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REVIEW

The Role of Peroxiredoxin Family in Cancer Signaling

Yosup Kim[1], Ho Hee Jang[1,2]

[1]Department of Health Sciences and Technology, Graduate School of Medicine, Gachon University, [2]Department of Biochemistry, College of Medicine, Gachon University, Incheon, Korea

Peroxiredoxins (Prxs) are antioxidant enzymes that protect cells from oxidative stress by reducing intracellular accumulation of reactive oxygen species (ROS). In mammalian cells, the six Prx isoforms are ubiquitously expressed in diverse intracellular locations. They are involved in the regulation of various physiological processes including cell growth, differentiation, apoptosis, immune response and metabolism as well as intracellular ROS homeostasis. Although there are increasing evidences that Prxs are involved in carcinogenesis of many cancers, their role in cancer is controversial. The ROS levels in cancer cells are increased compared to normal cells, thus promoting cancer development. Nevertheless, for various cancer types, an overexpression of Prxs has been found to be associated with poor patient prognosis, and an increasing number of studies have reported that tumorigenesis is either facilitated or inhibited by regulation of cancer-associated signaling pathways. This review summarizes Prx isoforms and their basic functions, the relationship between the expression level and the physiological role of Prxs in cancer cells, and their roles in regulating cancer-associated signaling pathways.
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Key Words: Peroxiredoxins, Oxidative stress, Cancer, Peroxidase activity, Tumorigenesis

INTRODUCTION

Cancer is a heterogeneous disease caused by multiple and complex risk factors, and it poses a substantial threat to the quality of human life [1]. An increase in reactive oxygen species (ROS) from endogenous or exogenous sources induces intracellular oxidative stress, causing various diseases. It has also been increasingly reported to promote tumorigenesis, including the proliferation, invasion, and metastasis of cancer cells [2,3]. Healthy cells have diverse anti-oxidative defense mechanisms to maintain ROS homeostasis, and enzymatic and non-enzymatic antioxidants provide the most effective system for cellular protection against ROS-driven oxidative stress by removing intracellular ROS [4,5].

Peroxiredoxins (Prxs) represent one of the diverse enzymatic antioxidant systems that are distributed across various organelles, and different subtypes of Prxs are stratified according to the number and the position of Cys residues [6,7]. Prxs are known to either facilitate or inhibit tumorigenesis, depending on the cancer type, by regulating the ROS level [8]. Furthermore, an increasing number of studies have reported that, in addition to the peroxidase function that removes hydrogen peroxide (H_2O_2), Prxs regulate cancer signaling pathways in a redox-dependent or -independent manner through interaction with other signaling proteins [9-12]. This review focuses on the physiological roles of Prx isoforms in cancer and the mechanism behind their ability to regulate signaling pathways by interacting with target proteins. Lastly, this review discusses the potential of Prxs as novel therapeutic targets.

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Correspondence to: Ho Hee Jang
E-mail: hhjang@gachon.ac.kr, ORCID: Ho Hee Jang, https://orcid.org/0000-0003-0314-8230

PEROXIREDOXIN ISOFORMS IN MAMMALIAN CELLS

Prx is a family of antioxidant enzymes that removes H_2O_2 using the thioredoxin (Trx)/Trx reductase/NADPH system as a reducing equivalent [13]. The six isoforms of mammalian Prxs (Prx1-6) possess one or two conserved Cys residues (peroxidatic Cys; C_P, resolving Cys; C_R). Prx isoforms are categorized into three different forms depending on the number and position of the conserved Cys residue and on the type of the disulfide bond created during the catalytic cycle. These include typical 2-Cys Prx, atypical 2-Cys Prx, and 1-Cys Prx that are represented by Prx1-4, Prx5, and Prx6, respectively (Fig. 1) [14].

