prx requires appropriate reductants for fast turnover and the Trx system is the most frequently employed. The Trx system comprises thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH as electron source (Oliveira et al. 2010). Although Trx enzymes are highly conserved, TrxR enzymes are distinct between microorganisms/plants and mammals and have been explored as drug targets (Koch et al. 2013). In both cases, TrxR are obligate dimers, but the enzymes present low molecular weight (molecular mass of monomers ~ 33 kDa) in bacteria, fungi, and plants. In mammals, TrxR possesses ~ 50 kDa per monomer and contains a selenocysteine residue (Oliveira et al. 2010). Below, we describe variations found in the reduction of Prx enzymes from the canonical Trx system.

AhpC-Prx1

A specialized Trx system in bacteria, named AhpF, is dedicated to the reduction of AhpC-Prx1 enzymes. AhpF is a multidomain enzyme, containing a TrxR portion fused to two Trx domains in a single polypeptide. Although AhpF can use either NADH or NADPH as the electron donor, NADH is the preferred reductant (~ 100×), in contrast to the canonical TrxR that preferentially uses NADPH (Poole and Ellis 1996).

Mycobacterium tuberculosis presents another specialized system for the reduction of some AhpC-Prx1 isoforms. This system comprises AhpD, a bacterial protein with thioredoxin-like activity, but without significant structural homology to Trx. It acts together with dihydrolipoamide succinyltransferase (SucB) and dihydrolipoamide dehydrogenase (Lpd), also using electrons from NADH (Bryk et al. 2002).

Protozoans from the *Trypanosoma* and *Leishmania* genera present a unique thiol-disulfide network that is able to reduce AhpC-Prx1 members (so-called in trypanosomatids as tryparedoxin peroxidase, TxnPx) (Netto et al. 2016; Piacenza et al. 2008). The system uses NADH as an electron donor and includes the enzymes tryparedoxin (Txn), an oxidoreductase homologue of thioredoxin, and tryparedoxin reductase (TR), a flavoenzyme structurally similar to the high molecular weight TrxR. The system also comprises trypanothione (TSH), an abundant low molecular weight thiol that is only present in trypanosomatids (Jaeger and Flohe 2006). In this case, peroxiredoxin disulfide is directly reduced by Txn, which is restored to the reduced state by trypanothione. The oxidized trypanothione molecules are reduced by TR using NADH.

Prx5

Prx5 enzymes can be reduced by the glutathione (GSH) system, which is composed of glutaredoxin (Grx), GSH, glutathione reductase (GR), and NADPH. GSH forms a mixed disulfide with C_P-SOH, which is then reduced by Grx, regenerating reduced Prx. A second GSH molecule recovers reduced Grx, generating oxidized glutathione (GSSG), which is then reduced by glutathione reductase using electrons from NADPH. It is worth to highlight that Prx domain is fused to a Grx domain (Fig. 5c) in some bacterial Prx5 enzymes, which appears to confer higher reducing efficiency to the system (Kim et al. 2003).

Prx6

For some Prx6, the GSH system was proposed to turnover the enzyme (Pedrajas et al. 2016). The Prx6 class is mostly composed of 1-Cys Prx enzymes and so distinct agents directly

reduce C_P-SOH intermediate. Although several biological reductants have been tested, most of them failed to reduce microbial Prx6, including Trx system (Longo et al. 2020; Rocha et al. 2018). Prx1 from *S. cerevisiae* is an exception, being reduced by the mitochondrial Trx system (Pedrajas et al. 2000). In contrast, ascorbate is a general reductant for Prx6 enzymes (Anschau et al. 2020). We demonstrated that the sulfenic acids in yeast Prx1 and mammalian Prx6 are reduced by ascorbate, the only biological and non-thiolic reductant described for peroxiredoxins so far (Monteiro et al. 2007). Later, we determined that Prx6 isoforms from pathogenic microorganisms, such as bacteria (LsfA, *P. aeruginosa*) are reduced by ascorbate at moderate rates (Anschau et al. 2020).

AhpE

Like Prx6 class, most AhpE enzymes are 1-Cys Prx and the identities of the biological reductants are still controversial. We have previously demonstrated that AhpE from *M. tuberculosis* can be reduced by ascorbate (Monteiro et al. 2007). Additionally, *M. tuberculosis* presents a thiolic enzymatic system that is involved in AhpE reduction. This system was only described in the actinobacteria group and is represented by mycoredoxin (Mrx1), mycothiol disulfide reductase (MR), and a low molecular weight thiolic compound named mycothiol (MSH) (Hugo et al. 2014).

