Peroxiredoxins wear many hats: Factors that fashion their peroxide sensing personalities

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ABSTRACT
Peroxiredoxins (Prdxs) sense and assess peroxide levels, and signal through protein interactions. Understanding the role of the multiple structural and post-translational modification (PTM) layers that tunes the peroxiredoxin specifities is still a challenge. In this review, we give a tabulated overview on what is known about human and bacterial peroxiredoxins with a focus on structure, PTMs, and protein-protein interactions. Armed with numerous cellular and atomic level experimental techniques, we look at the future and ask ourselves what is still needed to give us a clearer view on the cellular operating power of Prdxs in both stress and non-stress conditions.

1. Introduction

1.1. The involvement of peroxiredoxins in cellular homeostasis

Peroxiredoxins (Prdxs) are a unique set of proteins in several aspects: they have a high cellular abundance, are present in all known species, and in most cellular compartments [1–3]. They also display a variety of functions with the most well-known one being their role as peroxidase, but it is essential to point out that some Prdxs exhibit chaperone activity, while others exhibit phospholipase activity, although these functions are not a major focus of this review [4,5]. Prdxs are the most crucial proteins involved in maintenance of hydrogen peroxide (H2O2) levels by reduction, usually outcompeting other peroxidases in the cell like catalasles and glutathione peroxidases (Gpxs) [7–9]. Thus, as Prdxs are the main regulators of H2O2 levels, and dysregulated H2O2 levels are linked to disease development [12], Prdxs are associated with pathogenesis and are therefore immensely important to understand.

Originally, Prdxs were called ‘protector proteins’ [13] and were known for helping cells survive oxidative stress conditions by reducing H2O2 [2], peroxynitrous acid, the protonated form of peroxynitrite (ONOOH) [14], and lipid peroxides [15]. This protection role was assigned to them for a long time as H2O2 was believed to only play a damaging and detrimental role [16]. However, in the past two decades it has become clear that at fine-tuned and controlled levels between 1 and 100 nM, H2O2 is required for the homeostatic signaling/functioning of the cell, simultaneously prompting the question of how Prdxs participate in cellular homeostasis [17–19]. Previously, Prdx involvement in signaling was only considered indirect. It was associated with their peroxidase function in controlling H2O2 levels (Fig. 1) and their inactivation by hyperoxidation, which would allow for H2O2 to accumulate and trigger cellular stress responses [1]. Recently, however, they have been recognized to also play a more direct and central role as cellular H2O2 sensors involved in signaling hubs for non-stress, homeostatic signaling [20,21]. They act as sensors by participating in “redox-relays” where oxidative equivalents are transferred from the Prdxs to the target protein by thiol-disulfide exchange [22,23] (Fig. 1). More explicitly, two possibilities exist for how this may occur. In one scenario, the thiol of the partner protein reacts with the sulfenic acid Prdx species, followed by thiol-disulfide exchange with a vicinal thiol in the partner, if available. In the other scenario, the thiol of the partner protein reacts with the disulfide within Prdx using a typical thiol-disulfide exchange mechanism [22,23] (Fig. 1). Notably, Prdxs appear to be promiscuous, connecting with many different target proteins within structural complexes located in cellular microdomains [31,32].

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connects Prdxs to most key signaling networks responsible for cellular responses to both stress and non-stress messages, implicating them in overall cellular metabolism, fitness, and survival. However, only a handful of interactions (STAT3, ASK1, TIMELESS) have been explored in mechanistic detail [20,21,31,33,34] and even still, many questions remain. To further complicate matters, the Prdxs are also subject to post-translational modifications (PTMs), which regulate/control/organize their scavenging, signaling, and regulating functions [4, 35-47].

Thus, it seems that as much as we have learned about Prdxs, they continue to reveal additional, intriguing facets of themselves, and there is much unexplored territory around this fascinating family of enzymes. In this review, we begin with a tabulated overview of what is known about human and bacterial Prdxs in terms of structure and PTMs. We decided not to touch upon yeast Prdxs as they often display characteristics of both human and bacterial Prdxs, making them difficult to categorize. We summarize the methods and techniques that are being used to investigate Prdxs and the protein-protein interactions (PPI) they are involved in, and we conclude with a perspectives section highlighting the anticipated and required progress for this field of study in the next quinquennial.

1.2. Key mechanistic features of peroxiredoxins

In the social theory of intersectionality [48], an individual’s identity is influenced by many intersectional identities, meaning the identities are intertwined and interdependent, but not necessarily overlapping: race, gender, class, location, age, etc. It is similar for Prdxs in determining their functional identity. The functional identity (i.e. peroxidase, redox-relay participant, or other function) of a Prdx is determined by many "intersectional" factors. There are more factors than what will be covered in this review, but here the focus will be given to subgroup category, oligomeric state, protein motifs, redox state, and PTMs. Because these factors are intersectional, they are described together as it is difficult to explain one without referencing the others.

There are six different subgroups of Prdxs: Prdx1/AhpC, Prdx5, Prdx6, Tpx, BCP/PrdxQ, and AhpE. Typical, 2-Cys Prdxs (Prdx1 subgroup; mammalian Prdx1-4) and the 1-Cys Prdx (mammalian Prdx6) exist as obligate homodimers. Depending on the redox state and/or certain PTMs present (i.e. phosphorylation, acetylation), the typical, 2-Cys Prdxs can oligomerize further into a decameric (or pentamer of dimers), or dodecameric (hexamer of dimers) toroid structure (Fig. 2) [49, 50]. The reduced decamer is the most efficient peroxidase because of allosteric “buttressing” that makes a more fully-folded, stable active site. These toroid structures, depending on their redox state or additional PTMs present, can stack with one another to form high molecular weight (HMW) oligomers that look like “filaments”, which are associated with cell-cycling checkpoints [51] and in some cases, chaperone activity [36, 52]. The atypical, 2-Cys Prdxs (mammalian Prdx5) were originally described as monomeric proteins [33]. However, through an alternative interface observed in all Prdx5 structures, dimerization occurs, even independently of the redox state [3].

All the Prdxs progress through the typical 2-Cys Prdx catalytic cycle represented in Fig. 1 essentially the same way. This cycle is covered extensively in detail elsewhere [54-56]. In brief, during the catalytic cycle, the reduced peroxidatic cysteine (CysPrdx) is oxidized to a Cys sulfenic acid (CysPrdx-SOH), which is resolved by reaction with the resolving cysteine (CysRes) to form a disulfide (CysPrdx-S-S-CysRes). Despite all Prdxs going through this same cycle, the point of difference comes from whether the CysRes, depending on the functional identity of the Prdx at the time, comes from the adjacent monomer, the same monomer, or a separate nucleophile like glutathione or a redox-relay binding partner (Fig. 1). At least in the case of typical, 2-Cys Prdxs, we know that disulfide formation between CysPrdx and CysRes of the adjacent monomer

Fig. 1. Mechanism of the redox cycle and the redox-relay of typical 2-Cys Prdxs (shown family members are the cytosolic human Prdx1 and Prdx2). Prdx scavenges H2O2 through the formation of a sulfenic acid (Cys-SOH) on the peroxidatic cysteine (CysPrdx) with the subsequent formation of a disulfide bond between CysPrdx and the resolving cysteine (CysRes) [10]. Prdx is recycled via the thioredoxin pathway (Trx-TrxR-NADPH) [11]. Via a redox-relay, oxidative equivalents can be transferred to a binding partner in a process that, depending on the partner, may involve an additional scaffold protein.
requires quite a bit of local structural rearrangement, which affects the overall oligomeric state. The helix containing the Cysₚ must unwind and flips outwards to meet the Cysᵦ, which is in the C-terminal region. This C-terminal region is a semi-flexible region and is often difficult to capture in X-ray structures until the disulfide forms, as this “locks” the terminal region into an ordered state (Fig. 3, panel b and c). These structural rearrangements destabilize the decamer, making it “loose”, and ultimately causing it to dissociate back into dimeric subunits (Fig. 2) [6,50]. The Cysᵦ-S-S-Cysᵦ is then reduced by the NADPH-dependent thioredoxin-thioredoxin reductase system.

The difference across the subgroups is that the atypical, 2-Cys types contain two Cys residues in the monomeric subunit of the obligate homodimer, while the 1-Cys types get the resolving electron donor from another source, like glutathione [3,57,58]. Also, of note, 1-Cys Prdxs are incredibly robust against inactivation via overoxidation (–SO₂H or –SO₃H formation) [57], also known as hyperoxidation. Hyperoxidized Prdxs are repaired by the ATP-dependent sulfiredoxin enzyme, but human Prdx6, a 1-Cys Prdx, does not interact with sulfiredoxin [57].

