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Minireview

Multiple Roles of Peroxiredoxins in Inflammation

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Inflammation is a pathophysiological response to infection or tissue damage during which high levels of reactive oxygen and nitrogen species are produced by phagocytes to kill microorganisms. Reactive oxygen and nitrogen species serve also in the complex regulation of inflammatory processes. Recently, it has been proposed that peroxiredoxins may play key roles in innate immunity and inflammation. Indeed, peroxiredoxins are evolutionarily conserved peroxidases able to reduce, with high rate constants, hydrogen peroxide, alkyl hydroperoxides and peroxynitrite which are generated during inflammation. In this minireview, we point out different possible roles of peroxiredoxins during inflammatory processes such as cytoprotective enzymes against oxidative stress, modulators of redox signaling, and extracellular pathogen- or damage-associated molecular patterns. A better understanding of peroxiredoxin functions in inflammation could lead to the discovery of new therapeutic targets.

INTRODUCTION

After the first characterization of thiol-specific antioxidant (TSA) in the yeast *Saccharomyces cerevisiae* at the end of the 1980s (Kim et al., 1988), it turned out that this enzyme was a member of a major and highly expressed superfamily of thiol-dependent peroxidases able to reduce hydrogen peroxide, alkyl hydroperoxides and peroxynitrite in bacteria, archaea and eukaryotes (Perkins et al., 2015; Rhee et al., 2005; Wood et al., 2003). These peroxidases, named peroxiredoxins (Chae et al., 1994), are selenium- and heme-free peroxidases carrying a conserved peroxidatic cysteine (C_p) located in the N-terminal domain of all members of this superfamily. A classification has been proposed based on sequence homology and structural data that finally classify peroxiredoxins of all kingdoms of life into six subfamilies (Hofmann et al., 2002; Knoops et al., 2007; Nelson et al., 2011).

In a relatively simple but unexpectedly efficient mechanism, the C_p of peroxiredoxins attacks the O-O bond of the peroxide during the peroxidase reaction and is subsequently oxidized to a Cys sulfenic acid (Hall et al., 2010; Portillo-Ledesma, 2014). The Cys sulfenic acid is then reduced back during the resolution step either by an external thiol in peroxiredoxins of the so-called 1-Cys subgroup, either by a resolving Cys (C_r) of a second molecule resulting in the formation of an intermolecular disulfide bond in the typical 2-Cys subgroup, or by a C_r located within the same molecule resulting in the formation of an intramolecular disulfide bond in the atypical 2-Cys subgroup (Seo et al., 2000). The disulfide bond can be then reduced by thiol-dependent reductants such as thioredoxins (Perkins et al., 2015).

Although peroxiredoxins have been initially thought to be much less efficient peroxide reductases than catalases and glutathione peroxidases, it was shown that they are able to reduce hydrogen peroxide, alkyl hydroperoxides and peroxynitrite with rate constants as high as 10^7-10^8 $M^{-1}s^{-1}$ (Ferrer-Sueta et al, 2011). Moreover, it has been proposed, based on models of redox kinetics, that peroxiredoxins reduce more than 90% of cellular hydrogen peroxide (Adimora et al., 2010; Cox et al, 2010). Thus, their central role as peroxide and peroxynitrite scavenging enzymes among the cellular arsenal of antioxidant enzymes, such as well-characterized catalase and glutathione peroxidases, has been probably underestimated until recently (Perkins et al., 2015).