The unique aspects of some of the reductive systems of various Prx enzymes from microorganisms, without counterparts in the hosts, are frequently considered as important chemotherapeutic targets (Budde and Flohe 2003; Jaeger and Flohe 2006). In fact, inhibitors for peroxiredoxin reducing systems in bacteria and fungi have already been identified (Koshkin et al. 2004; Marshall et al. 2019) and inhibitors for the Prx trypanosomatid reducing system have recently shown promising results in preclinical studies (Tunes et al. 2020).

Substrate diversity and protective roles of peroxiredoxins

Prx enzymes display lower specificity towards hydroperoxides, decomposing them with high efficiency. For instance, Prx enzymes from several microbial pathogens decompose hydrogen peroxide and peroxynitrite very efficiently, at rate constants from 10^4 to 10^8 M^{-1} s^{-1} (Pineyro et al. 2011; Reyes et al. 2016; Tairum et al. 2016). The reduction of OHPs by Prx is also efficient (up to 10^8 M^{-1} s^{-1}) and important for pathogen survival (Estelle et al. 2020; Jacobson et al. 1989; Reyes et al. 2011). The vast majority of studies used synthetic organic molecules such as *tert*-butyl (*t*-BOOH) and cumene (CHP) hydroperoxides to mimic biological OHPs and members of all Prx classes efficiently decompose these molecules (Akerman and Muller 2005; Baker and Poole 2003; Parsonage et al. 2008; Tairum et al. 2016). Table 1 summarizes different kinds hydroperoxides used to challenge distinct Prx classes.

It is important to note that OHPs are bulkier than hydrogen peroxide or peroxynitrite, so Prx active sites are large and hydrophobic to accommodate such distinct molecules. In fact, some studies demonstrate that even bulky substrates are efficiently decomposed by Prx. For instance, *M. tuberculosis* AhpE achieves rate constants of approximately 10^8 M^{-1} s^{-1} over arachidonic acid hydroperoxide (15-HpETE), a very bulky hydroperoxide produced by reticulocytes, eosinophils, and T-lymphocytes (Reyes et al. 2011). Interestingly, arachidonic acid is an integrant of cell membranes and AhpE was detected in the membrane fraction of *M. tuberculosis* (Gu et al. 2003). In *H. pylori*, AhpC and BCP efficiently decompose OHP, making the pathogen tolerant to oxidative stress (Baker et al. 2001). In the fungus *Paracoccidioides brasiliensis*, a Prx6 isoform can decompose linoleic hydroperoxide more efficiently than *t*-BOOH and CHP (3-8-fold higher, respectively) (Longo et al. 2020). Accordingly, linoleic and linolenic acid hydroperoxides are also of high importance in infection by pathogens due to their pronounced microbicidal effect (Estelle et al. 2020). Together, the information presented in this section demonstrates the substrate versatility of Prx, indicating the role of these enzymes in cell protection, including against oxidative stress generated by OHPs.

Effects of Prx inactivation in pathogenic microorganism cells

Silencing of Prx usually renders cells more sensitive to hydroperoxides insults (Castro et al. 2020; Comtois et al. 2003; Cosgrove et al. 2007; Hillmann et al. 2016; Missall et al. 2004; Rocha et al. 2018; Teixeira et al. 2015). Their importance in hydroperoxide decomposition can be associated with DNA protection. In fact, the first bacterial peroxiredoxins described (AhpC from *Escherichia coli* and *S. typhimurium*) were identified by observing that strains lacking *ahpc* genes presented high mutation rates, while strains overexpressing AhpC suppressed DNA alterations (Storz et al. 1987). This protective role was later related to the ability of AhpC to decompose OHPs (Jacobson et al. 1989), a phenomenon also observed in other bacterial species and eukaryotic microorganisms. For instance, *ΔahpC* from *Bacteroides fragilis* presents five times more mutations than the wild-type strain (Rocha and Smith 1999). Although the deletion of one or more Prx isoforms in the yeast *S. cerevisiae* is not lethal, it compromises genome stability (Ogusucu et al. 2009). In *Candida albicans*, the *Δtsa1* strains also present increased mutation rates, indicating that Prx contributes to genome stability (Urban et al. 2005). The protective role of Prx in DNA