In terms of resistance against hyperoxidation, there are pronounced differences between bacterial and human Prdxs. Mammalian Prdxs1-4, despite being in the same subgroup as the bacterial AhpC, are significantly more prone to being overoxidized than AhpC, and this was

Fig. 2. Oligomeric states of Prdxs. There is dynamic equilibrium between dimer and decamer when Prdx is reduced, with the reduced (SH) decamer being the most efficient. Oxidation loosens the decamers causing them to dissociate back into dimers. The structures depicted are WT Salmonella typhimurium Prdx1/AhpC (reduced form (green): 4MA9; oxidized form (light blue): 1EYP). The decamers can stack also to form HMW oligomers, and this is usually linked to overoxidation, like what is shown in purple (human Prdx3: 5JCG). Oxidized Prdxs are repaired by sulfiredoxin (Srx) in an ATP-dependent mechanism, shown with the Prdx-Srx complex structure (dark blue, human Prdx1: 2RII). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Active site organization of peroxiredoxins. A. The low pKₐ of the peroxidatic cysteine (Cysₚ) and the conserved hydrogen bonding network that stabilizes the transition state determine the high second order rate constant of H₂O₂ sensing. Adapted from Hall et al. [6]. B. The formation of the intersubunit disulfide bond (Cysᵦ-S-S-Cysᵦ) in the presence of H₂O₂ requires the structural rearrangement of the active site from a fully folded (green) to a locally unfolded (light blue) loop for the Cysᵦ-S to access the oxidized Cysᵦ-S. C. The distance between the resolving Cys in the reduced (Cysᵦ-SH) and oxidized (Cysᵦ-S-) peroxiredoxin is shown. The structures depicted in b) and c) are WT Salmonella typhimurium Prdx1/AhpC (reduced form (green): 4MA9; oxidized form (blue): 1EYP). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
determined to be because eukaryotic Prdxs contain the GGLG and YF motifs that render them “sensitive” [2,3]. It is believed that the GGLG and YF motifs confer sensitivity to hyperoxidation by slowing down the structural rearrangements of the C-term necessary for Cys-S-S-CysR formation. Later, two additional motifs, Motifs A and B, were discovered that confer resistance to overoxidation across the eukaryotic and prokaryotic Prdx distinction [59]. This helped explain the stratification of overoxidation sensitivity observed across Prdx subgroups, but it blurred the lines of known Prdx categorization.

Indeed, it is difficult to neatly phylogenetically sort these enzymes [60]. Despite the difficulty with categorization, the theme of redox sensing is conserved in Prdxs along with the conservation of the redox sensitive, active site Cys, the CysR. The CysR has a pK_a value in the range of 5–6.3 [61–63]. However, whereas most deprotonated thiols react with H_2O_2 with a rate constant of ~1–10 M^−1 s^−1, the CysR residue of Prdxs reacts with H_2O_2 with rate constants of 10^5–10^7 M^−1 s^−1 [8,64,65].

Table 1

| Name | FDB Code | Oligomeric state | Description | Reference |
|------|----------|------------------|-------------|-----------|
| Prdx4 | 3TPK | dimer | C-term only of Prdx4 in complex with P5 a0 | [68] |
| Prdx4 | 3TRS | dimer | C-term only in complex with ERp46 Trx2 | [67] |
| Prdx4 | T118E/C145/ C87S | C-term only in complex with IRP44 | [67] |
| Prdx4 | 4QX | dimer | Disulfide between C124 and BNP7789 (MESNA) | [69] |
| Prdx5 | C72S | SS (some SH) | Oxidation/ disulfide formation of the active site C_p with the C_4 | [70] |
| Prdx5 | 2VL3 | SS (some SH) | Oxidation/ disulfide formation of the active site C_p with the C_4 | [71] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [72] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [73] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [74] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [75] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [76] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [77] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [78] |
| Prdx5 | C72S | SS | Oxidation/ disulfide formation of the active site C_p with the C_4 | [79] |

2. A structural summary of peroxiredoxins

As of November 2020, the search term for macromolecular identifier “peroxiredoxin” in the RCSB protein databank yields 113 entries for structures under the “Homo sapiens” category and 138 structures under the “Bacteria” category, with 135 being X-ray diffraction structures and the other 3 being NMR structures. All but one of the human structures were solved using X-ray diffraction, and one was solved by NMR. From the 113 human structures, 35 are included in Tables 1 and 2. The rest of the results come from human proteins functionally similar or (continued on next page)
exist in several different oligomeric states: monomer, dimer, decamer, bacterial Prdxs is still needed [68].

difficult to actually tally, making it clear that much information about species, the structures that still need to be solved are immense and actually bound in active site), but because of the expanse of bacterial

tries). However, there is not a single human Prdx structure solved with either another protein (5 PDB entries) or a small molecule (7 PDB entries). There are 12 structures where a Prdx is in complex with a ligand, 12 structures, respectively. The human Prdxs that have the least amount functionally related to Prdxs, for instance, thioredoxin and glutaredoxin.

Among the human Prdx structures, there are 8 reduced structures, and thus excluded from this review in detail, but PDB code 3A2V- H site (some

structures available for bacterial Prdxs where peroxides are in the active site (V. vulnificus from Table 4, PDB code 5K2J; archaeon A. pernix K1, thus excluded from this review in detail, but PDB code 3A2V- H2O2 actually bound in active site), but because of the expanse of bacterial species, the structures that still need to be solved are immense and difficult to actually tally, making it clear that much information about bacterial Prdxs is still needed [68].

As evident in Tables 1–4 and mentioned in the introduction, Prdxs exist in several different oligomeric states: monomer, dimer, decamer,
3. Peroxiredoxin modulation through various post-translational modifications

Human Prdxs are regulated by a variety of PTMs, including, but not limited to: acetylation, ubiquitination, glutathionylation, different types of oxidation (SOH, SS, SO₂, SO₃, S-nitrosylation, and phosphorylation [4]. There is also observation of tyrosine nitration in peroxiredoxins [110,111]. There have been 26 modified residues identified by low-throughput methods amongst the 6 different human isoforms: 10 for Prdx1, 5 for Prdx2, 2 for Prdx3, and 5 for Prdx6 (Table 5). For high-throughput methods, the residues have been identified through mass spectrometry (MS)-based proteomics and are summarized in Table 6. Notably, however, limited residues have been further verified in vivo through additional investigative methods. For example, phosphorylation of human Prdx1 has been detected on Thr18, Ser32, Thr90, Thr156, Thr183, Tyr194 by proteomics studies, but only Ser32, Thr90, Thr183, Tyr194 have been confirmed by immunoblot probing cell lysates. In fact, commercial antibodies have now been developed that recognize Thr90 and Tyr194. The other putative phosphorylation sites remain to be substantiated. PTM detection is discussed at further length.

### Table 4
Other bacterial Prdx structures

| Organism Name | PDB Name | Redox State | Description | Oligomeric State | Reference |
|---------------|----------|-------------|-------------|------------------|-----------|
| *Escherichia coli/Homo sapiens chimera* | AhpC-186-YFSKH | SS | Oxidation/disulfide formation of the active site Cᵦ with the Cᵦ | decamer | [87] |
| *Salmonella typhimurium* | AhpC | 5BMX | Oxidation/disulfide formation between active site Cᵦ and the Cᵦ | dodecamer | [81] |
| *AhpC* | 4EO3 | SS | Oxidation/disulfide formation between active site Cᵦ and the Cᵦ | monomer | [109] |

### Table 5
Prdx structures

| Name | Redox State | Description | Reference |
|------|-------------|-------------|-----------|
| Prdx1 | SS | Oxidation/disulfide formation of the active site Cᵦ with the Cᵦ | decamer | [87] |
| Prdx2 | SS | Oxidation/disulfide formation between active site Cᵦ and the Cᵦ | dimer | [99] |
| Prdx3 | SS | Oxidation/disulfide formation between active site Cᵦ and the Cᵦ | dimer | [97] |
| Prdx6 | SS | Oxidation/disulfide formation between active site Cᵦ and the Cᵦ | dimer | [97] |
have additionally yielded phosphorylation and acetylation sites on PTMs are the formation of sulfenic acid (SOH) upon the reaction with peroxynitrite (-SOH) and H$_2$O$_2$ (-SOH and -SSO$_2$H) - (proposed effect of PTM).