FUNCTIONS OF PEROXIREDOXINS

Functionally, it was shown that in prokaryotic but also in eukaryotic cells, peroxiredoxins may act as cytoprotective antioxidant enzymes, protecting cells against deleterious oxidation of DNA, proteins and lipids, but also other macromolecules, caused by physiological or pathophysiological production of intracellular as well as extracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Perkins et al., 2015). This cytoprotective antioxidant activity could be considered as an ancestral function, endowed by oxidative stress-inducible adaptative peroxiredoxin expression in microorganisms but also by constitutively expressed peroxiredoxins (with functions of house-keeping enzymes) in metazoa including mammals in which peroxiredoxin expression is poorly inducible by hydrogen peroxide (Desaint et al., 2004). More interestingly, in the early 2000s, the role of hydrogen peroxide as mediator in cell signaling processes emerged (Rhee et al., 2005). Given that several eukaryotic peroxiredoxins were also shown to be susceptible to regulation by reversible overoxidative inactivation or other post-translational modifications, it was proposed that

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these peroxidases may act as modulators of peroxide signaling (Rhee et al., 2005; Sies, 2014; Woo et al., 2010). Recently, several reports have been supporting these hypotheses and mammalian peroxiredoxins are now increasingly considered as regulators of peroxide signaling as local, at subcellular level, peroxide scavengers but also as redox relays (Rhee and Woo, 2011; Sobotta et al., 2015).

MAMMALIAN PEROXIREDOXINS AND IMMUNITY

In mammals, the six peroxiredoxin isoforms (PRDX1-6), encoded by six different genes, are ubiquitous and multifunctional peroxidases addressed to different subcellular compartments and also found in the extracellular milieu (Hanschmann et al., 2013; Leyens et al., 2003). Mammalian peroxiredoxins are constitutively expressed, although at different levels, in virtually all tissues and cell types (Hanschmann et al., 2013; Leyens et al., 2003; Perkins et al., 2015). However, it was reported in the literature that peroxiredoxin expression is significantly increased upon acute inflammation in the lung (Kinnula et al., 2002; Knoops et al., 1999) but also in other tissues (Wang et al., 2002; Yun et al., 2015). Moreover, in macrophages and microglial cells, several peroxiredoxins are highly upregulated upon stimulation by interferon gamma (IFN-γ) and lipopolysaccharide (LPS) (Abbas et al., 2009; Diet et al., 2007; Sun et al., 2010) suggesting that peroxiredoxins may actually play key roles as cytoprotective antioxidant enzymes in cells that generate high levels of ROS/RNS upon pro-inflammatory stimulation but also as redox signaling modulators in innate immunity and inflammation.

As emphasized by Nathan and Cunningham-Bussel (2013), in the immune system ROS, but also RNS, are neither unique products of one cell type, nor they have a unique effect that would be to kill microbes. It becomes clear that ROS/RNS have also physiological roles in signaling, that could probably extend to every cell type in immunology. However, as with any signaling system, ROS/RNS can trigger toxic mechanisms for the cells if the signal is too strong, if it lasts for too long or if it arises at the wrong time and place. In this context, peroxiredoxins might have unanticipated very specific and important roles.

Against this background, we tentatively report in this minireview published results of the notably increasing literature that suggests that peroxiredoxins are major players in inflammatory processes as: (1) cytoprotective enzymes for the host against elevated concentrations of ROS/RNS generated during inflammation, (2) modulators of redox signaling to control essential functions of inflammatory cells such as synthesis and release of inflammatory mediators, and (3) extracellular pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) to regulate inflammation via pattern recognition receptors (PRRs).

Here, we would like also to apologize for any omissions of pertinent original references owing to space constraints of this minireview and to note that more extensive reviews on the roles of peroxiredoxins in innate immunity and inflammation have been published previously (Ishii, 2015; Ishii et al., 2012).