Typical 2-Cys Prxs form a sulfenic acid (C_P-SOH) intermediate upon the oxidation of C_P-SH by H_2O_2, which creates an intermolecular disulfide bond with the C_R of another Prx subunit in the vicinity. Prx is subsequently reactivated as the disulfide bond is reduced from reducing equivalents [15]. Prx1-4 belong to the typical 2-Cys Prxs class. Prx1 and Prx2 reside mainly in the cytosol in abundance, but they are also found in the nucleus [16]. Prx3 has a mitochondrial leader sequence (MLS) at the N-terminal, directing its localization to the mitochondria [17]. Mitochondria is the major source of ROS, and Prx3 plays a key role in regulating mitochondrial redox homoeostasis [18,19]. Prx4 is found in the endoplasmic reticulum and the extracellular space [20,21]. Atypical 2-Cys Prx uses the same catalytic mechanism as typical 2-Cys Prxs to remove H_2O_2, with the only difference being the creation of an intramolecular disulfide bond between C_P and C_R within a single Prx subunit [22]. Prx5 belongs to the class of atypical 2-Cys Prx. it has a MLS and is largely located in the mitochondria as well as prx3, although it is also found in peroxisomes and the cytosol [17]. Lastly, Prx6 belongs to the 1-Cys Prx class. It is characterized by the lack of C_R, which is present in other members of the Prx family, and it is expressed in the cytosol [23].

THE PHYSIOLOGICAL ROLE OF PEROXIREDOXINS IN CANCER SIGNALING

The major enzymatic function of Prxs is to regulate cellular redox signaling as peroxidases, but they also function as molecular chaperones upon H_2O_2 concentration-dependent structural changes [24]. Furthermore, in many cancer types, including lung, breast, prostate, and gastric cancers, Prx expression has been known to be high and associated with poor patient prognosis [25-28]. In cancer signaling pathways, Prx has been increasingly reported to either facilitate or inhibit tumorigenesis through its interaction with other signaling proteins in a redox-dependent or redox-independent manner (Table 1) [16,26,28-38]. Among the Prx isoforms, Prx1 and Prx2 are localized abundantly in the nucleus and the cytosol, which has allowed numerous studies to focus on their expression and their interaction with signaling target proteins in cancer [39,40]. Nonetheless, the relatively low expression of Prx3-6 in cancer and their restricted localization have resulted in a comparatively small number of studies related to cancer.