| Name           | Residue | PTM Description          | Reference |
|----------------|---------|--------------------------|-----------|
| Prdx1          | Cys$^{32}$, Cys$^{63}$, Cys$^{171}$ | GSH – Glutathionylation; P – Phosphorylation; Ac – Acetylation; Ub – Ubiquitination; Sm – SUMOylation | [114]     |
| Prdx2          | Cys$^{31}$, Cys$^{172}$ | GSH – Protection against hyperoxidation | [115]     |
| Prdx6          | Cys$^{47}$, The$^{199}$, Ser$^{32}$, Ser$^{190}$ | GSH – Regeneration of the reduced Cys- | [58]      |
| Prdx1          | The$^{201}$, The$^{189}$, Ser$^{32}$, Ser$^{190}$ | P – Inhibits peroxidase activity; increases decamer formation and chaperone activity; except Ser32 which enhanced peroxidase activity | [37-39]   |
| Prdx2          | Ser$^{264}$, The$^{199}$ | P – Inhibits peroxidase activity and enhanced decamer formation and chaperone activity; * indicates that Ser76 was only identified through a mutational study | [43,116]  |
| Prdx6          | The$^{177}$ | P – Increases phospholipase A$_2$ activity | [46]      |
| Prdx1          | Lys$^{197}$, Lys$^{277}$ | Ac – Acetylation of Prdx increases peroxidase activity and hyperoxidation resistance; Lys27 acylation enhances chaperone activity | [41,42]   |
| Prdx2          | Lys$^{196}$ | Ac – Acetylation of Prdx increases peroxidase activity and hyperoxidation resistance | [42]      |
| Prdx3          | Lys$^{521}$ | Ac – Inhibits peroxidase activity | [45]      |
| Prdx6          | Lys$^{196}$ | Ac – Unknown | [117]     |
| Prdx1          | Lys$^{196}$ | Ub – Causes degradation | [44,118]  |
| Prdx3          | Lys$^{196}$ | Ub – Causes degradation | [119]     |
| Prdx6          | Lys$^{123}$, Sll1621 (PrdxII) | Sm – Increased GSH-peroxidase and Lys$^{145}$ activity; nPLA$_2$ activity | [120]     |
| Prdx1          | Cys$^{31}$ | SNO – Inhibits peroxidase activity; enhances chaperone activity | [40]      |
| Prdx2          | Cys$^{31}$, Cys$^{172}$ | SNO – Inhibits peroxidase activity | [47]      |
| Prdx5          | Cys$^{48}$ | SCoA – Inhibits peroxidase activity | [121]     |
| Prdx2          | Cys$^{31}$, Cys$^{48}$ | SSH – Protection against hyperoxidation | [112]     |

| Name           | Residue | PTM Description          | Reference |
|----------------|---------|--------------------------|-----------|
| Mycobacterium tuberculosis      | Cys$^{45}$ | SOH/ SOJH – Product of oxidation upon the reaction with peroxynitrite (-SOH) and H$_2$O$_2$ (-SOH and -SSO$_2$H) | [63]      |
| AhpE            | Cys$^{45}$ | MSH – Reduction of the sulfenic acid formed on the catalytic Cys by Mrx-1/Mtr, which proceeds via a monothiol mechanism; protection from overoxidation | [122]     |
| AhpE            | Cys$^{45}$ | SS – H$_2$S reacts with the sulfenic acid formed on the catalytic Cys, forming a persulfide, which can then be reduced back to a thiol by another molecule of H$_2$S or another thiol. As this reaction occurs at a rate sufficient for the catalytic cycle to restart, it constitutes an alternative mechanism of reduction to the MSH/MrX-1/Mtr system. Persulfidation of AhpE also enables it to be involved in transpersulfidation. | [113]     |
| Corynebacterium glutamicum   | Cys$^{36}$ | SOH – Product of reaction with H$_2$O$_2$ | [123]     |
| Mpx              | Cys$^{36}$ | MSH – Reduction of the sulfenic acid formed on the catalytic Cys by Mrx-1/Mtr, which proceeds via a monothiol mechanism, though it can also be reduced by Trx via a dihthiol mechanism; protection from overoxidation | [123]     |
| Tpx              | Cys$^{50}$, Cys$^{94}$ | MSH – Reduction of the sulfenic acid formed on the catalytic Cys (Cys$^{50}$) by Mrx-1/Mtr, which proceeds via a monothiol mechanism; protection from overoxidation | [124]     |
| Escherichia coli   | Cys$^{63}$ | SOH/ SOJH – Oxidation product upon the reaction with H$_2$O$_2$ and cumene hydroperoxide | [125]     |
| BCP             | Cys$^{45}$ | SOH – Oxidation product with H$_2$O$_2$ and other peroxides | [126]     |
| Model cyanobacterium Synechocystis sp.   | GSH | Bioindication purposes (proposed effect of PTM) | [127]     |

SOH – formation of a sulfenic acid; SO$_2$H – formation of a sulfenic acid; MSH = S-mycothiolation; SS – persulfidation; GSH = S-glutathionylation.
able to modulate the function of Prdxs warrants further investigation of PTMs of bacterial Prdxs.

4. Additional methods useful for investigating peroxiredoxins

50 years ago, transmission electron microscopy (TEM) yielded the first images of an erythrocyte protein (Prdx2) with an apparent tenfold symmetry oligomerization [128]. Since then, the combination of the continuously expanding repertoire of methods used to investigate Prdx has allowed the visualization of the Prdx structure on multiple scales, from individual oligomeric states to HMW assemblies of stacked decamers, and even surveilling different forms in living cells in real time [116]. Table 7 summarizes the experimental techniques that have been used for investigating Prdxs.

As the redox-relay function of Prdxs has come more into focus, PPI techniques have been used to identify redox-relay partners of Prdxs. For identifying Prdx interactomes, there are two main methods: immunoprecipitation (or co-affinity pulldown; IP) in tandem with MS or the yeast two hybrid system followed by co-immunoprecipitation. However, several other methods can also be utilized, including native PAGE separation, 2-dimensional gel electrophoresis, Bio-ID, IPOND (isolation of protein on nascent DNA), and kinetic trapping coupled with a variety of MS-based techniques such as LC-MS/MS, NanoLC-MS/MS, HPLC-MS, and MudPIT (MS-based multidimensional protein identification technology). The techniques that have been successfully utilized before are summarized in Table 8, along with the Prdx interactors they helped to identify.

For verifying specific interactors beyond initial MS identification, co-immunoprecipitation (or co-affinity pulldown) is the most predominant approach for in vivo validation. Other alternative approaches are proximity-based immunofluorescence (PLA, etc.), yeast two-hybrid and co-localization immunofluorescence for in vivo confirmation. While all the previous methods are employed in cells or cell lysates, there are some examples of in vitro verification techniques including: maintaining protein-complex in chromatography, the pre-co-incubation of two interactors followed by SDS-PAGE and MS analysis or even confirmation of protein interaction by X-ray crystallography co-crystalization. However, sometimes protein complexes may be difficult to maintain in vitro for numerous reasons, such as missing facilitator proteins, dissociation of the weak interactions, etc. The techniques used for PPI validation for Prdxs are tabulated in Table 9 along with the interaction partner the technique helped confirm.

In addition, there are tools available for PTM identification and verification. Apart from the most commonly used MS, there are other methods such as affinity beads for tyrosine phosphorylation, ubiquitination, acetylation, and SUMOylation-2/3 PTM that enable the trapping and identification of proteins containing these modifications [207]. There are also some specific antibodies that can be used to detect specific PTMs in proteins by immunoblot, such as the anti-peroxiredoxin-SO₃ antibody for overoxidation [208], anti-nitrotyrosine antibody for tyrosine nitration [110,209,210], as well as by immunofluorescence, like the pan-acetylation antibody [211], which allows visualizing proteins with PTMs in vivo. Furthermore, if a mutation can reverse the effect at the putative site of modification, then this is additional evidence to support that there is a PTM at the specific residue identified [212].

Overall, to understand the intersectional relationship of Prdx structure and their mechanism of action for whichever function requires a combinatorial approach. Indeed, it is rather uncommon that just a single technique will give information on redox state, oligomeric state, PTMs, structural architecture, etc. On the other hand, multiple experimental techniques in combination with computational methods can provide a more complete view on the structure-function dynamics and the mechanisms involved.

Table 7

| Level | Techniques | Application | Reference |
|-------|------------|-------------|-----------|
| Cell  | Optical techniques | Real-time monitoring of Prdx oligomerization dynamics | [116] |
|       | Homo-FRET | | |
|       | FRET-based Prdx2-based H₂O₂ biosensor | H₂O₂ biosensors which show that Prdx2 undergoes a slight structural change upon oxidation | [129] |
| Protein level | Confocal microscopy | Visualizing the subcellular distribution and trafficking of Prdx | [31] |
| Electron microscopy | Transmission electron microscopy (TEM), scanning electron microscopy (SEM) | Negative stain TEM is a powerful technique that was first used to characterize a heterogeneous population of Prdxs. A variety of microscopy techniques like TEM and SEM made advances in understanding Prdx oligomerization. The formation of stacked ring tubules (nanotubules) has been studied by TEM for application in nanotechnology. | [76,128,133–141] |
| Scanning probe microscopy: Atomic force microscopy (AFM), electrostatic force microscopy (EFM) and scanning tunneling microscopy (STM) | Apart from electron microscopy, also scanning probe microscopy has been used for visualizing Prdx oligomerization. For example, AFM was used to film biological molecules and examine the oligomeric state of Prdx at 10–16 frames/s, while EFM revealed the formation of nanorods containing Fe²⁺ in the central cavity as a result of the self-assembly of Prdx. | [136,139,141,142] |
| Mass spectrometry (MS): electrospray ionization MS (ESI-MS), time-resolved electrospray ionization time-of-flight MS, Hydrogen/deuterium exchange-MS (HDX-MS) | A variety of MS methods have been used to characterize Prdxs. Disulfide formation has been analyzed by ESI-MS, hyperoxidation by ESI TOF MS, and self-assemblies of Prdxs using native MS. HDX-MS relies on protein mass increases by isotopic labeling. It was used to assess the exchange rates of hydrogen for its isotopes deuterium in the C-terminal region of oxidized Prdxs suggesting the exposure of this region to solvent under oxidation. | [138,142–144] |