Table 1 List of different hydroperoxides that are decomposed by Prx of each class in bacteria, fungi, and protozoans

Prx class	Group	Hydroperoxide	Enzyme/organism	Reference(s)
AhpC-Prx1	Bacteria	H_2O_2; *t*-BOOH; CHP; peroxynitrite; ethyl hydroperoxide; linoleic acid hydroperoxide; 5′-hydroperoxymethyluracil (thymine hydroperoxide); 5-hydroperoxy-6-hydroxy-dihydrothymine; 5-hydroperoxy-6-methyl-6-hepten-2-one and 6-hydroperoxy-6-methyl-4-hepten-2-one; 7α-hydroperoxy-3β-hydroxycholest-6-ene; trans-9-hydroperoxyoctadec-10-enoic acid and trans-10-hy-droperoxyoctadec-8-enoic acid; trans-pinocarveyl hydroperoxide (3)	*Ec*AhpC, *Hp*AhpC, *Mt*AhpC, *St*AhpC	Baker et al. 2001; Bryk et al. 2000; Hillas et al. 2000; Jacobson et al. 1989; Jaeger et al. 2004; Parsonage et al. 2005
AhpC-Prx1	Fungi	H_2O_2; *t*-BOOH; CHP; peroxynitrite	*Sc*Tsa1, *Sc*Tsa2	Munhoz and Netto 2004; Ogusucu et al. 2007; Tairum et al. 2016
AhpC-Prx1	Protozoa	H_2O_2; *t*-BOOH; CHP; peroxynitrite; linoleic acid hydroperoxide; phosphatidylcholine hydroperoxide	*Cf*TXNPx, *Gi*Prx1a, *Gi*Prx1b, *Lm*TryP1, *Tbc*TXNPx, *Tc*cTXNPx, *Tc*mTXNPx, *Tg*cTXNPx	Akerman and Muller 2005; Flohé et al. 2002; König and Fairlamb 2007; Mastronicola et al. 2014; Nogoceke et al. 1997; Pineyro et al. 2011; Trujillo et al. 2004
BCP-PrxQ	Bacteria	H_2O_2; *t*-BOOH; CHP; peroxynitrite; linoleic acid hydroperoxide; fatty acids hydroperoxides	*Ec*BCP, *Hp*BCP, *Mb*PrxQB, *Xf*PrxQ	Horta et al. 2010; Jeong et al. 2000; Reyes et al. 2016; Wang et al. 2005
Tpx	Bacteria	H_2O_2; *t*-BOOH; CHP; peroxynitrite	*Ec*Tpx, *Mt*Tpx	Baker and Poole 2003; Jaeger et al. 2004
Prx5	Bacteria	H_2O_2	*Vv*Prx3	Ahn et al. 2018
Prx5	Fungi	H_2O_2; *t*-BOOH	*Af*Asp f3	Hillmann et al. 2016
Prx5	Protozoa	*t*-BOOH	*Pf*AOP	Staudacher et al. 2015
Prx6	Fungi	H_2O_2; *t*-BOOH; CHP; linoleic acid hydroperoxide	*Af*Prx1, *Af*PrxC, *Pb*Prx1	Longo et al. 2020; Rocha et al. 2018
AhpE	Bacteria	H_2O_2; *t*-BOOH; CHP; peroxynitrite; 15-HpETE (arachidonic hydroperoxide); 3-CPBA (3-chloroperoxybenzoic acid); HCO_4^- (peroxymonocarbonate); linoleic acid hydroperoxide	*Mt*AhpE	Hugo et al. 2009; Reyes et al. 2011

Af = *Aspergillus fumigatus*; *Cf* = *Crithidia fasciculata*; *Ec* = *Escherichia coli*; *Gi* = *Giardia intestinalis*; *Hp* = *Helicobacter pylori*; *Lm* = *Leishmania major*; *Mb* = *Mycobacterium bovis*; *Mt* = *Mycobacterium tuberculosis*; *Pb* = *Paracoccidioides brasiliensis*; *Pf* = *Plasmodium falciparum*; *Sc* = *Saccharomyces cerevisiae*; *St* = *Salmonella typhimurium*; *Tb* = *Trypanosoma brucei*; *Tc* = *Trypanosoma cruzi*; *Tg* = *Toxoplasma gondii*; *Vv* = *Vibrio vulnificus*

integrity was also observed under nitrosative stress in *Trypanosoma brucei*. Defective strains in the enzyme uracil-DNA glycosylase (UNG), a component of the base excision DNA repair system, exhibit reduced infectivity and increased levels of DNA damage (Yague-Capilla et al. 2019). Notably, surviving cells of the *T. brucei Δung* strain present increased expression of AhpC-Prx1 peroxiredoxin (Tryp1), which is correlated with peroxynitrite detoxification (Yague-Capilla et al. 2019).

