Technology in Cancer Research & Treatment
Volume 18: 1-10

DOI: 10.1177/1533033819864313
journals.sagepub.com/home/tct
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PRDX4 and Its Roles in Various Cancers

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Abstract

Reactive oxygen species play a vital role in cell survival by regulating physiological metabolism and signal transduction of cells. The imbalance of oxidant and antioxidant states induces oxidative stress within a cell. Redox regulation and oxidative stress are closely related to survival and proliferation of stem cells, cancer cells, and cancer stem cells. Peroxiredoxin 4, a typical endoplasmic reticulum-resident 2-Cys antioxidant of peroxiredoxins, can fine-tune hydrogen peroxide catabolism which affects cell survival by affecting redox balance, oxidative protein folding, and regulation of hydrogen peroxide signaling. Recent studies revealed the overexpression of peroxiredoxin 4 in several kinds of cancers, such as breast cancer, prostate cancer, ovarian cancer, colorectal cancer, and lung cancer. And it has been demonstrated that peroxiredoxin 4 causally contributes to tumorigenesis, therapeutic resistance, metastasis, and recurrence of tumors. In this article, the characteristics of peroxiredoxin 4 in physiological functions and the cancer-related research progress of mammalian peroxiredoxin 4 is reviewed. We believe that peroxiredoxin 4 has the potential of serving as a novel target for multiple cancers.

Keywords

PRDX4, H_2O_2, ROS, cancer, antioxidant

Abbreviations

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CBF, core binding factor; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERO1, endoplasmic oxidoreductin 1; GBM, glioblastoma multiforme; G-CSFR, granulocyte colony-stimulating factor receptor; HGG, high-grade glioma; H_2O_2, hydrogen peroxide; mRNA, messenger RNA; NADPH, nicotinamide adenine dinucleotide phosphate; NSCLC, non-small-cell lung cancer; OSCC, oral cavity squamous cell carcinoma; PDI, protein disulfide isomerase; PRDX4, peroxiredoxin 4; PTP, phosphotyrosine phosphatase; ROS, reactive oxygen species; RTK, receptors for tyrosine kinase; SOD, superoxide dismutases; Srx, sulfiredoxin; Trx, thioredoxin.

Received: December 8, 2017; Revised: May 27, 2019; Accepted: June 12, 2019.

Introduction

Reactive oxygen species (ROS) are a group of small molecules with unpaired electrons comprising free radicals and stable oxidizing molecules, such as hydroxyl radical (OH•), superoxide anion (O_2•−), and hydrogen peroxide (H_2O_2). Reactive oxygen species are highly reactive and yet short-lived. The generation of ROS in cells stays in equilibrium with a variety of endogenous antioxidant defences, for instance, peroxiredoxins (PRDXs), catalase, glutathione peroxidase, and superoxide dismutase.[1] Reactive oxygen species serve as double-edged swords in cellular processes depending on their concentration. Oxidative stress, induced by the damage of redox balance within a cell, is closely related to the survival and proliferation of stem cells, cancers, and cancer stem cells.[2,3]

Peroxiredoxins were discovered about a quarter-century ago.[4] Peroxiredoxins, consisting of 6 small anti-oxidant isozymes (PRDX1-6), belong to redox family proteins. They are expressed ubiquitously and spread extensively among a wide variety of tissues in human body. All 6 PRDXs are expressed in mammalian cells. Peroxiredoxins function as a cellular endogenous defense system against ROS, especially in catalyzing peroxide reduction to eliminate excessive cellular H_2O_2, which is an inevitable byproduct of metabolism in aerobic organisms.[5-8] Among these 6 PRDXs, only PRDX4 resides in the endoplasmic reticulum (ER). Peroxiredoxins 4 contains a hydrophobic signal sequence at the N-terminus which is responsible for its localization, whether resident in the ER or

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Table 1. Summary of the Cellular Locations of all PRDXs.

PRDX Subtype	PRDX1	PRDX2	PRDX3	PRDX4	PRDX5	PRDX6
Cellular location	Cytosol and nucleus	Cytosol and membrane	Mitochondria	Cytosol, Golgi and secreted	Mitochondria, peroxisome and cytosol	Cytosol

Abbreviations: PRDXs, peroxiredoxins.

secretion into the extracellular space.[9,10] The localization of all PRDXs is shown in Table 1.[6]

Extensive studies have suggested the potential of PRDX4 serving as a biological marker for many diseases,[11] such as type 2 diabetes, sepsis, atherosis, microalbuminemia, and stroke. But what attracts us more are the roles PRDX4 plays in cancers, which are not entirely clear yet. After the recent discovery of PRDX4 overexpression in multiple human cancers, the relationship between this antioxidant protein and tumorigenesis aroused considerable attention. A great deal of studies proved that PRDX4 facilitates tumor initiation and propagation, therapeutic resistance, and subsequent recurrence. These findings suggested that PRDX4 is a promising novel target for various cancers. In this article, recent studies that have shed lights on PRDX4 and its relationship to different cancers are reviewed.