(continued on next page)
Table 7 (continued)

| Level            | Techniques                        | Application                                                                 | Reference       |
|------------------|-----------------------------------|------------------------------------------------------------------------------|-----------------|
| Size Exclusion   | Chromatography (SEC)              | Apparent molecular weights and oligomeric properties of Prdxs are routinely analyzed by SEC. Additionally, liquid chromatography systems can be coupled to a mass spectrometer to analyze peptides. | [89,145]        |
| Size exclusion   | SEC-MALS was used to monitor oligomeric state and to determine molecular weights of 2-Cys peroxiredoxin. | Analytical ultracentrifugation can determine the different species present in solution, providing insight into whether there are dimers, rings, or tubes. Analyses of bacterial Prdxs by analytical ultracentrifugation linked the oligomeric state to the catalytic cycle, with the reduced protein forming a strong decamer and the oxidized protein tending to dissociate into dimers. | [146,147]       |
| Immunoblot       | The oligomeric state of Prdxs such as dimer and decamer can also be analyzed by immunoblot using non-reducing and native gels. | In situ Molecular dynamics (MD) simulations were used to predict how hyperoxidation of Prdx6 induces alteration from the dimeric to the oligomeric state. The catalytic mechanism of Prdx was studied using QM/MM. | [116,131]        |
| Secondary structure | Spectroscopy                      | Spectroscopic techniques use polarized light and interaction of light with proteins. |                 |
| Circular dichroism (CD) | Quantitative analysis of CD spectra allows the prediction of the protein secondary structure. In Prdx studies CD is used as a complimentary technique for following the conformational as well as oligomeric changes upon nitrilation, (hyper)oxidation and reduction. | | [111,148, 151] |
| Surface-enhanced Raman scattering (SERS) spectroscopy | In SERS, the non-destructive Raman signal of adsorbed molecules is amplified on the responsive surface with high specificity. The assembly of nanostructures that use Prdx as both a bio-linker and platform for attaching molecules has been assessed by SERS in nanoprobe development for intracellular imaging. | | [134] |

Table 7 (continued)

| Level            | Techniques                        | Application                                                                 | Reference       |
|------------------|-----------------------------------|------------------------------------------------------------------------------|-----------------|
| Protein shape    | Scattering                        | Small angle X-ray scattering (SAXS) has been used to confirm the toroidal nature of the oligomerization of reduced Prdx3. In combination with other methods, SAXS was applied to observe alterations of the overall Prdx structure in solution due to redox modulation. | [106,137]       |
|                  | Dynamic light scattering (DLS)    | DLS yields information on the size-distribution profile of molecules in solution. This can be used as a proxy to give an averaged perspective of the oligomeric state of the protein. In an early example it was shown that the oligomeric state of the Prdx is redox state dependent. | [50] |
| 3D structure model | X-ray crystallography            | Starting from the first X-ray structure of Prdx in 2000, the PDB contains many examples of X-ray structures of different Prdxs, mutants, monomers, dimers and oligomers, in oxidized and reduced states (Tables 1–4). | [75] |
|                  | Nuclear magnetic resonance (NMR) Spectroscopy | NMR techniques are used for the determination of the structure and dynamics of flexible biological macromolecules. The main advantage of NMR is that it provides information on proteins in solution. NMR has been used in combination with X-ray crystallography to link the oligomeric state of Prdx with their functionality. In combination with X-ray crystallography, SAXS and DLS, NMR revealed critical residues of Prdx involved in the protein-protein interactions. The conformational dynamics of the PrdxQ subgroup in both the reduced and oxidized states have been studied together with circular dichroism spectroscopy measurements. Moreover, Prdx from various species have been assessed for the interactions with ligands in screening for fragment-based leads. | [106, 152-158] |
|                  | Cryo-electron microscopy (cryo-EM) | Cryo-EM has long held the promise to deliver (continued on next page) | [5,159, 160] |
Table 7 (continued)

| Level | Techniques | Application | Reference |
|-------|------------|-------------|-----------|
| High-resolution structure determination of biomolecules in solution. | The temperature dependent structural rearrangements of reduced, 2-Cys Prdx in complex with a client protein in the center of the decamer ring was determined to 2.9 Å resolution. Large assemblies of Prdx filaments with varying lengths are particularly well suited for cryo-EM analysis. A separate study focused on cryo-EM method development and the benefits of Volta phase plates for single-particle analysis by structure determination of 257 kDa human Prdx3 dodecamers at 4.4 Å resolution. |

5. Overall insights and future perspectives

Fortunately, for the human Prdxs in general, every oligomeric state has been structurally captured and so has every oxidation state overall (meaning across several different isoforms; not for one isoform alone), except for substrate bound human Prdx. However, because it is highly likely that individual isoforms exhibit different structures for each state (i.e redox, oligomeric, etc), ideally in the future, complete structural portfolios for each isoform needs to be solved. Essentially the structural portfolio would be most complete if each oxidation state could be captured in each “conventional” oligomeric state. For example, the SH Prdx in both dimer and decameric context (or monomer, dimer context like in the case of PrdxS, an atypical, 2-Cys Prdx). This is assuming each isoform in the different subcategories oligomerizes in the same fashion. For example, because Prdx3 can crystallize in stacked decamers, can Prdx1 and Prdx2 also? These HMW oligomers have been observed for Prdx1 and Prdx2 in vivo [37,51], but for Prdx4 the evidence is less clear. For Prdx5 and Prdx6 so far, no decamerization or HMW structural forms have been reported.

For a full library of human Prdx structures to be completed, the structures that are required for Prdx1 are: -SOH, -SO₂, a decamer, and a stacked decamer. For Prdx2: -SO₂, a stacked decamer, and a dimer structure. Prdx3 only has the stacked 3-ring HMW, so the -SOH, SS, a single decamer, and a dimer structure are all missing. Prdx4, despite its abundant structures are available, still lacks a dimer and stacked decamer structure. Prdx5 needs a -SOH structure. Prdx6 is without an SS structure (in disulfide with a resolving partner). There is also a very pronounced demand for structures of human Prdxs in complex with binding partners involved in cell signaling. Additionally, a substrate-bound structure of a human Prdx is also vital.

For human Prdx structures, structural information for Prdxs that have PTMs or even PTM-mimicking mutations (aside from S-sulfenylating and disulfide formation, since those are included as PTMs in this analysis) are missing. From a structural and mechanistic perspective,
many questions on the layers and modes of Prdx regulation need to be answered. For example, all the residues listed in Table 10 are residues that have yet to be further explored and confirmed. Their verification will determine their significance.

Similar to human Prdxs, currently there are structures available for bacterial Prdxs of several classes (Prdx1/AhpC, Tpx, BCP/PrdxQ, AhpE), oligomeric and redox states (Table 3 and 4). As can be seen, so far, there have been no structures solved for bacterial representatives of the Prdx5 and Prdx6 class. However, even for the available classes, there is not a single Prdx with a complete portfolio. For example, structures of both reduced and oxidized AhpC have only been solved in the decameric and dodecameric forms, though AhpC is also known to exist as a dimer in solution [105]. As mentioned above, listing a full library of missing bacterial Prdx structures is an unsurmountable task, given the plethora of exciting advancements in other techniques that will increase our access and automated sample changers at synchrotrons are speeding up reducing the amount of protein needed for crystallization while remote true as laboratory automation and use of high-throughput screening is expected to contribute to Prdx research in the future. This is especially true as the PhosphoSite database [222, 223] returns a handful of publications when giving bacterial Prdx as an input, and all those are from high-throughput studies (Table 11), which also have yet to be validated and their role in Prdx function determined. Information on other PTMs of bacterial Prdxs can be extracted from publications documenting the results of high-throughput studies, in which redox proteomics, MS, and immunoblotting are used to find proteins harboring a specific modification after exposure to bacteria to oxidative stress, such as sodium hypochlorite [213]. Due to the bias of this experimental setup to redox modifications, most PTMs of bacterial Prdxs are reported for Cys residues (mostly the active site, peroxidatic Cys), and represent either the direct product of oxidation, or part of the reductive cycle (Table 11). Our literature search only yielded one example of acetylation of a bacterial Prdx, AhpC, again with an unexplored role. Therefore, identifying PTMs other than those occurring on the catalytic Cys and establishing their role in catalysis of the Prdx with a more systematic approach, is definitely an avenue to follow. We would also like to point out that a curated database of bacterial Prdx (and other protein) PTMs should be set up, or certainly an avenue to follow. We would also like to point out that a curated database of bacterial Prdx (and other protein) PTMs should be set up, or