PEROXIREDOXINS AS CYTOPROTECTIVE ANTIOXIDANT ENZYMES IN INFLAMMATION

The protective role of peroxiredoxins in inflammation was revealed by the higher sensitivity of peroxiredoxin knockout (KO) mice to pro-inflammatory lipopolysaccharide (LPS) challenge. Indeed, it was shown that intratracheal instillation of LPS triggered higher ROS levels in macrophages and more oxidative damages to DNA and proteins in PRDX3 KO mice compared to control animals (Li et al., 2007). Accordingly, PRDX2 KO mice are also more sensitive to LPS-induced endotoxic shock and can be rescued by intravenous injection of adenovirus encoding PRDX2 or administration of catalase (Yang et al., 2007). Of note, PRDX1 is also upregulated upon LPS exposure in microglia of the central nervous system and reduction of LPS-mediated PRDX1 upregulation was shown to sensitize the microglia to H_2O_2-mediated cell death suggesting that in this pro-inflammatory situation, PRDX1 is indeed able to protect cells against H_2O_2-mediated oxidative attacks (Kim et al., 2008). In the same context, PRDX1 KO mice are highly susceptible to bleomycin-induced pulmonary inflammation and fibrosis implicating oxidative damages (Kikuchi et al., 2011). It was also shown that in transgenic mice overexpressing human PRDX4 in a model of type 1 diabetes mellitus, β-cells in the islets are significantly protected against inflammatory insults and apoptosis (Ding et al., 2010). In the same transgenic mice, PRDX4 was shown to protect against nonalcoholic steatohepatitis, type 2 diabetes mellitus and the metabolic syndrome by reducing oxidative stress-induced injuries (Nabeshima et al., 2013).

PEROXIREDOXINS AS MODULATORS OF REDOX SIGNALING IN INFLAMMATION

ROS/RNS produced by inflammatory cells are increasingly recognized as key signaling molecules and no longer considered only as harmful molecules released to eradicate pathogens in host defense mechanisms of innate immunity (Mittal et al., 2014; Nathan and Cunningham-Bussel, 2013). As noted previously, the role of peroxiredoxins as modulators of redox signaling is now widely accepted (Rhee et al., 2005; Sies, 2014; Woo et al., 2010). So, although peroxiredoxins are constitutively expressed by virtually all cell types in mammals, and considering that peroxidase activity of many mammalian peroxiredoxins can be modulated by post-translational modifications including overoxidation, several reports have been focused on inducible peroxiredoxins in inflammatory cells and their potential roles as regulators in redox signaling during inflammatory processes. Notably, Drapier and collaborators have shown that expression of PRDX1, PRDX5 and PRDX6 is dramatically increased in mouse bone marrow-derived macrophages (BBMs) upon stimulation with IFN-γ and LPS (Abbas et al., 2009; Diet et al., 2007). Bast et al. (2010) also reported increased expression of PRDX1, PRDX2, PRDX4, PRDX5 and PRDX6 in murine BMMs stimulated with LPS and IFN-γ. It was speculated that the increased expression of several peroxiredoxins in such inflammatory situation could represent a negative feed-back loop to protect macrophages against oxidative insults but could also contribute to the control of redox-sensitive effectors (Diet et al., 2007). Interestingly, PRDX5 expression was shown to be upregulated via LPS/TLR4 and the Th1 cytokine IFN-γ pathways (Abbas et al., 2009). It was demonstrated that TLR4-dependent increase of PRDX5 expression in mouse macrophages was mediated by a TRIF-dependent/IFN-γ-independent pathway, and that IFN-γ increased PRDX5 gene expression via a MyD88- and TNF-dependent pathway (Abbas et al., 2009). MAPKs were shown to be a point of convergence downstream of IFN-γ and LPS signaling pathways leading to PRDX5 induction (Abbas et al., 2009). Furthermore, Sun et al. (2010) showed that PRDX5 expression is also highly sensitive to LPS stimulation in microglia. Induced PRDX5 expression was demonstrated to be under the control of cooperative action of ROS, RNS and the JNK signaling cascade. Interestingly, knockdown of PRDX5 increased microglial activation with