Prx also provide protection through a mechanism related to their chaperone/holdase activity. As explained before, the acquisition of chaperone activity can occur by C_P hyperoxidation (Jang et al. 2004). Since almost all bacterial AhpCs are resistant to C_P hyperoxidation (Wood et al. 2003), the acquisition of chaperone activity to these microorganisms probably involves a redox independent mechanism, which is dependent on thermal insults (Jang et al. 2004), but still poorly understood. Only few descriptions of chaperone activities of bacterial Prx isoforms have been performed to date (Buranajitpakorn et al. 2011; Kamariah et al. 2018). The chaperone function of *E. coli* AhpC was mostly investigated in cell-free systems. In one case, no evidence of heat shock protection by AhpC in *Xanthomonas campestris* was obtained (Buranajitpakorn et al. 2011).

In fungi, the acquisition of chaperone function was described for the two cytosolic isoforms of the AhpC-Prx1 class. Tsa1 and Tsa2 undergo transitions from peroxidase to chaperone in response to oxidative stress and thermal insults. Additionally, null individual mutants or the double mutant *Δtsa1/Δtsa2* present a significant reduction in cell viability compared with the wild-type strain when subjected to heat shock (Jang et al. 2004). A decrease in cell survival as a consequence of thermal insult has also been reported in *Cryptococcus neoformans Δtsa1* mutant (Missall et al. 2004).

In protozoans, the AhpC-Prx1 enzymes from *Schistosoma mansoni* and *Leishmania infantum* were described to switch from peroxidase to chaperone in response to oxidative stress or heat shock (Saccoccia et al. 2012; Teixeira et al. 2015). Furthermore, genetic inactivation of the *L. infantum* mitochondrial AhpC-Prx1 isoform (*Δmtxnpx*) rendered cells a thermosensitive phenotype. High levels of protein aggregation were detected at 37°C (Teixeira et al. 2015), which is compatible with the physiological temperature of mammalian hosts.

Besides inactivating Prx by genetic approaches, pharmacological inhibitors represent an alternative to investigate the roles of these proteins in pathogens. However, only a few microbial peroxiredoxin inhibitors have been identified to date. For instance, showdomycin is a potent C-glycosyl nucleoside antibiotic isolated from *Streptomyces showdoensis* that was detected as a ligand of AhpC catalytic cysteines from *Staphylococcus aureus* (Bottcher and Sieber 2010). In protozoans, conoidin A was initially described as an inhibitor of host cell invasion by the pathogenic protozoan *Toxoplasma gondii*; this compound was later shown to bind covalently to cysteine residues of *Tg*PrxII, a peroxiredoxin from the AhpC-Prx1 subclass. Conoidin A also prevents the growth of *Plasmodium falciparum* and increases the sensitivity of the parasite in host cells to chloroquine, an antimalarial drug (Haraldsen et al. 2009). Both conoidin A and showdomycin are bulky molecules with large hydrophobic backbones, which may mimic large biological substrates, as OHPs. Therefore, inactivating Prx isoforms may be a promising approach to enhance the death of pathogens resistant to multiple drugs.

Prx as virulence factors

Since Prx play important roles in pathogen survival, they may represent virulence factors. In fact, enzymes from five of the six Prx classes have been described as virulence factors in pathogens (Table 2). No studies have yet been performed to examine the involvement of AhpE enzymes in virulence. The role of different Prx classes in the virulence of the pathogenic microorganisms is summarized below.

AhpC-Prx1

AhpC-Prx1 isoforms were associated with *Helicobacter cinaedi* and *H. pylori* virulence, since *ahpC* mutants (*ΔahpC*) could not to colonize mice stomach and were more susceptible to killing by macrophages (Charoenlap et al. 2012; Olczak et al. 2003). Moreover, *H. cinaedi* lacking the *ahpC* gene presented a reduced ability to colonize the intestine of both wild-type and defective in interleukin-10 (IL-10) mice (Charoenlap et al. 2012).