Peroxiredoxin 4

Structure and Location of PRDX4

The structures of PRDXs are highly conservative. All 6 PRDXs have only 1 or 2 active-site cysteins which can be oxidized to sufenic acid (Cys-OH) by peroxide.[6,12,13] Mammalian PRDXs are divided into 3 groups based on their structure, which are named typical 2-Cys, atypical 2-Cys, and 1-Cys PRDXs. The typical 2-Cys family consists of PRDX1, PRDX2, PRDX3, and PRDX4 while the atypical 2-Cys group contains PRDX5. Both typical and atypical 2-Cys group members have 2 conserved cysteine residues, whereas the 1-Cys group contains 1 conserved cysteine residue. However, PRDX-Q, which is abundantly expressed in plants, possesses 2 cysteine residues.[14,15]

The PRDX4 has a chromosomal location of 10p22.13 and a polypeptide length of 256 aa.[6] It belongs to the typical 2-Cys PRDXs group which possesses 2 cysteine residues (1 peroxidative cysteine and 1 resolving cysteine). There are 271 amino acids in PRDX4.[6] Unlike other typical 2-Cys PRDXs, PRDX4 has signal peptides located at the N-terminal region that functions importantly for the localization of PRDX4.[9,10] Peroxiredoxin 4 could form pentamers with 5 homodimers units, whose subunits could assemble in a disulfide-linked head-to-tail pattern.[13,16-18]

Peroxiredoxin 4 is detected mainly in ER lumen, while also appears in the cytosol lysosome, nucleus, cellular matrix, and extracellular matrix (ECM).[19-21] It is retained within ER until the mature form being translocated into the cytoplasm but the mechanism of how it occurs is still unclear.[22] Cytoplasmic localization of PRDX4 is due to the interaction of PRDX4 and cytosolic domain of granulocyte colony-stimulating factor receptor (G-CSFR)[23] or the thromboxane A2 receptor[24] and thus PRDX4 functions efficiently in the cytoplasm. The ECM location of PRDX4 is attributed to the cleavable signal peptide which makes it possible for the enzyme to be extracellularly released.[15] On the other hand, some studies manifested no secretion evidence in some other kinds of cells.[10] So it seems that it is the cell type which determines the localization of PRDX4, either residing in ER lumen or secreting into extracellular space.

Besides the ER isoform, a new cytosolic isoform of PRDX4 is recently found to be transcribed from an alternative messenger RNA (mRNA) splicing uniquely in sexually matured testes.[25] Also, new evidence revealed that PRDX4 is not expressed in unicellular organisms such as yeast.[26] Peroxiredoxins are widely distributed and abundantly expressed in the various tissues of human body. Although PRDX4 is plentifully expressed in the heart, liver, pancreas, and muscle, it is lowly expressed in brain, spleen, and peripheral blood leukocytes.[27,28]

General Physiological Function of PRDX4

The ER-resident PRDX4 can guarantee the correct folding process of nascent proteins and avoid undergoing an alternative oxidative fate. Meanwhile, PRDX4 couples the H_2O_2 catabolism with oxidative protein folding in order to maintain ER redox balance and protect cells from development of misfolded proteins.[29] In addition, PRDX4 regulates signal transduction via fine-tune H_2O_2 concentration, which is critical in cell proliferation.[30]

Redox Balance and Oxidative Protein Folding

Reactive oxygen species serve as double-edged swords in cellular processes. At low to modest doses, ROS are considered crucial for regulation of normal physiological functions but excessive production of ROS induces oxidative-stress damage to proteins, lipids, nucleic acids, membranes, and even organelles, which sequentially lead to cell death processes such as apoptosis.[31] Moreover, ROS are shown to be important promoting factors in carcinogenesis.[32] External affecting factors such as hypoxia (low oxygenation) can cause excessive production of ROS in tumor cells, which contributes to hypoxia-induced radioresistance partially.[33,34] Oxidative stress, resulting from the damage of redox balance within a cell, is closely related to survival and proliferation of stem cells, cancers, and cancer stem cells.[2,3]

