Free Radical Biology and Medicine 83 (2015) 373–379

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Physiological and pathological views of peroxiredoxin 4

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ARTICLE INFO

Article history:
Received 3 November 2014
Received in revised form
21 January 2015
Accepted 23 January 2015
Available online 2 February 2015

Keywords:
Peroxiredoxin
Hydrogen peroxide signal
Oxidative protein folding
Sulfoxidase

ABSTRACT

Peroxiredoxins (PRDXs) form an enzyme family that exhibits peroxidase activity using electrons from thioredoxin and other donor molecules. As the signaling roles of hydrogen peroxide in response to extracellular stimuli have emerged, the involvement of PRDX in the hydrogen peroxide-mediated signaling has become evident. Among six PRDX members in mammalian cells, PRDX4 uniquely possesses a hydrophobic signal peptide at the amino terminus, and, hence, it undergoes either secretion or retention by the endoplasmic reticulum (ER) lumen. The role of PRDX4 as a sulfoxidase in ER is now attracting much attention regarding the oxidative protein folding of nascent proteins. Contrary to this role in the ER, the functional significance of PRDX4 in the extracellular milieu is virtually unknown despite its implications as a biomarker under pathological conditions in some diseases. Other than its systemically expressed form, a variant form of PRDX4 is transcribed from the upstream promoter/exon 1 of the systemic promoter/exon 1 and is uniquely expressed in sexually matured testes. Circumstantial evidence, together with deduced functions from the systemic form, suggests that there are potential roles for testicular PRDX4 in the reproductive processes such as the regulation of hormonal signals and the oxidative packaging of sperm chromatin. Elucidation of these PRDX4 functions under *in vivo* situations is expected to show the whole picture of how PRDX4 has evolved in multicellular organisms.
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Introduction

The vital activities of living organisms largely depend on oxidation-reduction (redox) reactions for survival. Many small molecules and proteins such as glutathione and thioredoxin (Trx), respectively, are involved in redox reactions [1,2]. New redox family proteins were discovered about a quarter-century ago [3] and were tentatively designated as thiol-specific antioxidants [4]. The name peroxiredoxin has been assigned to the genetic family named PRDX [4,5]. For the sake of simplicity in this paper, we used PRDX to identify both proteins and genes. A majority of PRDX members exhibit peroxidase activity using Trx as a preferred electron donor. The resultant oxidized Trx is recycled by Trx reductase, which is a member of the glutathione reductase family, and also utilizes NADPH as the primary electron donor (Fig. 1).

Six members that possess high similarities in their molecular structures are regarded as conventional PRDX in mammals [6–8]. PRDX1 to PRDX4 are typical members of the 2-Cys PRDX class, exhibiting high similarities across the catalytic domain. They exist as homodimers with a head-to-tail type of association and transiently form disulfide bridges during catalysis [6–8]. PRDX5 and PRDX6 are monomeric enzymes that show more divergent structures. Reductive detoxification of peroxides is an established catalytic activity, but additional enzymatic activities are also known [8]. Roles in signal regulation by reactive oxygen species (ROS), particularly hydrogen peroxide, would be the most profound function of PRDX [9]. Moreover, chaperone-like activity has been found in PRDX1 and 2 [10,11], although no consensus exists as to the relationship between peroxidase activity and the chaperone function.

Here we focus on mammalian PRDX4 from the viewpoint of its physiological and pathological roles. Because unicellular organisms such as yeast do not possess PRDX4 [12], the gene appears to have evolved with the advent of multicellular organisms, which require intercellular communication via secreted products. Compared with other mammalian PRDX members, the reports of the localization and roles of PRDX4 are conflicting [13–16]. Recently, an understanding of the roles of PRDX4 has markedly advanced, particularly concerning the sulfoxidase function in the endoplasmic reticulum (ER) [17]. Because PRDX4 is also present extracellularly, we are proposing a hypothetical function acknowledging that defining its function remains a future challenge. We also discuss a variant form, designated as PRDX4t, that is uniquely expressed in sexually matured testes.