augmented ROS generation and JNK-dependent NO production suggesting that PRDX5 might indeed modulate a ROS-dependent signaling cascade (Sun et al., 2010). Moreover, Choi et al. (2013) proposed that PDRX5 would be implicated in the regulation of LPS/TLR4-induced IL-6 production in mouse macrophages, by modulating the JAK-STAT signaling pathway. In the proposed mechanism, PRDX5 interacts with JAK2 via its C_p which leads to the inhibition of the sequential phosphorylation of JAK2 and STAT5 and consequently reduces IL-6 production. PRDX1 was also involved in the control of ROS/RNS-dependent microglial activation (Kim et al., 2013). Indeed, it was shown that PRDX1 is upregulated upon exposure of microglia to LPS (but not to H_2O_2 or paraquat) in a ROS/p38 MAPK-dependent manner (Kim et al., 2013). Under this pro-inflammatory situation, it was proposed that PRDX1 can serve as a regulator of microglial activation by inhibiting NO production via the suppression of a ROS/NF-κB/iNOS signaling pathway (Kim et al., 2013). PRDX6 was also shown to play an unexpected role in NADPH oxidase-2 (NOX2) activation (Chatterjee et al., 2011). Indeed, it was shown that in stimulated macrophages, PRDX6 is phosphorylated, translocated to the membrane and the activation of its phospholipase A2 activity facilitates assembly and activation of the NOX2 complex (Chatterjee et al., 2011).

PEROXIREDOXINS AS PAMPS AND DAMPS

Inflammation is triggered when innate immune cells, such as macrophages detect infection or tissue injury. At the molecular level, PRRs, including toll-like receptors (TLRs), on the cell surface or in the cytoplasm, respond to PAMPs or host-derived DAMPs to trigger expression of genes coding for chemokines, cytokines, adhesion molecules and regulators of the extracellular matrix that finally promote the recruitment and activation of leukocytes to eliminate microbes and host debris (Newton and Dixit, 2012). Several peroxiredoxins have been proposed to act as PAMPs or DAMPs (Robinson et al., 2010a; 2010b).

As ubiquitous enzymes involved in the defense against ROS/RNS, peroxiredoxins have been studied for their role in parasite survival and virulence that require efficient defenses against ROS/RNS produced by the host immune system (Gretes et al., 2012). Interestingly, it was also shown that PRDXs secreted by parasitic helminths (parasitic round- and flatworms) may act as PAMPs, triggering the recruitment of macrophages and a Th2 response with the production of high levels of IL-10 and prostaglandin E2 (Donnelly et al., 2005; 2008). Moreover, a typical 2-Cys malarial PRDX from *Plasmodium berghei* was reported to act as a PAMP by binding to TLR4 receptor on macrophages and triggering a pro-inflammatory response (Furuta et al., 2008).

It must be noted here that prior to its characterization as a peroxidase, mammalian PRDX1 was initially described as a soluble protein released from lysed cells and exhibiting immune modulating function able to enhance the cytotoxic activity of natural killer cells (Shau et al., 1993). Since these seminal works, it was shown that extracellular PRDX1 is able to act as a DAMP to trigger TLR4-dependent secretion of TNF-α and IL-6, and dendritic cell maturation when incubated with murine macrophages or immature bone marrow-derived dendritic cells (Riddell et al., 2010). It was also reported that PRDX1 interaction with TLR4 is independent of its peroxidase activity but dependent on its ability to form decamers (Riddell et al., 2010). Moreover, very recently, exosomal release by different cells upon exposure to LPS and TNF-α of oxidized dimeric forms of PRDX1 and PRDX2, as well as glutathionylated PRDX2 triggering the production of inflammatory cytokines by macrophages, has also been described (Mullen et al., 2015; Salzano et al., 2014). The role of PRDX1, PRDX2, PRDX5 and PRDX6 as DAMPs was emphasized in post-ischemic inflammation in the brain (Shichita et al., 2012). Indeed, Shichita et al. (2012) showed that following ischemic injuries, peroxiredoxins that are released from necrotic brain cells can induce expression of inflammatory cytokines in macrophages through activation of TLR2 and TLR4, leading to neural cell death.

WHAT CAN WE LEARN FROM NON-MAMMALIAN VERTEBRATES AND INVERTEBRATES?