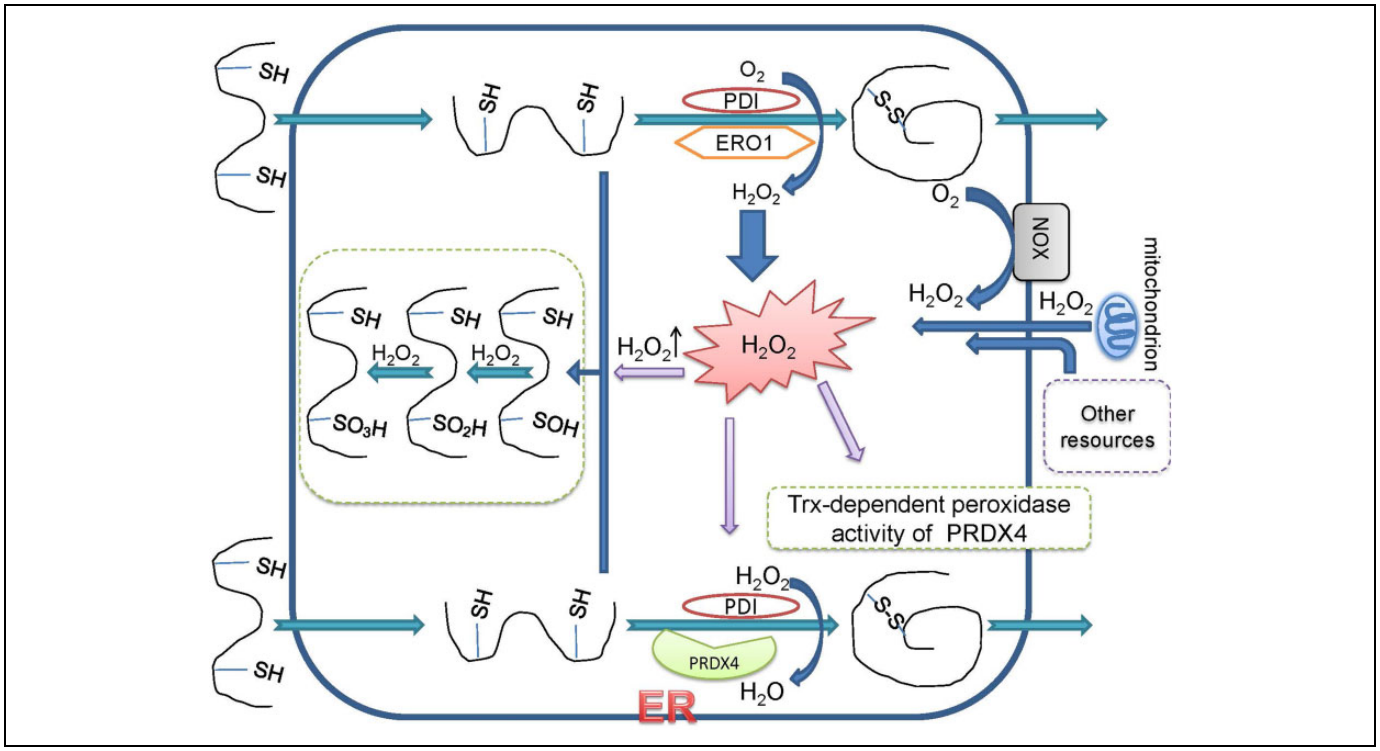

Figure 1. Peroxiredoxin 4 couples redox balance and oxidative protein folding. ER indicates endoplasmic reticulum; ERO1, endoplasmic oxidoreductin 1; H_2O_2, hydrogen peroxide, NOX, the NADPH oxidase complex; O_2, oxygen molecule; PDI, protein disulfide isomerase; PRDX4, peroxredoxin 4.

Hydrogen peroxide is one of the ROS which usually formed from O_2•- in the presence of superoxide dismutases (SOD) as a catalyst. Hydrogen peroxide is a deleterious oxidant as well as a signalling molecule. Because of the unpaired electrons, H_2O_2 is in an extremely unstable state and reacts easily with other molecules, such as protein, lipids, DNA, and so on.[35] Hydrogen peroxide can be generated from various pathways, including endoplasmic oxidoreductin 1 (ERO1)-mediated protein folding pathway, stimulation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex (NOX), the oxidation of fatty acids and the mitochondrial respiration that might diffuse to the ER lumen.[26,29] Enyedi has confirmed that the ER has the highest concentration level of H_2O_2 within a cell. And the redox state of the ER is controlled by Ero1-α and intraluminal calcium.[36] The main source of H_2O_2 is the ERO1-dependent oxidative protein folding process in the ER.

