



Peroxiredoxins

By:

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- Peroxiredoxins (Prxs) are ubiquitous enzymes that have emerged as arguably the most important and widespread peroxide and peroxynitrite scavenging enzymes in all of biology .
- Discovered to be widely-distributed peroxidases in the mid-1990's , the role of Prxs was long overshadowed by well-known oxidative stress defense enzymes such as catalase and glutathione peroxidase (Gpx). However, refined kinetics measurements now imply that Prxs reduce more than 90% of cellular peroxides

- Reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), are normal byproducts of cellular metabolism, and play a key role in signal transduction, cell differentiation and proliferation (reviewed in Lennicke et al., 2015). The amount of ROS in cells is tightly regulated by endogenous antioxidants, such as peroxiredoxin, and thioredoxin, both under regulation of the transcription factor nuclear-factor-erythroid 2 p45-related factor 2 (NRF2). Under normal circumstances, these antioxidant molecules maintain the cellular homeostasis of H_2O_2 reducing it into water and oxygen, thus keeping the cellular concentration of H_2O_2 moderately low.

- Reactive oxygen species (ROS), including superoxide, hydrogen peroxide and hydroxyl radical ($\text{OH}\bullet$), are converted directly or indirectly from free oxygen but are more chemically reactive. The low-to-moderate ROS level is indispensable to normal cellular proliferation, differentiation and survival. The net emission of ROS depends upon the balance between free radical production (pro-oxidative process) and its elimination by antioxidants (antioxidant defense process)

- Peroxiredoxins (PRDXs), a family of this kind of antioxidants, are classified on the basis of having either one (1-Cys) or two (2-Cys) conserved cysteine residues . PRDX1 is a member of the 2-Cys PRDXs subfamily and is present mainly in the cytosol . PRDX1 containing a cysteine at the N-terminal Cys52 detoxifies peroxides at the expense of Cys52 oxidation through intermolecular disulphide formation with the other conserved C-terminal Cys173 residue . Oxidized PRDX1 could be converted to its active form by various mechanisms .

- PRDX1 was firstly reported as an antioxidant enzyme, but its physiological role in oxidization–reduction balance remains unclear because it is highly susceptible to oxidative stress. Upon peroxidatic Cys oxidation, 2-Cys PRDX1 is structurally converted from a peroxidase enzyme to a molecular chaperone under stress conditions . In addition to its peroxidase and chaperone functions, PRDX1 could also enhance natural killer cell cytotoxicity and suppress oncogenic proteins .

- Recent studies have shown that abnormal expression of PRDX1 has been observed in several human cancers, including breast, oesophageal, lung and prostate cancers . Furthermore, PRDX1 also regulates several ROS-dependent signalling pathways and is thought to be a key intracellular intermediate balancing cell survival and apoptosis

Structure, functions of PRDX1 and its role in ROS-dependent signalling

- Mammalian PRDXs are divided into three categories based on their number of conserved Cys residues and catalytic mechanism: 2-Cys PRDXs (PRDX1–4), atypical 2-Cys PRDX (PRDX5) and 1-Cys PRDX (Prx6) . All PRDXs contain a thioredoxin fold with a few additional secondary structure elements present as insertions . PRDX1 contains a conserved Cys52 at the N-terminal and a conserved Cys173 at the C-terminal . PRDX1 is domain-swapped homodimers in which the C terminus of one subunit reaches across the dimer interface to interact with the other subunit . In addition, PRDX1 crystallized as toroid-shaped complexes consisting of a pentameric arrangement of dimers , consistent with observations that PRDX1 dimers can form discrete higher-order oligomers

Genomic studies in cancer

- DNA amplification or chromosomal losses is a common mechanism leading to oncogenic activation in human cancers. PRDX1 gene is located on chromosomal band 1q34.1. Loss of heterozygosity (LOH) of 1q has been suggested in tumour progression . Mice lacking PRDX1 develop severe haemolytic anaemia and various types of malignancies, indicating that PRDX1 functions as a tumour suppressor

The identification of PRDX1 as a potential oncogene was reported in the cases of lung adenocarcinomas , colorectal cancer and soft tissue sarcomas . 1q is amplified in approximately 35.5% of lung cancer , and the PRDX1 expression is significantly elevated in lung cancer patients as compared with patients with benign lung disease

PRDX1 and breast cancer

- The specific role for PRDX1 in mammary carcinomas is controversial. PRDX1 protein was found to be overexpressed in breast cancer tissues from most patients compared with normal tissues, but no significant relationship was found between PRDX1 levels and clinicopathological factors, including oestrogen receptor (ER) status .
- Similar to these data, Wang X et al. found that PRDX1 is more abundant in breast cancer cell lines (including ER+ and ER-) than in normal or pseudonormal breast cell lines, but not found a significant difference in PRDX1 levels between ER+ and ER- breast cancer cell lines

- Biomarker studies have confirmed that PRDX1 is one of the diagnostic biomarkers for invasive ductal carcinoma of breast with human epidermal growth factor receptor-2 (HER2)-enriched subtypes , and PRDX1 protects ERα from oxidative stress-induced suppression and is a protein biomarker of favourable prognosis in mammary tumours

PRDX1 and oesophageal cancer

- Similar to breast cancer, the functions of PRDX1 in oesophageal cancer remain enigmatic. Proteomic study has found that the expression level of PRDX1 is elevated in oesophagus squamous cell carcinoma (ESCC) tissue . Further study demonstrated that PRDX1 is significantly increased in ESCC tissues compared with the paired adjacent normal tissues . In addition, several studies have identified that PRDX1 is overexpressed in ESCC cells compared with the noncancerous oesophageal epithelial cells . Elevated PRDX1 promotes tumourigenesis through regulating the activity of mTORp70S6K pathway in ESCC

PRDX1 and lung cancer

- Previous studies have shown that PRDX1 is expressed at significantly higher levels in lung cancer tissues compared with normal lung tissues , and elevated PRDX1 associated with shorter survival in nonsmall cell lung cancer (NSCLC) . Furthermore, PRDX1 is upregulated in NSCLC tissue interstitial fluid, and high level of PRDX1 expression is related with lymph node metastasis and tumour differentiation, suggesting that PRDX1 may act as a marker of neoplastic progression .

RDX1 and prostate cancer

- PRDX1 overexpression is also found in human prostate cancer specimens and prostate cancer cell lines . Prostate cancer risk and prognosis are adversely associated with a number of inflammatory and angiogenic mediators, including Toll-like receptor 4 (TLR4), NF- κ B and VEGF . Elevated PRDX1 increases prostate tumour vasculature, and shows up-regulation of angiogenic proteins such as VEGF in the tumour region.

Conclusion and future perspectives

- As discussed above, the expression and functional roles of PRDX1 in many human tumours remain controversial , and further researches need to be done to reveal its underlying role in the progression and metastasis of cancer. In spite of the various functions of PRDX1 in cancers, we could acutely discover that when PRDX1 acts as antioxidant enzyme but not chaperone, it plays a positive role in radio/chemoresistance