### Table 10

| Name   | Residue | PTM                  |
|--------|---------|----------------------|
| Prdx1  | Thr18, Thr111, Thr356, Thr166, Ser70, Ser77, Ser80, Ser106, Ser120, Lys9, Lys158, Lys185 | P, Ac, Ub, Sm |
|        | Lys75, Lys27, Lys28, Lys109, Lys126, Lys168, Lys178, Lys192, Lys92 | Ac, Ub, Sm |
| Prdx2  | Thr18, Thr110, Thr142, Thr142, Ser31, Ser102, Ser131, Ser130, Lys40, Lys115, Lys126, Lys193 | P, Ac, Ub, Sm |
|        | Lys10, Lys16, Lys29, Lys29, Lys119, Lys125, Lys170, Lys34, Lys35, Lys77 | P, Ac, Ub, Sm |
| Prdx3  | Thr211, Thr234, Ser86, Ser179, Ser199, Ser237, Tyr71, Tyr172 | P, Ac, Ub, Sm |
|        | Lys83, Lys91, Lys158, Lys248, Lys35, Lys281, Lys253 | Ac, Ub |
| Prdx4  | Ser68, Ser72, Ser188, Tyr19, Tyr206 | P, Ac, Ub |
| Prdx5  | Thr2, Ser2, Ser1, Ser1, Ser1 | P, Ac, Ub |
| Prdx6  | Thr44, Thr130, Ser32, Ser80, Ser166, Ser186, Tyr89 | P, Ac, Ub, Sm |
|        | Lys59, Lys61, Lys182, Lys209 | Ac, Ub, Sm |
|        | Lys97, Lys122, Lys141 | Ac, Ub, Sm |
|        | Lys128, Lys199 | Ac, Ub, Sm |
|        | Lys142, Lys144, Lys216 | Ac, Ub, Sm |
|        | Lys54, Lys200 | Ac, Ub, Sm |
|        | Lys214 | Ac, Ub, Sm |

P = Phosphorylation; Ac = Acetylation; Ub = Ubiquitination; Sm = SUMOylation.

### Table 11

| Name   | Organism | Residue | PTM | Stress | Reference |
|--------|----------|---------|-----|--------|-----------|
| AhpC   | Mycobacterium smegmatis | Cys61 | MSH | NaOCl | [214,215] |
|        | Corynebacterium diptheriae | | | | |
|        | Mycobacterium tuberculosis | | | | |
| YkuU   | Bacillus subtilis | Cys77, Cys169 | S-S | NaOCl | [217] |
|        | Bacillus megaterium | Cys169 | CoA | Diamide | [216] |
| Tpx    | Mycobacterium tuberculosis | Cys80 | S-S | NaOCl | [213] |
|        | Synechocystis sp. | Ser77, Ser79, Ser2, Ser23, Ser26, Thr4, Ser25, Ser34, Thr29, Ser122, Ser181 | P | | [222,223] |

MSH = S-myoctyloliation; CoA = S-CoAlation; P = phosphorylation; S-S = disulfide bond formation; Ac = acetylation; BSH = bacillithiolation. 

* Belong to the AhpC/TSA subfamily of peroxiredoxins.
high-resolution protein structures by electron crystallography of three-dimensional crystals in an electron microscope [225]. Compared to X-ray crystallography, MicroED additionally provides valuable information on the charged state of the protein because the diffraction patterns are generated with charged particles (electrons) rather than X-rays. Neutron diffraction is one of the few approaches so far that allows to locate mobile or highly polarized H atoms and protons, once the key bottleneck of obtaining suitable diffraction quality crystals is overcome [226]. This technique could therefore allow us to better visualize rearrangements of the H-network of Prdx during the peroxidatic cycle, perhaps revealing molecular details that were missed by X-ray crystallography. It could also be used to obtain the lacking human structures of Prdx bound with H₂O₂. Of note, an important aspect regarding these biophysical techniques is their availability and accessibility to new users. To this end, large-scale research facilities offer various programs, where experts provide support in planning and preparation of experiments, data collection, and data analysis. Hence, it is likely that these techniques that so far have not been used to study Prdxs will join the repertoire of methods in the field.

The structural portfolios of Prdxs in different redox and oligomerization states could be enhanced by dynamic information, especially in the context of PTMs and PPIs. This would be particularly relevant, for instance, when Prdx HMW oligomer formation triggers cell cycle checkpoints [51]. This suggests that the HMW oligomers could be detected by the cells and interpreted as stress signals, but there are also other examples where the HMW forms behave as chaperones and the HMW formation is caused by phosphorylation [36]. Thus, the dynamics of oligomerization states are important to query further in order to understand the delineation and time frames of the putative roles for HMW Prdx oligomers. For this purpose, nanotechnology techniques such as high-speed atomic force microscopy (HS-AFM), which has already been used for Prdx (Table 7) can be employed. They would enable us to visualize and even manipulate (e.g. with optical tweezers) Prdx molecules in dynamic action at high spatiotemporal resolution [319].

As discussed above, a big question in the Prdx field remains the PPIs they are involved in. As outlined in Table 8, there are several methods available for the generation of lists of interactors candidates by high-throughput approaches, but the true challenge lies in knowing how to properly select the real binding partners among them for further validation. An accurate prediction technique for PPIs would therefore help to streamline the process of selecting potential binding partners. This could be accomplished by the many protein-protein docking simulators that have been developed recently. The HADDOCK server [227] (http://milou.science.uu.nl/services/HADDOCK2.2/) is currently one of the widely-used simulators. Using the existing structure information of two proteins as an input, the protein-protein docking simulator is able to give a relatively accurate prediction on whether there is a binding site between them. However, it should be kept in mind that most of the time those predictions are focused on direct PPI and will yield no results if the two proteins are indirect interactors within a protein complex, which is often the case when PPIs are detected by high-throughput methods. Unfortunately, there are only very limited tools on protein complex prediction currently available, such as one that relies on the assumption that proteins that do not interact directly, yet share interaction partners, can be part of the same complex [228]. Other computational techniques, such as molecular dynamic simulations could also be employed to make new predictions about PPIs [1-48]. These could become especially useful, for example, when investigating the influence of certain PTMs on PPIs Prdxs are involved in. However, it should be kept in mind that computational techniques have rather a predictive nature and should be cross-validated in a wet lab experimental set-up.

Ideally, Prdx redox-relays and other PPIs should be confirmed and characterized on several levels: the structural level (e.g. using methods outlined in this section), a biochemical one, i.e. the determination of stoichiometry of complex formation, as well as in cells (Table 9). While X-ray crystallography has been used in the past for studying complexes, stabilizing complexes for crystallization is a notable challenge and requires such approaches as chemical crosslinking and Nanobody technology [229]. An emerging technique that is simpler and less time-consuming is Mass Photometry (MP), which uses light scattering to detect and measure the molecular mass of individual unlabeled biomolecules that had adsorbed from solution to a glass surface in biologically relevant environments. The big advantage of this method is that it allows the direct detection of protein complex formation in solution [230], and therefore holds particular promise for studying Prdx redox-relays and other PPIs.

Yet another outstanding question in the Prdx field that can only be addressed in cells is whether their subcellular localization is influenced by PTMs or PPIs. For answering this question, techniques for detecting PPI or PTMs will have to be utilized in combination with immunolabelling and fluorescence microscopy. Finally, despite everything we know on Prdxs summarized in this review, we still do not have a clear picture on their role in physiology, and especially signaling. To investigate this, the obvious approach is to knock-down Prdx in the cell of interest. Fortunately, modern techniques including CRISPR/Cas9, haploid cells [31,32] and Trim-Away – a technique that exploits the protein TRIM21 to directly and rapidly deplete specific proteins in cells [231] – allows this to be done in most labs working with cell culture without resorting to mice.

We would like to reiterate that the missing structures and outstanding questions outlined above, such as the role of specific PTMs in modulating Prdx function, can only be fully answered using a combination of techniques. Even though here we divided the techniques into “atom level”, “cell level”, “in vitro” and “in vivo”, in reality, with the development of new techniques the classification of them, just as Prdxs themselves, is becoming difficult. A good example is cryo-electron tomography, which brings molecular-level views into cellular biology [232]. This opens the possibility to study Prdxs in situ with increased resolution and to discern how the Prdx intersectional functions are controlled and switched, as well as shed light on the mechanistic details surrounding their versatility.

In conclusion, we are entering a new era of integrative structural biology that allows us to ‘see’ the Prdx structure on multiple scales, from atom to organism and vice versa. The time has never been better to finally understand the intersectional factors of Prdxs (structure, redox state, PPI, PTMs, localization, etc) and how they influence the many key roles Prdxs play. Ultimately this information will give us a clearer view of the power Prdxs exert on cellular (patho)physiology through their involvement in both stress and non-stress signaling.

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Declaration of competing interest

The authors declare no competing interests.

References

[1] A. Hall, P.A. Karplus, L.B. Poole, Typical 2-Cys peroxiredoxins–structures, mechanisms and functions, FEBS J. 276 (2009) 2469–2477.

[2] Z.A. Wood, L.B. Poole, P.A. Karplus, Peroxiredoxin evolution and the regulation of hydrogen peroxide signaling, Science 300 (2003) 650–653.