Nascent proteins enter the ER in an unfolded form with free thiols on cysteines. The free thiols on the nascent proteins are oxidized by enzyme-mediated processes and every 2 thiols form a disulfide bond. They go through an extremely refined and rigorous protein folding process, the new client proteins only leave after the correct folding and assembling.[37] This process is called oxidative folding. The disulfide bonds formation is the main feature of oxidative protein folding. Alternatively, the free protein thiols can be exposed to and react with H_2O_2, and be oxidized into sulfenic/sulfinic/sulfonic acid forms under oxidative ER stress[38] (Figure 1).

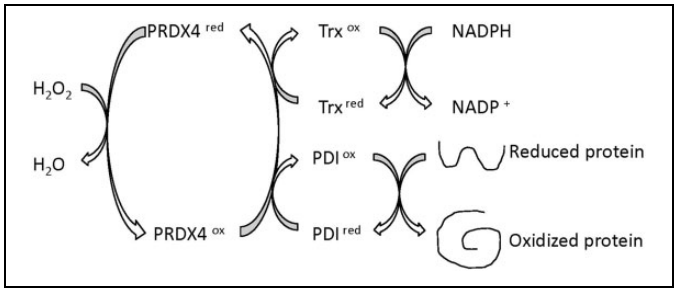

Figure 2. Thioredoxin-dependent peroxidase activity of PRDX4 and PRDX4-mediated oxiditive protein. H_2O_2 indicates hydrogen peroxide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; PRDX4, peroxredoxin 4; PDI, protein disulfide isomerase; Trx, thioredoxin.

Peroxiredoxin 4 functions vitally in regulating redox balance and oxidative folding by reducing H_2O_2 level in the ER. Firstly, the peroxidative cysteine residue of PRDX4 can be oxidized into sulfenic acid (Cys-SOH) via reducing H_2O_2 to water. Secondly, the oxidized cysteine can react with the resolving cysteine of another PRDX4 molecule and give rise to PRDX4 dimer. Then the dimer can be resolved by protein disulfide isomerase (PDI) for PRDX4 recycling.[26,39,40] Protein disulfide isomerases directly catalyze the formation of native disulphide bond in the new client protein[41] (Figures 1 and 2). In addition, PRDX4 exhibits thioredoxin (Trx)-dependent peroxidase activity, similar to other typical 2 Cys PRDXs, of