In the pathogenic marine bacterium *Vibrio vulnificus*, AhpC is related to both the bacterial capacity to grow during infection of human intestinal cells and the ability to infect mice (Baek et al. 2009). Infecting wild-type mice with a *ΔahpC* strain of *Listeria monocytogenes* diminishes bacterial virulence. This *ΔahpC* strain was virulent when infecting mice with iNOS deficiency, indicating that AhpC protects bacteria from nitric oxide-derived oxidants, such as peroxynitrite (Dons et al. 2014).

AhpC-Prx1 members from the *Mycobacterium* genus are indirectly related to the actions of catalase and isoniazid (INH), a drug largely employed in the treatment of tuberculosis. *Mycobacterium tuberculosis* is able to grow inside host macrophages using diverse strategies to detoxify distinct ROS and RNS. In addition, some strains of *M. tuberculosis* present INH resistance that is related to catalase (KatG) mutations (Rintiswati et al. 2011). INH is a prodrug that requires "activation" by KatG to inhibit enoyl-acyl carrier protein reductase from *M. tuberculosis* by the formation of an isonicotinoyl-NAD adduct (Yu

Table 2 Prx enzymes and virulence

Prx class	Virulence factor	Protein(s)	Organism	Reference
AhpC-Prx1	Yes	AhpC	*Helicobacter cinaedi*	Charoenlap et al. 2012
	Yes	AhpC	*Helicobacter pylori*	Olczak et al. 2003
	Yes	Prx	*Listeria monocytogenes*	Dons et al. 2014
	Yes	AhpC	*Mycobacterium bovis*	Wilson et al. 1998
	No	AhpC	*Mycobacterium tuberculosis*	Heym et al. 1997
	No	AhpC	*Mycobacterium tuberculosis*	Kaufmann et al. 2001
	No	AhpC	*Porphyromonas gingivalis*	Johnson et al. 2004
	No	AhpC	*Salmonella typhimurium*	Taylor et al. 1998
	No	AhpC	*Staphylococcus aureus*	Cosgrove et al. 2007
	Yes	AhpC	*Streptococcus pyogenes*	Brenot et al. 2005
	No	AhpC	*Streptococcus pyogenes*	Brenot et al. 2005
	Yes	AhpC1	*Vibrio vulnificus*	Baek et al. 2009
	No	Tsa1	*Candida albicans*	Urban et al. 2005
	Yes	Tsa1/Tsa2	*Candida glabrata*	Gutierrez-Escobedo et al. 2020
	Yes	Tsa1	*Cryptococcus neoformans*	Missall et al. 2004
	Yes	Prx	*Entamoeba histolytica*	Davis et al. 2006
	Yes	mTXPx	*Leishmania infantum*	Castro et al. 2011
	No	GPrx	*Leishmania infantum*	Castro et al. 2020
	Yes	Prx	*Plasmodium berghei*	Usui et al. 2015
	Yes	TXNPx	*Trypanosoma cruzi*	Piñeyro et al. 2008
BCP-PrxQ	Yes	BCP	*Brucella melitensis*	Zygmunt et al. 2006
	No	Prx1	*Helicobacter pullorum*	Parente et al. 2017
	Yes	BCP	*Helicobacter pylori*	Wang et al. 2005
Tpx	Yes	Tpx	*Enterococcus faecalis*	La Carbona et al. 2007
	Yes	Tpx	*Helicobacter pylori*	Olczak et al. 2003
	Yes	Tpx	*Mycobacterium tuberculosis*	Hu and Coates 2009
	No	Tpx	*Salmonella enterica*	Horst et al. 2010
	Yes	TpxD	*Streptococcus pneumoniae*	Hajaj et al. 2012
Prx5	Yes	Prx5	*Brucella abortus*	Hu et al. 2019
	Yes	Prx5-Grx	*Neisseria meningitidis*	Aljannat et al. 2020
	Yes	Prx3	*Vibrio vulnificus*	Lim et al. 2014
	Yes	Aps f3	*Aspergillus fumigatus*	Hillmann et al. 2016
Prx6	Yes	LsfA	*Pseudomonas aeruginosa*	Kaihami et al. 2014
	Yes	Prx1	*Aspergillus fumigatus*	Rocha et al. 2018
	No	PrxB	*Aspergillus fumigatus*	Rocha et al. 2018
	No	PrxC	*Aspergillus fumigatus*	Rocha et al. 2018
	No	Tsa3	*Cryptococcus neoformans*	Missall et al. 2004
	Yes	MoPrx1	*Magnaporthe oryzae*	Mir et al. 2015