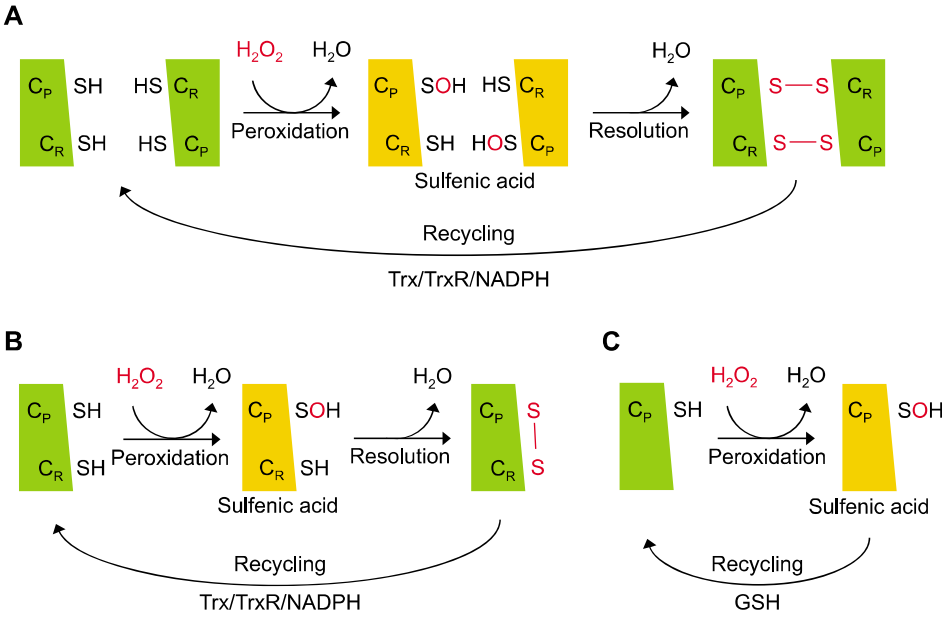

Figure 1. Catalytic cycle of peroxiredoxin (Prx) isoforms. (A) Typical 2-Cys Prxs (Prx1-4) first mediate the oxidation of C_P residues to sulfenic acid by H_2O_2, followed by the formation of an intermolecular disulfide bond with the C_R of another Prx subunit. Lastly, the oxidized Prx undergoes reduction by the thioredoxin (Trx)/Trx reductase (TrxR)/NADPH system. (B) Atypical 2-Cys Prx (Prx5) is similar to typical 2-Cys Prxs, except that they mediate the formation of an intramolecular disulfide bond with the C_R of the same Prx subunit. (C) 1-Cys Prx (Prx6) has only one conserved Cys residue so that they are recycled in sulfenic acid without forming a disulfide bond, which is reduced by glutathione (GSH) instead of Trx.

Table 1. Expression of Prx isoforms in cancer

Class	Isoform	Expression	Cancer type	Ref. No.
Typical 2-Cys	Prx1	Up	Lung	[29,30]
		Up/down	Thyroid	[31]
		Up	Pancreas	[32]
		Up	Bladder	[33]
		Up	Breast	[26]
		Up	Prostate	[34]
	Prx2	Up	Lung	[29]
		Up	Ovary	[35]
	Prx3	Up	Breast	[26,36]
		Up	Cervix	[37]
		Up	Prostate	[38]
	Prx4	Up	Lung	[29]
		Up	Breast	[26]
		Up	Prostate	[38]
Atypical 2-Cys	Prx5	Up	Breast	[26]
		Up	Stomach	[28]
1-Cys	Prx6	Up	Lung	[29]
		Up	Bladder	[33]
		Up	Ovary	[35]

Prx, peroxiredoxin.

1. Prx1

Smoking, one of the multiple causes of malignant lung cancer, results in 80% to 90% of lung cancer deaths [41]. Numerous therapies, including radiation therapy (radiotherapy), have been developed and used to treat lung cancer and many other types of malignancies [42]. Radiation therapy increases the level of ROS to facilitate apoptosis in cancer cells [43,44]. Prx1 is highly expressed in several human cancers, including lung cancer. Prx1 enhances lung cancer cell survival by suppressing radiation-induced apoptosis [29,30]. Glutathione-*S* Transferase Pi (GSTP) is a protein that binding to the c-Jun N-terminal kinase (JNK) to prevent its activation, thereby inhibiting apoptosis. Radiation dissociates the interaction between the two proteins, and the released JNK is activated to promote apoptosis. However, Prx1 overexpression increases the binding of the GSTP-JNK complex independently of its peroxidase activity. Consequently, Prx1 inhibits the release of JNK from GSTP, thereby suppressing the radiation-induced JNK activation in lung cancer and preventing apoptosis [45].

Prostate cancer (PCa) is the most common malignancy in males [46]. Dihydrotestosterone (DHT), which is converted form androgen testosterone by 5α-reductase, binds to the androgen receptor (AR) in the cytosol, and the androgen/AR complex enters the nucleus to bind to androgen response element (ARE) on the target gene promoter. The resulting increase in expression of the downstream target genes such as prostate specific antigen (PSA) promotes the progression of PCa [47]. Hormone therapies, the androgen deprivation therapy (ADT), are commonly used treatment, in which inhibitors of androgen production or AR are used. However, once PCa develops resistance to ADT, the condition becomes castration-resistant PCa, rendering hormone therapy ineffective [48]. The expression of Prx1 is highly in prostate cancer cells [34]. The DHT binding affinity of AR is increased by Prx1 which is independent of its peroxidase activity, and this promotes androgen-stimulated prostate cancer growth. Furthermore, in hypoxia, Prx1 binds to AR independently of its peroxidase activity, and this increases the binding affinity of AR to the ARE of the PSA promoter to increase ligand-stimulated AR activation [49].