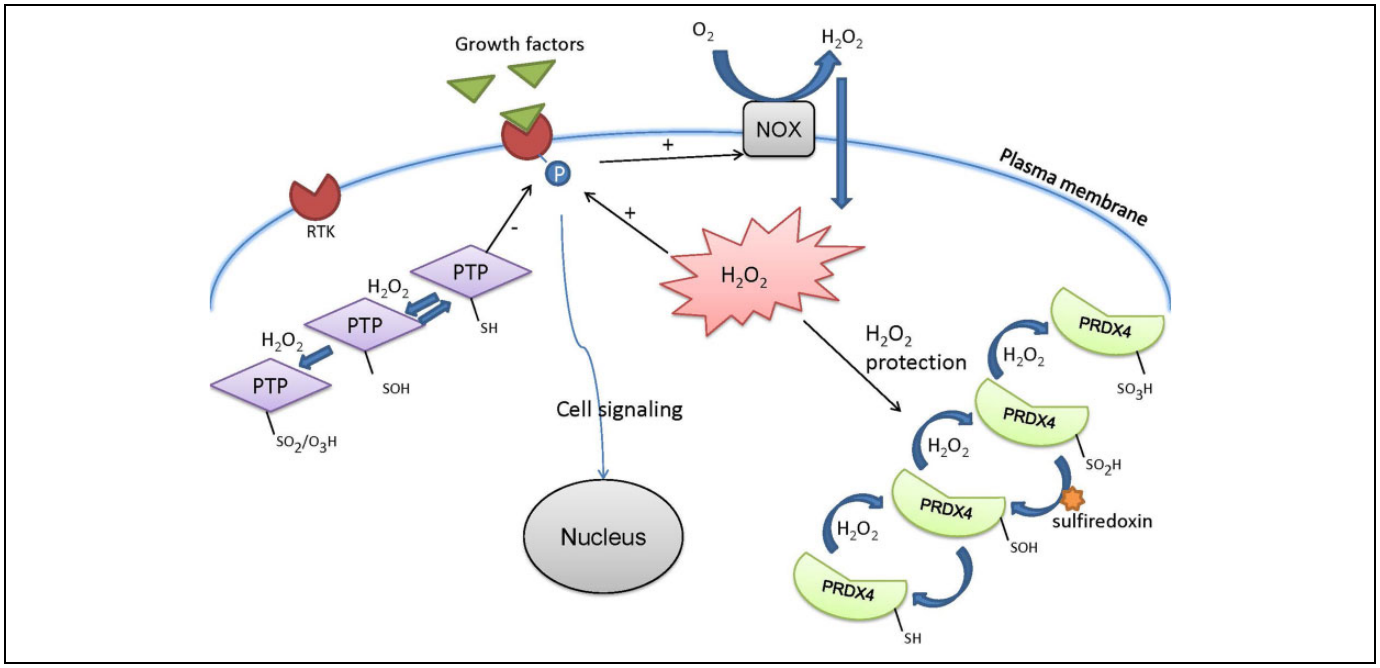

Figure 3. Peroxiredoxin 4 fine-tunes the H_2O_2 signal. H_2O_2 indicates hydrogen peroxide; NOX, the NADPH oxidase complex; PTP, phosphotyrosine phosphatase; PRDX4, peroxredoxin 4; RTK, receptors for tyrosine kinase.

reducing H_2O_2 *in vitro*. Peroxiredoxin 4 that is oxidized by H_2O_2 receives electrons provided by reduced Trx. Then the oxidized Trx receives the electrons from NADPH to be reduced[42-44] (Figure 2).

Regulation of H_2O_2 Signaling

Reactive oxygen species have been historically known as harmful by-products of aerobic organisms since their discovery; however, extensive information suggests that oxidants are generated also as secondary messengers.[45] Hydrogen peroxide modulates various physiological responses, such as cell proliferation, differentiation, and migration.[46,47] A transient increase in H_2O_2 level was observed in cells with extracellular growth stimulates treatment, for instance, platelet-derived growth factor and epidermal growth factor.[45] The phosphorylation and dephosphorylation levels of proteins, which are catalyzed by protein kinases and phosphatases, respectively, are controlled by growth signals.[48] As soon as growth factors bind to the receptors for tyrosine kinase (RTK), they will undergo tyrosine phosphorylation and the phosphorylation signals will be sent to the nucleus to stimulate cell proliferation. The phosphorylation signals also activate NOX located in cell membrane and organelles membrane to produce H_2O_2. "Cytosolic H_2O_2 enhances protein tyrosine phosphorylation by inactivating protein tyrosine phosphatases while activating protein tyrosine kinases."[30] On the other hand, active phosphotyrosine phosphatase (PTP) dephosphorylates RTK, which suppresses growth signals from being sent to the nucleus. H_2O_2 transiently oxidizes PTP to cysteine sulfenic acid form (-SOH) and the oxidized PTP could be irreversibly oxidized to sulfinic/sulfonic acid ($-SO_2/SO_3H$) by excess H_2O_2, causing inactivation of PTP[15] (Figure 3). Thus, under oxidative stress, the phosphorylation cell signals will continue to stimulate the nucleus and cause uncontrollable cell proliferation, which can induce tumorigenesis over a long period of time.

As stated above, the peroxidative cysteine residue of PRDX4 can be oxidized into sulfenic acid form ($-SOH$) by reducing H_2O_2 into water. And the sulfenic acid form of PRDX4 can be oxidized to sulfinic acid form ($-SO_2H$). The sulfinic acid form of PRDX4 could be reduced back to sulfenic acid form through catalyzation of sufiredoxin. Moreover, the sulfinic acid form could be irreversibly oxidized into the sulfonic acid form ($-SO_3H$) under oxidative stress. Peroxiredoxin 4 achieves the fine-tuning of the ROS signal by diminishing the overmuch H_2O_2 which is also a protecting process of H_2O_2 signal since the first 2 steps of the process is reversible, even though they require different enzymatic assistance[49,50] (Figure 3).

Peroxiredoxin 4 in Various Cancers

The overexpression of PRDX4 is identified recently in several human cancers. The roles PRDX4 play in cancers have received considerable attention. Abundant research have been done regarding the relationship between PRDX4 and cancers (Table 2).