et al. 2003). Mutants of KatG are defective in the activation of INH and in the elimination of hydrogen peroxide. Therefore, increased levels of AhpC compensate the loss in KatG activity and are relevant in *M. tuberculosis* resistance to INH (Sherman et al. 1996).

Catalase (KatA) and AhpC also have compensatory roles in *S. aureus*, especially during aerobic growth, even though

these enzymes are not required for bacterial virulence in mice or for survival of the bacteria in human neutrophils (Cosgrove et al. 2007). AhpC deletion did not affect the virulence of *Porphyromonas gingivalis* and *S. typhimurium* in murine models (Johnson et al. 2004; Taylor et al. 1998). Curiously, *Streptococcus pyogenes ΔahpC* was less virulent in one of two murine models tested, suggesting a differential immune response according to the host's genetic background or related to infection technique (Brenot et al. 2005).

In the fungus *C. glabrata*, deletion of *tsa2* gene has a profound impact on virulence compared with the *Δtsa1* strain, while Tsa1 and Tsa2 are highly induced when challenged by neutrophils and are important for both the survival and growth of this pathogen in the immune cells (Gutierrez-Escobedo et al. 2020). Similarly, mice infected with *C. neoformans Δtsa1* strains are able to survive for a longer period than animals infected with wild-type pathogenic yeast. The levels of the pathogen in the lung and in the brain of animals infected with the mutant strain were significantly lower (Missall et al. 2004). In contrast, *C. albicans* Tsa1 is an important component against oxidative stress, but it has no impact on virulence (Urban et al. 2005).

In *T. cruzi*, overexpression of two AhpC-Prx1 isoforms made the pathogen more efficient against the oxidative defenses of macrophages, indicating virulence role of both enzymes (Leitsch et al. 2018). In *Plasmodium berghei*, *Δ prx1* cells were not able to survive in a murine model (Usui et al. 2015). For *Entamoeba histolytica*, nonvirulent strains had low expression levels of AhpC-Prx1 and overexpression of this enzyme rendered higher resistance to oxidative stress and partially restored pathogenicity to this strain, while gene deletion in virulent strains lead to avirulence (Davis et al. 2006). Deletion of the mitochondrial isoform of *L. infantum* decreased the long-term persistence of the pathogen in the liver and spleen of guinea pigs compared to the wild-type strain (Angelucci et al. 2016; Castro et al. 2011). Conversely, experiments using the *L. infantum* strain with a deletion of the glycosomal isoform Prx showed that this enzyme is dispensable for virulence in mice (Castro et al. 2020).

BCP-PrxQ

The *H. pylori Δbcp* mutant has a significantly lower ability to colonize and survive in mouse stomach than the wild-type strain, mainly after 3 weeks of infection (Wang et al. 2005). In contrast, *Helicobacter pullorum Δprx1* and wild-type strains show no differences when challenged with hydrogen peroxide and peroxynitrite, or during macrophage infection (Parente et al. 2017). *Brucella melitensis* expresses a BCP-PrxQ required for bacterial virulence in the caprine host, which is probably related to its capacity to survive inside host macrophages (Zygmunt et al. 2006). The BCP-PrxQ from the phytopathogen *Candidatus Liberibacter asiaticus* is able to repress the recognition of some pathogen-associated molecular patterns (PAMPs) in tobacco. This BCP-PrxQ can also protect bacteria from lipid peroxidation, preventing the formation of oxylipin (Jain et al. 2018), a class of oxygenated derivatives of polyunsaturated fatty acids that contribute to plant defense.