[3] Z.A. Wood, E. Schroder, J. Robin Harris, L.B. Poole, Structure, mechanism and regulation of peroxiredoxins, Trends Biochem. Sci. 28 (2003) 32–40.

[4] S.G. Bhan, H.A. Wex, Multiple functions of 2-Cys peroxiredoxins, 1 and II, and their regulations via post-translational modifications, Free Radic. Biol. Med. 152 (2020) 107–115.

[5] F. Teixeira, E. Tsch, H. Castro, K.A.T. Makepeace, B.A. Meinzen, C.H. Borchers, L. B. Poole, J.C. Bardwell, A.M. Toman, D.R. Southworth, U. Jakub, Chaperone
Redox Biology 42 (2021) 101959

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[38] H.A. Woo, S.H. Yim, D.H. Shin, D. Kang, D.Y. Yu, S.G. Rhee, Inactivation of peroxiredoxin I by phosphorylation allows localized H2O2(2) accumulation for cell signaling, Cell 140 (2010) 517–528.

[39] T. Sykova, F. Zhu, T.I. Vazquez, J. Zhang, L.A. Higgins, D.V. Urusova, A. M. Bode, Z. Dong, T-LAK cell-urinated protein kinase (TOP) phosphorylation of Prx1 at Ser-32 prevents UVB-induced apoptosis in RPMI7951 melanoma cells through the regulation of Prx1 peroxidase activity, J. Biol. Chem. 285 (2010) 3987–3996.

[40] M. Chung, F. Alem, S.G. Hamer, A. Narayanan, K. Shatalin, C. Bailey, E. Nudler, The tumor suppressor Mst1 promotes changes in the cellular redox state by phosphorylation and inactivation of peroxiredoxin 1, J. Biol. Chem. 288 (2013) 8762–8771.

[41] H.A. Woo, S.H. Yi, D.S. Shin, K. Shin, Y.M. Lee, S.G. Rhee, The isolation and purification of a specific “protector” protein which inhibits enzyme inactivation by a thiol/Fe(II)/III)2 mixed-function oxidation system, J. Biol. Chem. 263 (1998) 4704–4711.

[42] R. Bryk, P. Griffin, C. Nathan, Peroxynitrite redox activity of bacterial peroxiredoxins, Nature 497 (2000) 211–215.

[43] S.G. Rhee, H.A. Woo, I.S. Kil, S.H. Bae, Peroxiredoxin functions as a peroxidase and a regulator and sensor of local peroxides, J. Biol. Chem. 287 (2012) 16307–16314.

[44] S.G. Rhee, Cell signaling, H2O2, a necessary evil for cell signaling, Science 312 (2006) 1882–1883.

[45] H. Sies, D.P. Jones, Reactive oxygen species (ROS) as pleiotropic physiological signals, Nat. Rev. Mol. Cell Biol. (2000) 273–286.

[46] H. Sies, Role of metabolic H2O2 generation: redox signaling and oxidative stress, J. Biol. Chem. 275 (2000) 15411–15414.

[47] H. Sies, Peroxiredoxins and a regulator and sensor of local peroxides, J. Biol. Chem. 287 (2012) 6296–6303.

[48] H. Sies, Peroxiredoxin-2 promotes S-nitrosoglutathione-mediated lung cancer cells apoptosis via AMPK-SIRT1 pathway, Cell Death Dis. 10 (2019) 329.

[49] X. Gu, Y. Zhong, L. Wang, L. Ma, S. Jin, H. Gao, W. Li, Q. Han, W. Wei, Q. He, J. Qin, N. Li, S. Li, J. Yang, A novel function of peroxiredoxin 1 in phospholipase A(2) activity, J. Biol. Chem. 289 (2014) 8735–8741.

[50] H. Sies, Peroxiredoxin functions as a regulatory enzyme for the bacterial peroxiredoxin AhpC, Biochemistry 47 (2008) 12860–12867.

[51] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[52] J. Bolduc, K.J. Nelson, Distribution and features of the six classes of peroxiredoxins, Nature 407 (2000) 211–214.

[53] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[54] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[55] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[56] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[57] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[58] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.

[59] J. Bolduc, K.J. Nelson, A.C. Haynes, J. Lee, J.A. Reisz, A.H. Graff, J. Ocker, M. Maurer, T. Ruppert, A.N. Scharf, Peroxiredoxin-2 and STAT3 redox relay complex, Nat. Commun. 11 (2020) 4512.
[62] R. Ogusucu, D. Rettori, D.C. Munchow, L.E. Netto, O. Augusto, Reactions of yeast thioredoxin peroxidases I and II with hydrogen peroxide and peroxidoxin: rate constants by competitive kinetics, Free Radic. Biol. Med. 42 (2007) 526–534.

[63] M. Hugo, L. Turelli, B. Manta, H. Botti, G. Monteiro, L.E. Netto, B. Alvarez, R. Radi, M. Trujillo, Thiol and sulfenic acid oxidation of AhpE, the one-cysteine peroxiredoxin from Mycobacterium tuberculosis: kinetics, acidity constants, and conformational dynamics, J. Biol. Chem. 284 (2009) 16496–16506.

[64] A.V. Peskin, F.M. Low, L.N. Paton, G.J. Maghaz, M.B. Hampton, C. Winterbour, The high reactivity of peroxiredoxin 2 with H2O2(2) is not reflected in its reaction with other oxidants and thiol reagents, J. Biol. Chem. 282 (2007) 11885–11892.

[65] M. Trujillo, G. Ferrer-Suetra, L. Thomson, L. Flohe, R. Radi, Kinetics of peroxiredoxin and their role in the decomposition of peroxynitrite, Subcell. Biochem. 4 (2007) 103–112.

[66] J.C. Toledo Jr., R. Audi, R. Ogusucu, G. Monteiro, L.E. Netto, O. Augusto, Horseradish peroxidase complex I as a tool to investigate reactive protein-cysteine residues: from quantification to kinetics, Free Radic. Biol. Med. 50 (2011) 1032–1038.

[67] D. Young, B. Pedra, D. Ezerina, B. De Smet, A. Lewandowska, M.A. Tossounian, J.C. Toledo, R. Radi, Protein engineering of the quaternary structure of the sulphiredoxin-peroxiredoxin IV disulphide bond reveals a stable oxidized decamer and a non-dissulfide-bonded intermediate in the catalytic cycle, J. Biol. Chem. 286 (2011) 42257–42266.

[68] K.H. Kim, W. Lee, E.E. Kim, Crystal structures of human peroxiredoxin 6 in different oxidation states, Protein Sci. 17 (2008) 1717–1722.

[69] T.J. Jonsson, L.C. Johnson, W.T. Lowther, Structure of the sulphiredoxin-peroxiredoxin complex reveals a essential repair embrace, Nature 451 (2008) 98–101.

[70] T.J. Jonsson, L.C. Johnson, W.T. Lowther, Protein engineering of the quaternary structure of peroxiredoxin enzyme. substate complex reveals the molecular basis for cysteine sulfenic acid phosphorylation, J. Biol. Chem. 284 (2009) 33505–33510.

[71] K.J. Cho, Y. Park, T. Khan, J.-H. Lee, S. Kim, J.H. Seok, Y.B. Chung, A.E. Cho, T.J. Jonsson, L.C. Johnson, W.T. Lowther, Protein engineering of the quaternary structure of peroxiredoxin and glutaredoxin proteins by overexpression of a novel intermediate-ligand complex structures, J. Biol. Chem. 390 (2009) 951–966.

[72] A. Hall, B. Sankaran, L.B. Poole, P.A. Karplus, Structural changes common to catalysis in the Tpx peroxidoxin subfamily, J. Mol. Biol. 393 (2009) 867–881.

[73] R.K. Beckham, O. Byron, A. Denicola, M. Gabrielis, The structure of an orthorhombic crystal form of a ‘forced reduced’ thiol peroxidoxin reveals lattice formation aided by the presence of the affinity tag, Acta Crystallogr. Sect. F Struct. Biol. Cryst.Commun. 62 (2015) 522–526.

[74] M. Gabrielis, K.B. Beckham, V.A. Peher, C.E. Juarréstom, D. W. Suzuki, S. Muller, M. Elofsson, R.E. Amoro, O. Byron, A.J. Roe, Structural characterisation of Tpx from Yersinia pseudotuberculosis reveals insights into the binding of salicylaldheyde coenzymes, PLoS One 7 (2012), e52217.

[75] P.V. Dip, N. Kamariah, W. Nartey, A. Kohlmeier, P.V. Dip, S. Bhushan, A. M. Balakrishna, F. Eisenhaber, B. Eisenhaber, G. Gruber, Structure, mechanism and ensemble formation of the alkylhydroperoxide reduce subunits AhpC and AhpF from Escherichia coli, Acta Crystallogr. D Biol. Crystallogr. 70 (2014) 2848–2862.