Breast Cancer and Prostate Caner

Recent studies demonstrated that the accumulation of PRDX4 is enhanced in breast cancer samples compared to the normal tissue.[51,52] One study reported that higher level of PRDX4 is

Table 2. Summary of the Roles of PRDX4 in Different Cancer Types.

			Role of PRDX4 in Cancers		
Cancer Type	Expression Level	Effects and Mechanisms	Pro-Tumorigenic	Anti-Tumorigenic	No Association/ Not Clear
Breast cancer	Increased in breast cancer tissue	Higher level of PRDX4 is an indicator of better survival.[51]		※	
		High oxidative stress is associated with better BCSS, small tumor size and low tumor grade.[52]			※
		Promote bone metastasis by inducing osteoclastogenisis[53]	※		
	Loss of PRDX4 gene on chromosome X in cell lines evolving acquisition of docetaxel resistance	Partially explain the development of docetaxel resistance[54]		※	
Prostate caner	Increased in prostate cancer tissue	PRDX4 overexpression increases the growth rate of tumor cells.[55]	※		
		Promote bone metastasis by inducing osteoclastogenisis[53]	※		
Lung cancer	Increased in lung cancer tissue	Up- or downregulation of the Srx–PRDX4 axis leads respectively to increase or decrease of colony formation and invasion through signaling cascades including MAPK pathway, CREB pathway and the AP-1/MMP 9 axis.[56]	※		
		PRDX4 was required for lung cancer cells to form anchorage independent colony to invade through matrigel in culture.[57]	※		
		SNPs coding for PRDX4 are associated with clearance of docetaxel in patients with locally advanced NSCLC.[58]			※
		High PRDX4 expression is a worse prognostic factor in patients with early-stage lung squamous cell carcinoma who has undergone curative surgery.[59]	※		
Colorectal caner	Increased in colorectal cancer tissue	High PRDX4 expression is related to the depth of invasion, lymph node metastasis and short survival time.[60]	※		
		Promote liver metastasis[61]	※		
		PRDX4 is associated with the curcumin-enhancing efficacy of irinotecan-induced apoptosis of colorectal cancer LOVO cell.[62]		※	
		Both IRI and CUR+IRI treatments could decrease the expression PRDX4 of the tumors implanted by LOVO cells in nude mice.[63]			※
Glioma	Increased in glioblastoma tissue	PRDX4 knockdown reduces tumor cell growth rate, accelerates apoptosis and decreases radioresistance.[64]	※		
		Piperlongumine treatment kills HGG cells by inactivating PRDX4 and exacerbating oxidative stress.[65]	※		
Ovarian cancer	Increased in ovarian cancer tissue	PRDX4 expression level is significantly higher in borderline than in benign epithelial ovarian tumors.[66]	※		
Hematologic malignancy tumor	Decreased in APL	The decrease of PRDX4 expression negatively regulates G-CSFR mediated signaling.[67]			※
		PRDX4 is a novel AML1 part gene in an X;21 translocation in a patient with AML–M2.[68]			※
	Increased in multiple myeloma	PRDX4 provides favorable conditions for differentiation density of neoplastic B cells through association with immunoglobulin accumulation.[69]	※		
Oral cavity squamous cell carcinoma	Increased in oral cavity squamous cell carcinoma	Overexpression of PRDX4 is a significant prognostic factor for worse disease-specific survival. Knockdown of PRDX4 cause attenuation of cell migration and invasiveness ability.[70]	※		

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BCSS, breast cancer-specific survival; CUR, curcumin; G-CSFR, granulocyte colony-stimulating factor receptor; HGG, high-grade glioma; IRI, irinotecan; NSCLC, non-small-cell lung cancer; PRDX4, peroxiredoxin 4; Srx, sulfiredoxin; SNP, single-nucleotide polymorphisms.

associate with better survival in unselected breast cancer cases.[51] However, another study found no association between PRDX4 and survival of patients with triple-negative breast cancers.[52] Tumors could become resistant to taxane treatment despite the significant survival benefit of taxane therapy for breast cancer patients. Hansen[54] proved that there are various somatic genomic alterations in breast cancer cell lines associated with the acquisition of docetaxel resistance and a lot of PRDX4 copy number losses on chromosome X, which could contribute to the development of docetaxel resistance.