Abbreviations: ER, endoplasmic reticulum; ERO1, endoplasmic reticulum oxidoreductin 1; GCSF, granulocyte colony-stimulating factor; PDI, protein disulfide isomerase; PRDXs, peroxiredoxins; PTP, phosphotyrosine phosphatases; ROS, reactive oxygen species; GPX, glutathione peroxidase.

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http://dx.doi.org/10.1016/j.freeradbiomed.2015.01.025
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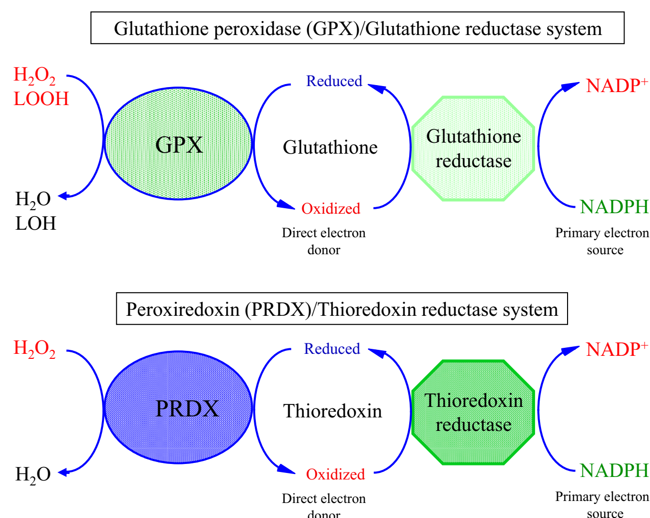

Fig. 1. Comparison of electron transfer systems in the GPX- and PRDX-catalyzed peroxidase reactions. GPX reduces hydrogen peroxide and lipid peroxides (LOOH) to water and corresponding alcohol, respectively, using electrons from reduced glutathione. Oxidized glutathione is then reduced back by glutathione reductase via the reducing power of NADPH. PRDX reduces mainly hydrogen peroxide using electrons from reduced Trx. Oxidized Trx is then reduced back by Trx reductase using the reducing power of NADPH.

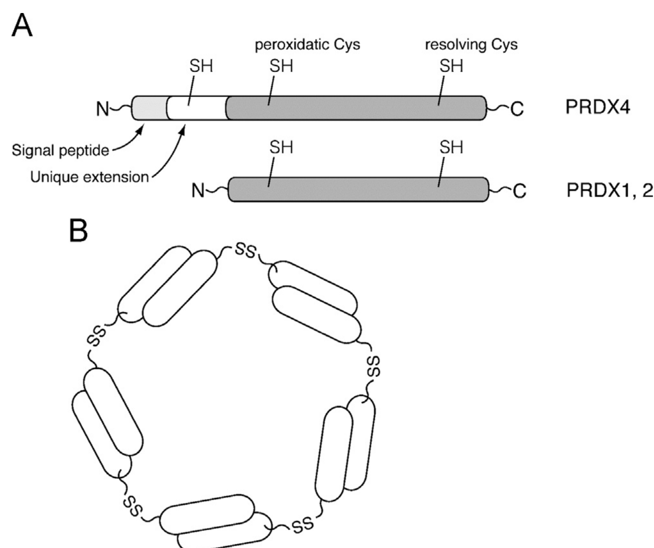

Fig. 2. Schematic presentation of the structure and molecular organization of PRDX4. (A) The heavily shaded region of PRDX4 is homologous to PRDX1 and 2, and contains two catalytic cysteine residues, peroxidatic Cys and resolving Cys. The lightly shaded portion represents the signal sequence that allows translocation across the ER membrane and thereafter should be cleaved off. (B) The homodecameric structure consists of five units of the functional dimer and reveals a toroidal organization. The disulfide bonds shown are formed between the cysteine residues that are contained by the N-terminal extension. In the oxidized state, the functional dimer units are covalently linked by these disulfides. The disulfide bridges by the catalytic Cys residues in the active sites are not represented here.