[76] P.V. Dip, N. Kamariah, W. Nartey, C. Beushausen, V.A. Kostyuchenko, T.S. Ng, S. Lok, W.G. Saw, F. Eisenhaber, B. Eisenhaber, G. Gruber, Key roles of the Escherichia coli AhpC-terminal in assembly and catalysis of alkylhydroperoxide reductase, an enzyme essential for the alleviation of oxidative stress, Biochem. Biophys. Acta 1837 (2013) 1932–1943.

[77] K. Miyono, A. Smeets, M. Alonso, A. Pallo, F.D. Proft, J. Messens, Structural properties of the peroxiredoxin AhpE2 from the hyperthermophilic bacterium Aquifex aeolicus, Biochim. Biophys. Acta Gen. Subj. 1862 (2015) 2797–2805.

[78] K. Kitano, A. Kita, T. Hoshikoma, Y. Niimi, K. Kritskiy, Crystal structure of deamidated peroxiredoxin (AhpC) from Amphibacillus syllarum, Protein 59 (2005) 644–647.

[79] B.G. Guimaraes, H. Souchon, N. Honore, B.J. Reoan, B. Broch, W. Shephard, S.T. Cole, P.M. Alrza, Structure and mechanism of the alkyl hydroperoxide AhpB, a key element of the Mycobacterium tuberculosis defense system against oxidative stress, J. Biol. Chem. 280 (2005) 25735–25742.

[80] A. Kamar, A.M. Balakrishna, W. Nartey, M.S.S. Manimekalai, G. Gruber, Redox chemistry of Mycobacterium tuberculosis alkylhydroperoxide reductase E (AhpE): structural and mechanistic insights into the oxidised thioredoxin domain of AhpE and into intramolecular disulfide bond formation and substrate binding in atypical 2-Cys peroxiredoxins, J. Mol. Biol. 367 (2007) 98–104.

[81] E. Papinutto, H.J. Windle, L. Cendron, R. Battistutta, D. Kelleher, G. Zanotti, R. Stehr, H.J. Hecht, T. Jager, L. Flohe, M. Singh, Structure of the inactive variant of papA2 from Aeropyrum pernix K1 complexed with its substrate, hydrogen peroxide, J. Biochem. 147 (2008) 1703–1710.

[82] I.V. Turko, L. Li, K.S. Aulak, D.J. Stuehr, J.Y. Chang, F. Murad, Protein tyrosine nitration in the mitochondria from diabetic mouse heart. Implications to pathway of AhpE via mycothiol, Free Radic. Biol. Med. 97 (2016) 588–596.

[83] W. Liu, A. Liu, H. Guo, Q. Wang, L. Wang, E. Warkentin, Z. Rao, H. Michel, G. Wang, Structural properties of the peroxiredoxin Prx5 from Haemophilus influenza reveal interactions with myoglobin and nitric oxide, IUCrJ 5 (2018) 82–92.

[84] I.V. Turko, L. Li, K.S. Aulak, D.J. Stuehr, J.Y. Chang, F. Murad, Protein tyrosine nitration in the mitochondria from diabetic mouse heart. Implications to pathway of AhpE via mycothiol, Free Radic. Biol. Med. 97 (2016) 588–596.

[85] I.V. Turko, L. Li, K.S. Aulak, D.J. Stuehr, J.Y. Chang, F. Murad, Protein tyrosine nitration in the mitochondria from diabetic mouse heart. Implications to pathway of AhpE via mycothiol, Free Radic. Biol. Med. 97 (2016) 588–596.

[86] I.V. Turko, L. Li, K.S. Aulak, D.J. Stuehr, J.Y. Chang, F. Murad, Protein tyrosine nitration in the mitochondria from diabetic mouse heart. Implications to pathway of AhpE via mycothiol, Free Radic. Biol. Med. 97 (2016) 588–596.
resembles its disulfide-oxidized form, Arch. Biochem. Biophys. 590 (2019) 101–108.

[112] E. Doka, T. Ids, M. Dagnell, Y. Abiko, N.C. Luong, N. Balog, T. Takata, B. Espinosa, A. Nishimura, Q. Yan, Y. Fanuto, H. Miki, J.M. Fukuto, J.R. Prigge, E.E. Schmidt, E.J.S. Arner, Y. Kumagai, T. Alaike, P. Nagy, Control of protein function through oxidation and reduction of perufasitized states, Sci. Adv. 6 (2020) eabc1563.

[113] E. Cuevasanta, A. 117 (2020) 16313–16323.

[114] H.J. Shim, S.Y. Park, H.S. Kwon, W.J. Song, T.B. Kim, K.A. Moon, J.P. Choi, S. J. Kim, Y.S. Cho, Oxidative stress mediates the expression pattern of peroxiredoxin-c in peripheral blood mononuclear cells of atopic patients and bronchial epithelial cells, Allergy Asthma Immunol. Res. 12 (2020) 523–536.

[115] J. Nanu, K. Murakami, S. Miyagawa, R. Yamashita, T. Ichimura, T. Wakita, H. Hotta, T. Miyamura, T. Suzuki, T. Satoh, I. Choji, e6AP ubiquitin ligase mediates ubiquitin-dependent degradation of peroxiredoxin I, J. Biol. Cell. 111 (2010) 676–685.

[116] X. Li, D. Lu, F. He, H. Zhou, Q. Liu, Y. Wang, C. Gao, Y. Gung, Cullin 4b protein ubiquitin ligase targets peroxiredoxin III for degradation, J. Biol. Chem. 286 (2011) 32344–32354.

[117] B. Chhunhna, E. Kubo, P. Singh, D.P. Singh, Sumoylation-deficient Prx6 repairs aberrant Sumoylation-mediated Sp1 dysregulation-dependent Prdx6 repression and cell injury in aging and oxidative stress, Aging 10 (2018) 2284–2302.

[118] J. Bakovic, B.Y.K. Yu, D. Silva, S.P. Chew, S. Kim, S.H. Ahn, L. Palmer, L. Aloum, G. Stanzani, O. Malanchuk, M.R. Duchen, M. Singer, V. Filenko, T.H. Lee, M. Skebel, I. Gout, A key metabolic integrator, coenzyme A, modulates the activity of peroxiredoxin 5 via covalent modification, Mol. Cell. Biochem. 461 (2019) 91–102.

[119] M. Hugo, K. Van Laer, A.M. Reyes, D. Vertommen, J. Messens, R. Radi, A. Tursch, T.P. Dick, Real-time monitoring of basal H2O2 levels with activity of bacterioferritin comigratory protein (BCP) as a new member of the AhpC family, J. Biol. Chem. 275 (2000) 2924–2930.

[120] A. 117 (2020) 16313–16323.

[121] M. Radjainia, H. Venugopal, A. Desfosses, A.J. Phillips, N.A. Yewdall, M. Perrots, J. Aden, M. Wallgren, P. Storm, C.F. Weise, A. Christiansen, W.P. Schr¨oder, M.N. Isupov, D. Scheffler, P. Kristensen, J.A. Littlechild, C.C. Winterbourn, Glutathionylation of the active site cysteines of peroxiredoxin – peroxiredoxin is specifically catalyzed by sulfiredoxin, J. Biol. Chem. 284 (2009) 23374–23383.

[122] G. K. Ahuie, H. Gagnon, P.E. Pace, A.A. Mitra, J.E. Kelly, J.E. Ciofledt, K.A. Morano, W.T. Lowther, Molecular basis for the resistance of human mitochondrial 2-Cys peroxiredoxin 3 to hyperoxidation, J. Biol. Chem. 288 (2013) 29714–29723.

[123] H. Erdogan, L.M. Mateos, J. Messens, The CysCysteine glutathionylation mechanism in cytosolic cysteine desulfurase dependent antioxidation, Biochimie 16051 (2020) 103674–103685.

[124] S. Barelier, D. Linard, J. Pons, A. Clippe, B. Knoops, J.M. Lancelin, I. Krimm, A. Echalier, X. Trivelli, C. Corbier, N. Rouhier, O. Walker, P. Tsan, J.P. Jacquot, A. Turner, L.J. Domigan, J.A. Gerrard, D.E. Williams, J. Malmstrom, Assembly of peroxiredoxin 1 from Chlamydomonas reinhardtii, Acta Crystallogr. F Struct. Biol. Commun. 74 (2018) 86–91.

[125] S. Caroli, A. D’Aprile, E. Ciciarelli, D. Carbone, E. Piccioli, A. Marini, G. Lafranchi, N. Malaguarnera, J. Altherr, J. Marchisio, E. Giaccone, I. Scandurra, E. Mancini, L. Ambrosi, A. Grasso, F. De Martino, D. Chiti, G. Capparelli, M. L. Bianchi, J. Biol. Chem. 289 (2014) 18540–18550.

[126] J.R. Harris, Release of a macromolecular protein component from human erythrocyte ghosts, Biochim. Biophys. Acta 150 (1968) 534–537.

[127] T.F. Langford, B.K. Huang, J.B. Lim, S.J. Moon, H.D. Sikes, Monitoring the action of redox-directed cancer therapeutics using a human peroxiredoxin-2-based probe, Nano Lett. 18 (2018) 5138–5145.

