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REVIEW

The interplay between nitric oxide and peroxiredoxins

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Abstract

Peroxiredoxins participate in the antioxidant response by reducing H_2O_2, organic peroxides and peroxynitrite. Peroxiredoxins have a conserved NH_2-terminal cysteine residue that is oxidized to sulfenic acid during catalysis of peroxide reduction. In eukaryotes, the sulfenic acid can be further oxidized to a sulfinic acid. Resulting inactivation of peroxiredoxins favors H_2O_2 signaling but may eventually result in oxidative stress. Interestingly, it has recently been shown that overoxidized peroxiredoxins progressively recover activity owing to sulfiredoxin, an enzyme recently characterized in yeast and mammals. This reversible peroxide-sensitive switch represents a new type of regulation that controls reactive oxygen species-mediated cytoxicity and signaling. This report presents a brief overview of the regulation by peroxiredoxins of the messenger function of H_2O_2 and comments on the results of recent studies that addressed the consequence of nitric oxide production on both expression and redox state of peroxiredoxins in various physiopathological processes including macrophage immunostimulation, the response of dopaminergic neurons to *N*-methyl-D-aspartate-stimulation and the plant hypersensitive response.

Keywords: Immunostimulation; Macrophage; Nitric oxide; Peroxiredoxins; Redox signaling; Sulfiredoxin

Contents

Abbreviations: BMM, bone marrow-derived macrophage; DETA-NO, diethyltriamine-NONOate; IFN-γ, interferon-γ; LPS, lipopolysaccharide; NO, nitric oxide; NOS, nitric oxide synthase; PMA, phorbol myristate acetate; Prx, peroxiredoxin; ROS, reactive oxygen species; Srx, sulfiredoxin; Trx, thioredoxin; TrxR, thioredoxin reductase.

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Introduction

Peroxiredoxins (Prxs) are a recently discovered family of thiol peroxidases. These ubiquitous antioxidant enzymes are expressed at high levels in cells and they play an important role in cell peroxide and peroxynitrite detoxification. Interestingly, there is increasing evidence that in eukaryotes, Prxs control H_2O_2 signaling. Here, we address the capacity of Prxs to protect various organisms against nitrosative stress and review current knowledge regarding the regulation of their expression and activity by nitric oxide (NO) in various cells, with an emphasis on murine macrophages.

Peroxiredoxins and redox signaling

In recent years, redox signaling mediated by oxygen- and nitrogen-derived intermediates has attracted growing attention as its involvement in diverse cell functions has become clear (Finkel, 1998; Forman et al., 2002). The efficacy of these reactive species mainly comes from the ability to modulate the expression of a large variety of genes (Ehrt et al., 2001; Hofseth et al., 2005; Bedard and Krause, 2007) and to fine tune the activity of critical upstream regulators by reacting with metal centers or thiol groups at critical catalytic or allosteric sites (Drapier and Bouton, 1996; Stamler et al., 2001; Kamata et al., 2005; Rhee, 2006).

In the network of cell metabolism, the interplay between reactive oxygen species (ROS) and NO pathways is of prime importance for cell physiology, pathophysiology and host defense (Nathan and Shiloh, 2000). At the crossroads between ROS and NO signaling pathways, Prxs occupy a central position because they can reduce both hydroperoxides and peroxynitrite (Wood et al., 2003b; Rhee et al., 2005a). In all kingdoms of living organisms, including bacteria (Bryk et al., 2000), yeast (Wong et al., 2002), protists (Komaki-Yasuda et al., 2003), insects (Peterson and Luckhart, 2006), and humans (Dubuisson et al., 2004), Prxs protect against ROS and NO-derived products, notably peroxynitrite. In mammals, the Prx family comprises six members, five of which are so-called "2-Cys"-Prx and use the thioredoxin (Trx) system as reductant, and one is a "1-Cys"-Prx. 2-Cys-Prx are further divided into two subtypes: the typical 2-Cys Prx (Prx 1–4) and one atypical 2-cys Prx (Prx5). The catalytic cycle of 2-Cys Prxs involves a conserved "peroxidatic" cysteine (Cp) with a low p*K*a which is oxidized by peroxides to sulfenic acid. A disulfide bridge forms with a "resolutive" cysteine (Cr), which is then reduced by Trx. In typical 2-Cys-Prx, the enzyme functions as a homodimer, and the Cp and Cr residues form an intermolecular disulfide bridge in a head-to-tail arrangement. The atypical 2-Cys-Prx exhibit the same mechanism but the two active cysteine residues are located on the same monomer thus yielding an intramolecular disulfide bond (Wood et al., 2003b). By contrast, in 1-Cys-Prx only the Cp is conserved, and the sulfenic acid generated by peroxides is presumably reduced by glutathione (GSH). All mammalian Prxs differ in their cellular localization, as Prx1, 2 and 6 are mainly located in the cytosol, Prx3 is restricted to mitochondria, Prx4 is present in the endoplasmic reticulum whereas Prx5 is distributed in nucleus, mitochondria and peroxisomes (Wood et al., 2003b).

Prxs are associated with many cellular functions including proliferation, cell cycle, apoptosis, and differentiation (Hirotsu et al., 1999; Neumann et al., 2003; Phalen et al., 2006). These observations have lead to questioning of the real function of Prxs, especially with respect to their catalytic constants, which have long been assumed to be low compared with catalase and glutathione peroxidases ($\sim 10^5\,M^{-1}\,s^{-1}$ vs. $\sim 10^7\,M^{-1}\,s^{-1}$. However, a, recent reassessment of the catalytic efficiency of Prx2 revealed that it reacts 100-fold faster with H_2O_2 than once believed (Peskin et al., 2007). Besides, reactivity of Prx5 evaluated by pre-steady state fluorometric methods has indicated that it is highly reactive with organic hydroperoxide and peroxynitrite and less efficient with H_2O_2 (Trujillo et al., 2007). In brief, it appears that Prxs are efficient peroxidases, but each of the isoforms may have selectivity towards the peroxide substrate.

Interestingly, the cytosolic 2-Cys-Prx1 and -Prx2 in yeast, as well as human 2-Cys-Prx2 are bifunctional proteins, switching from a peroxidase activity in the dimeric form to a chaperone activity upon aggregation into a high-molecular complex structure. The chaperone function of Prx2 results from overoxidation of the Cp and appears to prevent H_2O_2-induced cell death and to protect citrate synthase, insulin, and α synuclein from stress-induced aggregation in human cells (Jang et al., 2004; Moon et al., 2005).

Regulation of Prx gene expression

Little is known about the regulation of mammalian Prx gene expression. Only Prx1 has been a subject of profound investigation in this matter. Prx1 gene expression is up-regulated in response to various stresses, including oxidative stimuli (Ishii et al., 1999), LPS via NO and PMA in murine macrophages (Immenschuh et al., 1999; Immenschuh and Baumgart-Vogt, 2005) and in response to shear stress in bovine endothelial cells (Mowbray et al., 2008). In a recent paper, we reported that Prx1, Prx5, and Prx6 were up-regulated at the mRNA and protein levels in primary