Innate immunity and inflammation are ancient evolutionary mechanisms which have been partly conserved from invertebrates to mammals (Royet et al., 2005). Interestingly, it has been reported that several PRDXs are significantly regulated in immune cells upon virus, bacteria or parasite infection in non-mammalian vertebrates such as fishes (reviewed in Valero et al., 2015) or in invertebrates such as insects (Ahn et al., 2012; Chen et al., 2014; Radyuk et al., 2010; Zhang and Lu, 2015) and molluscs (Genard et al., 2013) to cite only a few reports.

In fishes, large yellow croaker (*Pseudosciaena crocea*) PRDX4 was shown to be upregulated upon bacterial challenge in spleen cells (Yu et al., 2010). Moreover, *PRDX4* gene knockdown resulted in increased NF-κB activity, increased expression of TNF-α and CC chemokine, as well as downregulation of IL-10 expression in the spleen (Yu et al., 2010). Furthermore, Ren et al. (2014) showed that miiuy croaker (*Miichthys miiuy*) PRDX3 and PRDX5 are highly upregulated in spleen and kidney, two lymphoid organs in fish, after bacterial infection suggesting that these peroxiredoxins may also play an important role in fish immune response.

In insects, it was shown that *Drosophila* PRDX5 confers resistance to oxidative stress and extend fly life span by up to 30% (Radyuk et al., 2009). PRDX5 KO flies are also more susceptible to oxidative stress and have a higher incidence of apoptosis as well as a shortened life span (Radyuk et al., 2009). Furthermore, in the silkworm (*Bombyx mori*) PRDX5 was shown to be upregulated by hydrogen peroxide injection and bacterial infection in haemocytes indicating that PRDX5 could also play an important role in immune response and oxidative stress in insects (Zhang and Lu, 2015). Accordingly, PRDX5 expression is increased by gut-specific dual oxidase (DUOX) activation in gut epithelia upon oral bacterial infection in *Drosophila* and this PRDX5 upregulation was shown to be mediated by the JNK-FOXO signaling pathway (Ahn et al., 2012). Radyuk et al. (2010) proposed also that PRDX5 plays an important modulatory role in *Drosophila* immune response via the JNK signaling pathway albeit as a negative regulator according to PRDX5 KO fly model.

CONCLUSION

Peroxiredoxins are now recognized as a major superfamily of peroxidases conserved throughout evolution in bacteria, archaea and eukaryotes (Perkins et al., 2015). In mammals, peroxiredoxins are constitutively expressed in virtually all tissues and cell types where they can act as peroxide and peroxynitrite scavenging enzymes in collaboration with catalase and glutathione peroxidases. Functionally, peroxiredoxins have been shown to protect cells against deleterious oxidation of macromolecules triggered by physiological or pathophysiological production of ROS and RNS. This cytoprotective function of

peroxiredoxins could be considered as a more ancestral function endowed initially by bacterial and archaeal peroxiredoxins. However, as the role of peroxides, and notably hydrogen peroxide, as signaling molecules is emerging, and because peroxiredoxin activity is regulated by post-translational modifications, it is now recognized that peroxiredoxins may modulate peroxide signaling implicated in essential cell functions. Accordingly, during the last decade, several lines of evidence pointed that peroxiredoxins may be major players in immunity including innate immunity and inflammation. Indeed, it was demonstrated that peroxiredoxins may act as cytoprotective enzymes against high levels of ROS/RNS produced during inflammatory processes, as modulators of redox signaling involved in the control of inflammatory cell functions, and as extracellular PAMPs or DAMPs. In this context, and considering the multiple potential roles of these peroxidases, challenges for the coming years will be to determine where (in which inflammatory cells, in which subcellular compartment or extracellularly), when (at which step of the inflammatory process) and how (as peroxide reductase, as redox relay or as ligand for membrane or intracellular receptors) peroxiredoxins act in innate immunity and inflammation.

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