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Review

The oligomeric conformation of peroxiredoxins links redox state to function

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ABSTRACT

Protein–protein associations, i.e. formation of permanent or transient protein complexes, are essential for protein functionality and regulation within the cellular context. Peroxiredoxins (Prx) undergo major redox-dependent conformational changes and the dynamics are linked to functional switches. While a large number of investigations have addressed the principles and functions of Prx oligomerization, understanding of the diverse in vivo roles of this conserved redox-dependent feature of Prx is slowly emerging. The review summarizes studies on Prx oligomerization, its tight connection to the redox state, and the knowledge and hypotheses on its physiological function in the cell as peroxidase, chaperone, binding partner, enzyme activator and/or redox sensor.

1. Introduction

Peroxiredoxins (Prx) function as thiol peroxidases independent of cofactors such as metal ions or prosthetic groups. Peroxide reduction takes place by an oxidation of the peroxidatic thiol (C_P) residue that acts on the O–O bond of the peroxide (Fig. 1). In a second step the generated sulfenic acid derivative of the C_P reacts with an adjacent thiol (resolving cysteine C_R) forming an intra- or intermolecular disulfide bond. In a third step the dithiol state is re-reduced via electron donors such as thioredoxin reductase C, thioredoxin, glutaredoxin, glutathione, cyclophilin, ascorbate or DTT [1].

Disulfide bridge formation depends on a slow structural rearrangement of Prx protein to bring closer both cysteinyl residues [2,3]. In some cases, the sulfenic acid group is subjected to glutathionylation, hyperoxidation to sulfinic acid (SOOH) or S-nitrosylation [4]. Hyperoxidation of C_P to sulfinic acid was thought to be an irreversible modification until the discovery of the sulfinic acid reductase sulfiredoxin (Srx) [5] (Fig. 1D). The floodgate theory suggests that H_2O_2 is kept low by Prx activity in normal cell, while Prx inhibition by hyperoxidation enables H_2O_2 signaling. Although Prxs are present in all studied organisms, marked differences exist between them. For example, only eukaryotic Prxs are highly sensitive to hyperoxidation probably due to the presence of the GGLG and YF motifs, absent from bacterial AhpC, which facilitates the conformational switch needed for disulfide formation in the catalytic cycle [6].

Prxs are classified by number of cysteines implicated in catalysis (1-CysPrx and 2-CysPrx), by formation of either inter- or intramolecular disulfide bonds (typical and atypical) or by oligomerization properties as discussed below (Fig. 1A–C). Non-uniform classification and use of diverse trivial names for the same Prx protein impede simple text mining and complete searches. Table 1 and Fig. 1 summarize the catalytic mechanisms, the regenerators, the biological sources, trivial names and abbreviations of those Prx addressed in the review. Since the first observation of doughnut-shaped Prx-oligomers by transmission electron microscopy, the dynamic equilibrium between assembly and disassembly has been extensively studied and shown to depend on ionic strength, protein concentration, pH, phosphorylation and first of all on the redox state.

1.1. Structural basis for dimer and oligomer formation

Except for the monomeric Prx of the C-type (bacterioferritin comigratory protein and PrxQ), Prxs are obligate dimers [7]. These dimers can form intermolecular disulfide bonds or remain reduced.

Abbreviations: HMW, high molecular weight; ITC, isothermal titration microcalorimetry; LMW, low molecular weight; Prx, peroxiredoxin; SEC, size exclusion chromatography.