The PI3K/AKT signaling pathway is crucial for cancer survival because it facilitates tumorigenesis through increased cell growth and proliferation [50,51]. In this pathway, when a growth factor binds to the receptor to activate the receptor-bound PI3K, the activated PI3K phosphorylates the precursor PIP_2 to convert it to PIP_3 as a mediator. PIP_3 activates AKT phosphorylation by PDK1 to regulate various downstream cancer-associated signaling pathways [52]. Furthermore PTEN is a tumor suppressor protein that uses its lipid phosphatase activity to dephosphorylate PIP_3 and convert it to PIP_2, which subsequently prevents AKT activation and consequently the activation of the PI3K/AKT signaling pathway [53]. However, oxidation of PTEN caused by oxidative stress leads to its inactivation. Prx1 binds to PTEN to prevent its oxidation, thereby inhibiting tumorigenesis in breast cancer [12].

2. Prx2

DNA methylation, which induces gene silencing, can occur on the promoters of tumor suppressors, increasing the growth of cancer cells [54]. DNA methyltransferases (DNMTs), enzymes essential for DNA methylation, catalyze the transfer of a methyl group to the CpG structure in the DNA. DNMTs include DNMT1, DNMT3A and DNMT3B [55]. This methylation occurs in the Prx2 gene promoter in gastric cancer, lymphoma, and melanoma. Unlike Prx1, Prx2 shows decreased mRNA and protein expression in approximately 32% (9 out of 28) of gastric cancer cell lines. DNMT1 suppresses Prx2 expression by promoting the methylation of Prx2. Contrarily, increased Prx2 expression in gastric cancer suppresses Src kinase activation through its peroxidase activity to inhibit the survival and migration of gastric cancer cells [56].

In patients with metastatic disease, the 5-year survival rate is less than 15%, indicating that tumor metastasis is a considerable

threat to the patient's survival [57]. As a highly metastatic cancer, melanoma is the deadliest skin cancer. H_2O_2 increases the ERK and Src activation, and these in turn suppress the expression of E-cadherin and promote the phosphorylation of β-catenin, respectively. This promotes the dissociation of E-cadherin/β-catenin complexes to cause epithelial-to-mesenchymal transition (EMT). As a result, cells metastasize to the lung or other organs. However, Prx2 removes H_2O_2 in melanoma cells, thereby increasing E-cadherin expression by suppressing ERK and Src activities. Additionally, the removal of H_2O_2 increases the membrane retention of β-catenin by suppressing Src-mediated β-catenin phosphorylation. The peroxidase-inactive (C51/172S) Prx2 mutant fails to remove H_2O_2, leading to melanoma metastasis. These results suggest that the peroxidase activity of Prx2 is essential to prevent metastasis. Thus, Prx2 removes H_2O_2 in melanoma cells to promote the E-cadherin/β-catenin complexes, preventing metastasis [58].

3. Prx3

Prx3 is mainly localized to the mitochondria, and is highly expressed in various cancer types including PCa, breast cancer, and hepatocellular carcinoma [26,36,59,60]. In PCa, non-steroidal anti-androgen bicalutamide antagonizes the binding between androgen and AR, and is therefore used in anti-androgen treatment. However, PCa gradually develops resistance to this treatment. Anti-androgen resistant cells contain an increased number of mitochondria, with a consequent increase in mitochondrial Prx3 expression. The increased level of Prx3 protects the mitochondria from H_2O_2-induced oxidative stress, thereby inhibiting apoptosis in PCa [61].