Structure and enzymatic reactions of PRDX4

Structure and molecular organization of PRDX4

PRDX4 is a member of the 2-Cys-type peroxiredoxin family and is homologous to typical 2-Cys peroxiredoxins such as PRDX1 and PRDX2, thus serving as a Trx-dependent peroxidase via the same catalytic mechanism as other 2-Cys peroxiredoxins [6–8]. PRDX4 has an additional N-terminal region, which is unique to this enzyme, following a signal peptide that is responsible for translocation across the ER membrane into the luminal space (Fig. 2A) [18,19]. The signal sequence is cleavable and allows the enzyme to be extracellularly released. In cultured cells, secretion of PRDX4 protein into the medium has been observed, and significant levels of PRDX4 were also detected in human and rat serum by immunological assay using specific antibodies [20,21].

PRDX4, like PRDX1 and PRDX2, forms homodimers with subunits assembling in a head-to-tail manner. These form disulfide links within the dimeric subunits during catalytic peroxidase activity [22]. The dimers are also structurally organized into homodecamers, each carrying five dimeric units (Fig. 2B) [23–25]. However, in contrast to PRDX1 and PRDX2, the five homodimeric units of PRDX4 are further covalently linked by unique cysteine residues found in the N-terminal extension of PRDX4 [19,25,26].

Trx-dependent peroxidase activity of PRDX4

PRDX4 is capable of catalyzing the detoxification of peroxides, wherein Trx is used as an electron donor *in vitro*, as with other typical 2-Cys types of peroxiredoxins [16,26,27]. This peroxiredoxin shows significant structural similarities to PRDX1 and PRDX2, and two cysteine residues that are catalytically essential for 2-Cys types of PRDX are perfectly conserved in PRDX4, consistent with its Trx-dependent reduction of peroxides.

In a typical reaction with peroxides, the conserved peroxidatic cysteine, which is one of the two catalytic cysteine residues and is located more N-terminally, first reacts with hydroperoxides, forming cysteine sulfenic acid (Cys-SOH), while the substrate peroxide is reduced by two electrons. The resultant cysteine sulfenic acid then reacts with the other catalytic cysteine, the resolving Cys, to form their disulfide and generate a water molecule. The reaction with Trx as an electron donor finally reduces the disulfide, thus completing the catalytic cycle of PRDX4 in the detoxification of peroxide.

Hyperoxidation of PRDX

The catalytic cycle of PRDX4 as well as other 2-Cys peroxiredoxins involves the formation of Cys-SOH, which subsequently reacts with another catalytic Cys-SH. Alternatively, the Cys-SOH can further react with peroxide and is “hyperoxidized” or “overoxidized” into cysteine sulfinic acid, Cys-SO_2H [28,29]. Thus, the interchain disulfide formation competes with hyperoxidation for the Cys-SOH. The disulfide is reduced generally by Trx to maintain the catalytic cycle. However, the hyperoxidation into Cys-SO_2H, or possibly cysteine sulfonic acid by further oxidation, terminates the catalytic cycle because Trx is incapable of restoring Cys-SH from these oxidized forms. It is probable that a sulfiredoxin family protein regenerates such an inactivated form of PRDX4 in an ATP-dependent manner, which is known to happen with other peroxiredoxins [30,31].

In general, when peroxiredoxins are inactivated by the formation of Cys-SO_2H, the enzymes no longer exhibit any significant reducing activities of peroxides. This inactivation process is more prominent with higher concentrations of peroxide as the substrate. In the case of PRDX4, however, activity was observed even after hyperoxidation of the catalytic Cys [29]. It appears that the enzyme still functions, albeit with altered kinetic properties, probably by an alternative catalytic mechanism in which the resolving Cys residue directly reacts with peroxide and interacts with Trx. This altered form of PRDX4 shows a substrate preference that differs from that of an intact fully active enzyme. The altered form displayed higher activity toward hydrogen peroxide compared to *t*-butyl hydroperoxide while the intact acts more actively on *t*-butyl hydroperoxide [29].

Structural features associated with hyperoxidation

While eukaryotic 2-Cys peroxiredoxins readily undergo inactivation due to the hyperoxidation of the catalytic Cys, the prokaryotic

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