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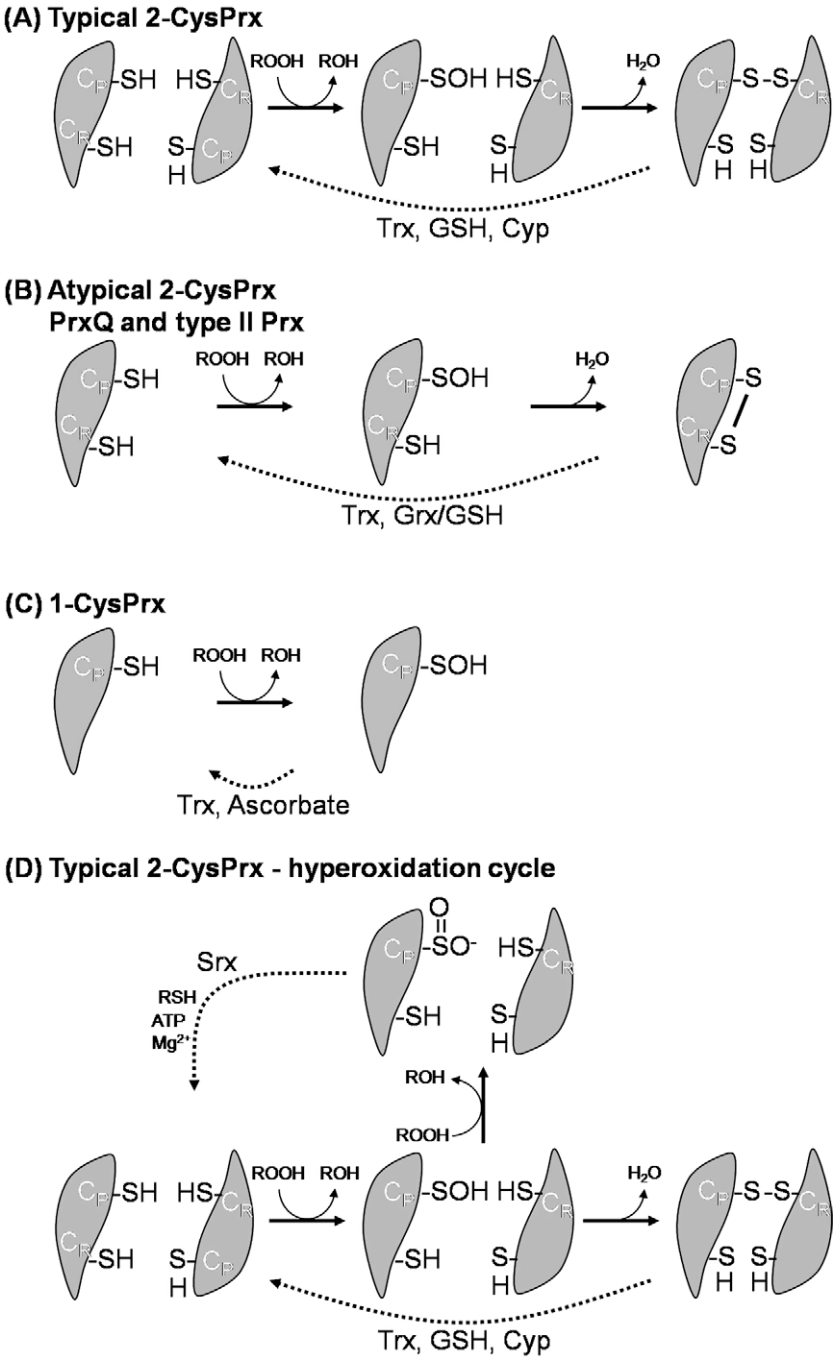

Fig. 1. Catalytic mechanism of the three types of peroxiredoxins. The peroxidatic catalytic Cys residue C_P primarily reacts with the peroxide substrate. In typical 2-CysPrx, C_P reacts with a resolving Cys residue C_R on the second subunit of the dimer (A), while in atypical 2-CysPrx the resolving Prx is located on the same polypeptide chain (B) either in close vicinity (PrxQ) or more distantly (TypeII Prx, Prdx5). The sulfenic acid derivative of 1-CysPrx is directly regenerated by an electron donor to the thiol form (C). Cyp: cyclophilin; Grx: glutaredoxin; GSH: glutathione; ROOH: peroxide; RSH: electron donor; Srx: sulfiredoxin; Trx: thioredoxin.

The interfaces between the dimer subunits are categorized as parallel (A, B and F homodimers) or perpendicular (D and E homodimers), the interface between dimers as perpendicular (A and F decamers) according to the orientation of the central β-sheet [3,7]. The parallel orientation appears more stable than the perpendicular one [7–9]. With C_p and C_R reduced, the structure of 2-CysPrx is fully-folded. The reaction with the peroxide substrate oxidizes the C_p to sulfenic acid which is protected in the active site pocket by the first turn of the helix α_2. To enable the attack and reduction of C_p a partial unfolding of the structure by movement of helix α_2 is needed to form the 'C_p-loop' [2]. This intermediate structure is partial-unfolded in dynamic equilibrium with the fully-folded Prx. Finally the disulfide bridge is formed and the oxidized Prx is locked in the partially-unfolded state. The conformational change weakens the perpendicular interface and in many cases the decamer disassembles to dimers. The C_P-loop acts as molecular switch in oligomerization. Site-directed mutation of Thr^{77} at the dimer–dimer interface (variants T77I and T77D) disrupts the decamer while the variant T77V stabilizes the decamer [10]. This implies that the decameric form and the fully-folded active site conformation are linked. Cyclin-dependent protein kinases phosphorylate Thr^{90} in human PrxI and inhibit its activity by about 80% [11], an effect which was attributed to decamer breakdown favored by electrostatic repulsion of two adjacent negatively charged