4. Prx4

Sulfiredoxin (Srx) is a protein that reversibly reduces the Cys-SO_2H form of hyperoxidized Prx. The peroxidase activity of the reactivated Prx through the Srx-mediated Prx reversible reaction, protects the cells from oxidative stress [62]. However, Srx is highly expressed in lung cancer, where it increases cancer cell proliferation and invasion [63]. Among the typical 2-Cys Prxs, Prx4 exhibits the strongest binding affinity upon interaction with Srx, and similar to Srx, Prx4 shows a high level of expression in lung cancer, where it promotes cancer cell proliferation [29]. Such facilitation of tumorigenesis via the Srx-Prx4 axis is regulated by two pathways. In the first pathway, c-Jun phosphorylation is increased by Srx, resulting in activation of the transcription factor AP-1 and increased expression of the downstream target MMP9, which lead to the regulation of Srx-Prx4. In the second pathway, this regulation relies on an Srx-dependent increase of ERK1/2 phosphorylation. Srx activates the phosphorylation of c-Jun, a transcription factor activator protein (AP-1, a heterodimer of c-Fos and c-Jun), to increase MMP9 expression, which promotes the invasion and metastasis of lung cancer. Srx also facilitates lung cancer proliferation by increasing the phosphorylation of ERK1/2 and CREB. Likewise, Prx4 activates the phosphorylation of ERK1/2, AKT, CREB, and c-Jun. Therefore, the Srx-Prx4 axis plays a role in promoting tumor growth and metastasis of lung cancer [64].

5. Prx5

EMT is a cellular process that promotes cell proliferation, invasion, and metastasis in various cancer types [65]. ROS facilitates gastric and lung cancer cell migration and invasion [66,67]. Unlike Prx1-4, a high level of Prx5 expression in patients with gastric cancer is associated with a markedly reduced 5-year rate of survival. Prx5 increases vimentin expression and decreases E-cadherin expression in gastric cancer cells, thereby promoting not only EMT, but also tumorigenesis through increased invasion and proliferation [28].

6. Prx6

Prx6 differs from other Prx isoforms as it contains only one conserved Cys (C47), but it is highly expressed in lung cancer, similar to others [23]. As Prx6 exhibits calcium-independent phospholipase A2 (iPLA2) and glutathione peroxidase (GPx) activities, an increase in Prx6 leads to elevated activities of iPLA2 and GPx. The iPLA2 and GPx activities are used by Prx6 to promote the expression of cell cycle regulatory proteins (CDK1, CDK2, and cyclin D1). Moreover, by activating MAP kinase pathway proteins (ERK1/2 and p38), Prx6 enhances the DNA binding activity of AP-1, which consequently promotes the growth and viability of lung cancer cells. A mutant form of Prx6 (C47S) lacking the iPLA2 and GPx activities suppresses the p38 and ERK1/2 activation and DNA binding activity of AP-1, consequently decreasing tumorigenesis. Prx6 thus facilitates tumorigenesis in lung cancer through its peroxidase activity [68].

CONCLUSION

Prxs exert their key function of regulation of redox homeostasis through their antioxidant enzymatic activity, which removes intracellular H_2O_2. The 6 Prx isoforms act as H_2O_2 scavengers in different intracellular compartments. Additionally, at high H_2O_2 concentrations, Prxs become molecular chaperones

through gain of function. Thus, Prxs are multifunctional proteins which play different roles. Recently, a growing number of studies have found that Prxs regulate their expression and activity, acting as oncogenes that promote carcinogenesis in various cancer types. In addition, Prxs are known to promote the cancer cell stemness [69-71]. Nevertheless, as Prxs have also been shown to suppress tumorigenesis, more studies are required to verify the potential of Prxs as therapeutic targets in each cancer type.

Furthermore, Prxs influence the progression of diseases including cancer, depending on their protein-protein interactions. Among the Prx isoforms, Prx1 and 2 are the most abundant, and hence their interaction partners have been more extensively studied. In addition, to investigate the possibility that each Prx isoform mediates a different mechanism of cancer signaling regulation as they are located in different intracellular organelles, further studies should focus on the identification of interaction partners of each isoform and the elucidation of underlying mechanisms. In conclusion, the potential application of Prxs as therapeutic strategies for cancer treatment is promising.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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