Sudies revealed that the expression level of PRDX4 is higher in prostate cancer tissue .[55,71-74] The enhanced expression of PRDX4 is negatively related to the TMPRSS2-ERG gene fusion status in human prostate cancer.[55] Overexpression of PRDX4 remarkably improves the growth rate of the prostate cancer cell lines while knockdown of PRDX4 differentially affects the proliferation depending on the cellular background.[55]

Bone metastasis is a common phenomenon for patients with prostate cancer and breast cancer.[75] These cancer cells produce soluble factors to stimulate ostolasts differentiation from precursors which induces bone resorption and destruction.[76-83] Peroxiredoxin 4 was found in both the cells and the media conditioned by prostate or breast cancer cells.[53] Knockdown of PRDX4 results in less efficient in inducing osteolastogenesis for both prostate and breast cancer cells.[53] So, PRDX4 might be identified as a secreted soluble factor produced by prostate and breast cancer cells to induce osteolastogenesis and bone destruction.

Lung Cancer

The PRDX4 expression levels are higher in non-small-cell lung cancer (NSCLC) cells and NSCLC-derived endothelial cells than normal cells.[84] Sulfiredoxin (Srx) is an antioxidant protein induced by H_2O_2. Sulfiredoxin serves as a catalyst in reducing the hyperoxidized PRDXs to restore their peroxidase activity.[49,85] Sulfiredoxin prefers to bind to PRDX4 over other PRDXs. Wei *et al* revealed that Srx and PRDX4 are significantly overxepressed in cells from both lung adenocarcinoma and lung squamous cell carcinoma. In addition, up- or down-regulation of the Srx–PRDX4 axis leads respectively to increase or decrease in colony formation and invasion in orthotopic mouse models by means of enhancing specific phosphokinase signaling cascades including mitogen-activated protein kinase pathway, cAMP-response element binding protein pathway, and the activator protein-1/the matrix metalloproteinase axis.[56] Peroxiredoxin 4 is required for lung cancer cells to form anchorage independent colony to invade matrigel in culture.[57]

Single-nucleotide polymorphisms in genes coding for PRDX4 were confirmed to be significantly associated with clearance of docetaxel in patients with locally advanced NSCLC.[58] The results suggest the possibility of adjusting the docetaxel dosage model that is used currently. Positive PRDX4 expression is closely related to shorter disease-free survival and recurrence in patients with early-stage lung squamous cell carcinoma who had undergone curative surgery.[59]

Colorectal Cancer

Peroxiredoxin 4 is over expressed in colorectal cancer tissues compared to normal tissues and high PRDX4 expression level is related to the depth of invasion, lymph node metastasis, and short survival time.[60] A hierarchical cluster analysis and q-PCR conducted by Li[61] proved that PRDX4 is overexpressed in tumors with liver metastasis than those without metastasis. It manifests that PRDX4 might be an indicator for metastasis.

Irinotecan is a semisynthetic camptothecin derivative extracted from Chinese unique plant Camptotheca acuminata and was approved by US Food and Drug Administration in 2000 as first-line regimens of advanced colorectal cancer treatment. Recent studies found that curcumin could improve the anticancer effects of irrinotecan.[62,63] Western blot analysis and immunohistochemical analysis showed that irinotecan and curcumin + irinotecan treatments could decrease the expression of PRDX4 in tumors implanted by LOVO cells in nude mice. And curcumin + irinotecan treatment exacerbates oxidative stress severely than irinotecan treatment.[63] So the decreased PRDX4 may be one of the mechanisms related to the curcumin-enhancing efficacy of irinotecan. But another research identified that the enhanced expression of PRDX4 is associated with the curcumin-enhancing efficacy of irinotecan-induced apoptosis of colorectal cancer LOVO cell.[62] Based on all results, we are inclined to believe that PRDX4 protects tumor cells from oxidative stress, so decreased PRDX4 contributes to the reduction of tumor cell growth rate. However, more investigations are necessary for to clear the role PRDX4 plays in colorectal cancer.

Glioma

Peroxiredoxin 4 was found to be overexpressed in both human and mouse glioblastoma multiforme (GBM). And PRDX4 knockdown by shRNA in high-grade glioma (HGG) cells reduces tumor cell growth rate and accelerates apoptosis. Meanwhile, down-regulation of PRDX4 decreases radioresistance of GBM cells.[64]

Kim *et al*[65] recently discovered that piperlongumine (a natural compound of Indian long pepper) treatment could inactivate PRDX4. Sequentially oxidative stress within HGG cells could induce cell death. It selectively kills tumor cells and has little impact on normal brain cells. Evidence has shown that piperlongumine treatment kills several cancer types besides HGG cells.[86-89] Piperlongumine could cross the blood–brain barrier, which makes it particularly promising for brain tumor therapies.[90] These data, in turn, suggest that PRDX4 can serve as a potential target for gliomas in the near future.