[128] G.K. Ahuie, H. Gagnon, P.E. Pace, A.A. Mitra, J.E. Kelly, K. Klarskov, Investigating protein thiil chemistry associated with dehydroascorbate, homocysteine and glutathione using mass spectrometry, Rapid Commun. Mass Spectrom. 34 (2020) 9211–9218.

[129] M.A. Loberg, J.E. Hurtig, A.H. Graff, K.M. Allan, J.A. Buchan, M.K. Spencer, J. 117 (2020) 16313–16323.

[130] A. 117 (2020) 16313–16323.

[131] J.A. Semelak, F. Battistini, R. Radi, M. Trujillo, A. Zeida, D.A. Estrin, Multiscale modeling of thiol overoxidation in peroxiredoxin by hydrogen peroxide, J. Chem. Inf. Model. 60 (2020) 843–853.

[132] S. Porillo-Ledesma, F. Saridi, B. Manta, M.V. Tournier, L. Fournier, B. Knoops, J.M. Lancelin, I. Krimm, Discovery of fragment molecules that bind the human peroxiredoxin 5 active site, PLoS One 5 (2010) e9744.

[133] J. Aden, M. Wallgren, P. Storm, C.F. Weise, A. Christiansen, W.P. Schr¨oder, C. Funk, M. Wolf-Watz, Extraordinary mass loss in cryo-microscopy in Arabidopsis thaliana peroxiredoxin Q, Biochim. Acta 1841 (2011) 1880–1890.

[134] G.W. Buchko, A. Perkins, D. Parsonage, L.B. Poole, P.A. Karplus, Backbone chemical shift assignments for Xanthomonas campestris peroxiredoxin Q in the reduced and oxidized state: dramatic change in backbone dynamics, Biomol. Struct. Biol. Commun. Mass Spectrom. 34 (2020), e8774–e8784.

[135] T. Ando, Directly watching biomolecules in action by high-speed atomic force microscopy, Biophys. 42 (2020) 431–429.

[136] L.J. Domigan, A. M. N. Kinet, M. A. J. S. M. R. A. J. A. M. T. M. J. A. R. A. K., F. De Angelis, F. Fata, I. Silvestri, A. Cimini, F. Gianfanti, F. Angelucci, R. Ippoliti, A ring-shaped protein cluster proteins gold nanoparticles acting as molecular scaffold for plasmonic surfaces, Biochim. Biophys. Acta Gen. Subj. 1864 (2020) 129617.

[137] M. 117 (2020) 16313–16323.
human peroxiredoxin-3 filament reveals the assembly of a putative chaperone, Structure 23 (2015) 912–920.

[16] S. Taillefer, A. Planche, C. Blasi, L. Zolla, Oxidative stress-dependent oligomeric status of erythrocyte peroxiredoxin II (PrxII) during storage under standard blood banking conditions, Biochimie 93 (2011) 845–853.

[17] Y. Yan, P. Sahharwal, M. Rao, S. Sockanathan, The antioxidant enzyme Prx1 controls macrophage migration by thiol-redox-dependent activation of G2D2, Cell 138 (2009) 1209–1221.

[18] M. Gertz, F. Fischer, M. Leipolt, D. Webers, C. Steebborn, Identification of Peroxiredoxin 1 as a proteasome targeting partner for the lifespan regulator protein p66Shc, Aging 1 (2009) 254–265.

[19] H. Nassour, Z. Wang, A. Saad, A. Papalucu, N. Broose, A. Bafar el, M.A. Alaouii-Jamali, D. Ramotar, Peroxiredoxin 1 interacts with and blocks the redox factor Nrf2 from activating Nrf2 expression, J. Biol. Chem. 286 (2011) 29389.

[20] L. Deng, X. Gan, M. Ito, M. Chen, H.H. Aiy, C. Matsui, T. Abe, H. Watashi, T. Wakita, T. Suzuki, O. Matsuura, M. Mizokami, I. Shoji, H. Hotta, Peroxiredoxin 1, a novel H-box-interacting protein, interacts with exosome component 5 and negatively regulates hepatitis B virus (HBV) propagation through degradation of HBV RNA, J. Virol. 93 (2019).

[21] A. Matte, M. Bertoldi, N. Mohandas, X. An, A. Bugatti, A.M. Brunati, M. Rusnati, A. Matte, M. Bertoldi, N. Mohandas, X. An, A. Bugatti, A.M. Brunati, M. Rusnati, The antioxidant enzyme Prdx1 and target gene expression, J. Biol. Chem. 277 (2002) 43175.

[22] P. Radicella, M.R. Kelley, C. D’Elios, A. Denicola, Nitration transforms a sensitive peroxiredoxin 2 into a more active antioxidant PRDX6, J. Cell. Biochem. 118 (2017) 4697.

[23] J. Bolduc et al. and target gene expression, J. Biol. Chem. 277 (2002) 43175.

[24] R. Chang, E. Wang, Mouse translation elongation factor eEF1A-2 interacts with the Myc Box II domain of c-Myc and selectively alters its biological function with the Myc Box II domain of c-Myc and selectively alters its biological function, FEBS Lett. 581 (2007) 3863–3868.

[25] J. Bolduc et al. and target gene expression, J. Biol. Chem. 277 (2002) 43175.

[26] D.Y. Jin, H.Z. Chae, S.G. Rhee, K.T. Jeang, Regulatory role for a novel human thioredoxin peroxidase in NF-kappaB activation, J. Biol. Chem. 272 (1997) 39052–39061.

[27] R.B. Moore, S.K. Shriver, Protein 7.2b of human erythrocyte membranes binds to calpromotin, Biochem. Biophys. Res. Commun. 232 (1997) 294–297.

[28] S. Zhou, Y.C. Lien, T. Shuavea, K. Delbott, S.J. Feinstein, A.B. Fisher, Functional interaction of glutathione S-transferase pi and peroxiredoxin 6 in intact cells, Int. J. Biochem. Cell Biol. 45 (2013) 401–407.

[29] M.H. Choi, I.K. Lee, G.W. Kim, B.U. Kim, Y.H. Han, D.Y. Park, S.K. Shriver, Protein 7.2b of human erythrocyte membranes binds to calpromotin, Biochem. Biophys. Res. Commun. 232 (1997) 294–297.

[30] S.Y. Park, X. Yu, C. Ip, J.L. Mohler, P.N. Bogner, Y.M. Park, Peroxiredoxin 1 interacts with androgen receptor and enhances its transactivation, Cancer Res. 67 (2007) 9294–9303.

[31] J.B. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[32] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[33] J. Cao, J. Schulte, A. Knight, N.K. Leslie, A. Zagoudouz, R. Brunson, Y. Manevich, C. Neumaier, J.M. O’Connor, Hyperoxidized peroxiredoxin 2 interacts with the protein disulfide-isomerase, Biochim. Biophys. Acta Mol. Cell Res. 1866 (2019) 1298.

[34] J.R. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[35] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[36] S.Y. Park, X. Yu, C. Ip, J.L. Mohler, P.N. Bogner, Y.M. Park, Peroxiredoxin 1 interacts with androgen receptor and enhances its transactivation, Cancer Res. 67 (2007) 9294–9303.

[37] J.B. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[38] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[39] J. Cao, J. Schulte, A. Knight, N.K. Leslie, A. Zagoudouz, R. Brunson, Y. Manevich, C. Neumaier, J.M. O’Connor, Hyperoxidized peroxiredoxin 2 interacts with the protein disulfide-isomerase, Biochim. Biophys. Acta Mol. Cell Res. 1866 (2019) 1298.

[40] J.R. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[41] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[42] S.Y. Park, X. Yu, C. Ip, J.L. Mohler, P.N. Bogner, Y.M. Park, Peroxiredoxin 1 interacts with androgen receptor and enhances its transactivation, Cancer Res. 67 (2007) 9294–9303.

[43] J.B. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[44] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[45] J. Cao, J. Schulte, A. Knight, N.K. Leslie, A. Zagoudouz, R. Brunson, Y. Manevich, C. Neumaier, J.M. O’Connor, Hyperoxidized peroxiredoxin 2 interacts with the protein disulfide-isomerase, Biochim. Biophys. Acta Mol. Cell Res. 1866 (2019) 1298.

[46] J.R. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.

[47] Y.J. Kim, W.S. Lee, C. Ip, H.Z. Chae, E.M. Park, Y.M. Park, Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase signaling in lung cancer cells through interaction with the glutathione S-transferase Pi-c-Jun NH2-terminal kinase complex, Cancer Res. 66 (2006) 7136–7142.

[48] S.Y. Park, X. Yu, C. Ip, J.L. Mohler, P.N. Bogner, Y.M. Park, Peroxiredoxin 1 interacts with androgen receptor and enhances its transactivation, Cancer Res. 67 (2007) 9294–9303.

[49] J.B. Riddell, X. Yang, H. Minderman, S.O. Gollnick, Peroxiredoxin 1 stimulates secretion of proinflammatory cytokines by binding to TLR4, J. Immunol. 184 (2010) 1022–1030.