Tpx

Concerning the Tpx class, the *H. pylori Δtpx* strain has a reduced capacity to colonize mouse stomach, revealing its importance during infection (Olczak et al. 2003). It is worth mentioning that isoforms from three different Prx classes are related to the virulence of *H. pylori*. Deletion of the *tpx* gene of *Enterococcus faecalis* affects survival during macrophage infection and dependence on virulence in a mouse peritonitis model (La Carbona et al. 2007). Mice infected with the *ΔtpxD* strain of *Streptococcus pneumoniae* showed significantly longer survival. However, this difference is not observed during blood infection, which is probably related to the high oxygen levels in the respiratory system (Hajaj et al. 2012). The inactivation of the *tpx* gene of *Salmonella enterica* makes bacteria more sensitive to hydrogen peroxide than the single mutants of the other Prx. During macrophage infection, the *Δtpx* strain mutant was more sensitive, while no difference was detected in a mice infection model (Horst et al. 2010). *Mycobacterium tuberculosis* mutants lacking *tpx* cannot grow in organs of infected mice, fail to induce an inflammatory response, and show low resistance to macrophage infections. Additionally, Tpx is able to protect *M. tuberculosis* against the RNS generated by macrophages, as demonstrated by infecting iNOS knockout host cells (Hu and Coates 2009). This finding is important since *M. tuberculosis* AhpC-Prx1 isoforms are unable to exert virulence effects.

Prx5

Studies on the virulence of members from the Prx5 class are scarce. *Vibrio vulnificus* strain lacking the *prx5* isoform causes a delay in mice death by intragastric infection (Lim et al. 2014). Remarkably, a Prx5-Grx fusion of *N. meningitidis* has been related to virulence, as verified using an ex vivo human whole blood model of meningococcal bacteremia (Aljannat et al. 2020). As mentioned before, the bacterial Prx5-Grx enzymes have no counterparts in the host and may represent an important target for drugs. In fungi, an isoform from Prx5 subfamily has also been characterized as a virulence factor in *A. fumigatus* (Hillmann et al. 2016).

Prx6

Only one bacterial Prx6 has been related to virulence so far. LsfA from *P. aeruginosa* is able to specifically protect

bacteria against the oxidative burst promoted by the macrophages. The authors used an acute pneumonia model to infect mice with the mutant lacking the *lsfa* gene strain and observed an improved survival rate compared with those infected with wild-type strain (Kaihami et al. 2014).

Virulence studies were also performed on members of Prx6 subfamily in fungi. *Aspergillus fumigatus* presents three Prx6 enzymes. Experiments using the individual mutant strains for each isoform revealed that the absence of only one of them (Prx1) caused lower mortality rates compared with the wild-type. Additionally, the organs of animals infected with the *Δprx1* strain have an elevated rate of pathogenic cell death and high levels of immunological defense cells (Rocha et al. 2018). For *Magnaporthe oryzae*, the lack of a Prx6 class enzyme impacts virulence in a rice seedling root model (Mir et al. 2015).

Although no obvious general rule emerges from these studies, several Prx from five subfamilies are involved in virulence of distinct pathogens. The obvious role of Prx in virulence is related to pathogen protection from the host's oxidative responses. However, the demonstration of the role of Prxs enzymes in virulence may be hampered by the fact that some pathogens have a large repertoire of antioxidant enzymes. On the other hand, Prx have additional activities such as phospholipase and chaperone that can also be involved in pathogen virulence. Therefore, two key points are probably relevant to understand the complex mechanisms underlying virulence: (i) investigating the cooperation among antioxidant enzymes to fight oxidative insults in different developmental stages and in different cell compartments and (ii) the role of each Prx activity during microbial infection and colonization.

Concluding remarks

The relevance of Prx in microorganism's response to oxidative stress has been demonstrated since their discovery in *S. typhimurium* and *E. coli* in the 1980's. Over the years, Prx have been biochemically and structurally characterized in diverse microorganisms, along with the identification of reducing and oxidizing substrates, and structural peculiarities. It has become clear that Prx enzymes display unique and key roles in the establishment and progression of infectious diseases. In fact, a number of Prx enzymes among bacteria, fungi, and protozoans present virulence properties, which may be related to any peroxiredoxin function (e.g., peroxidase, phospholipase, chaperone, or cell signaling to eukaryotes). Despite these enzymes being important for pathogen survival, few studies have applied knowledge on Prx to fight pathogenic microorganisms. An obstacle to applications like inhibitors or vaccines is that only a small number of molecules capable of efficiently and selectively inhibiting Prx enzymes is known. Overall, Prx should be regarded as an important alternative for the development of new therapeutical approaches to overcome the globally relevant growing resistance of pathogenic microorganisms to antimicrobials.

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Declarations

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