Ovarian Cancer

The PRDX4 expression level is significantly higher in borderline than in benign epithelial ovarian tumors and higher in serous tumors than mucinous tumors. However, oxidative stress, measured by 8-OHdG and nitrotyrosine, is high in both benign and borderline ovarian tumors.[66]

Hematologic Malignancy Tumor

Palande found PRDX4 expression is significantly lower in acute promyelocytic leukemia (APL) than other subtypes of acute myeloid leukemia (AML) or normal promyelocytes. The reason for reduced PRDX4 production is "increased trimethylation of histone 3 lysine residue 27 (H3K27me3) and lysine residue 4 (H3K4me3) at the transcriptional start site (TSS) of PRDX4."[67] Peroxiredoxin 4 attenuates G-CSFR signaling by eliminating ROS. The decreased PRDX4 expression can contribute to the hyper reactivity of APL to G-CSF.[67,91]

The human AML1 gene, coding for core binding factor (CBF) α, is located at the chromosome 21q22. Core binding factor accounts for a considerable proportion of hematopoietic malignancies through chromosome translocations.[92,93] In a case report, PRDX4 was firstly cloned as a novel AML1 part gene in an X;21 translocation in a AML-M2 patient. This translocation is involved in the PRDX4 gene on chromosome Xp22 and the AML1 gene on chromosome 21.[68] Furthermore, another fusion gene related to PRDX4 was observed resulted from a translocation (X;18)(p22;q23) in one patient with acute lymphocytic leukemia.[94] On the other hand, some data showed that PRDX4 is a rare locus for chromosomal translocations in AML.[67,95] So, we are not certain if PRDX4 plays a valuable role in AML.

Multiple myeloma belongs to B cell neoplasms. The expression of PRDX4 is related to the light chain secretion in multiple myeloma cells at the levels of both mRNA and protein. Peroxiredoxin may provide favorable conditions for differentiation density of neoplastic B cells through its association with immunoglobulin accumulation.[69]

Oral Cavity Squamous Cell Carcinoma

Cervical metastasis is a major obstacle and prognosticator for oral cavity squamous cell carcinoma (OSCC) management. Peroxiredoxin 4 expression levels are much higher in tumor tissue and metastatic lymph node than adjacent normal epithelial tissue and corresponding primary tumor tissue. *In vitro* knockdown of PRDX4 induces reduction of cellular invasiveness and metastasis. Additionally, PRDX4 is a significant prognosticator for disease-specific survival.[70] So PRDX4 might serve as a promising metastasis related prognostic marker for OSCC.

Concluding Remarks

With the growing understanding of ROS/H_2O_2, the roles PRDXs play, especially PRDX4, in normal cell survival, proliferation, tumorgenicity, and progression attracted extensive attention. Peroxiredoxin 4 is an ER-resident antioxidant that scavenges the excess H_2O_2 to provide a favorable microenvironment for cell proliferation and fine-tune H_2O_2 catabolism to achieve the regulation of H_2O_2 signaling, redox balance and oxidative protein folding. Reactive oxygen species/H_2O_2 is a harmful byproduct of metabolism, but on the other hand, an important secondary messenger for cell signaling depending on its concentration. If the redox balance is broken, the cell might undergo an incontrollable cell proliferation, which may cause oncogenesis.

The overexpression of PRDX4 has been discovered in multiple cancer tissues except APL. This antioxidant protein has been shown to causally facilitate tumor initiation and propagation, therapeutic resistance, and subsequent recurrence of tumors. A lot of research has been conducted regarding the relationship between PRDX4 and cancers, including breast cancer, prostate cancer, ovarian cancer, colorectal cancer, lung cancer, glioma, hematologic malignancy tumor, and oral cavity squamous cell carcinoma. The accumulation of PRDX4 could protect tumor cells from the toxic damage associated with ROS and influence medicine metabolism to some extent. In addition, PRDX4 serves as a prognostic factor of several cancers. Although a lot of work has been done, it is not enough to understand the mechanisms of how PRDX4 works in different cancers. We believe that PRDX4 can be a promising novel diagnostic target and a prognosticator even a new treatment approach for various cancers in the near future, that requires more in depth research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding.

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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