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The Sulfiredoxin-Peroxiredoxin (Srx-Prx) Axis in Cell Signal Transduction and Cancer Development

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Abstract

Redox signaling is a critical component of cell signaling pathways that is involved in regulation of cell growth, metabolism, hormone signaling, immune regulation and variety of other physiological functions. Peroxiredoxin (Prx) is a family of *thiol-based peroxidases* that acts as a regulator of redox signaling. Members of Prx family can act as antioxidants and chaperone. Sulfiredoxin (Srx) is an antioxidant protein that exclusively reduces over-oxidized *typical 2-Cys Prx*. Srx have different affinities for individual Prx and it also catalyzes deglutathionylation of variety of substrates. Individual components of *Srx-Prx system* play critical roles in carcinogenesis by modulating cell signaling pathway involved in cell proliferation, migration and metastasis. Expression levels of individual components of Srx-Prx axis has been correlated with patient survival outcome in multiple cancer types. This review will summarize the molecular basis of differences in affinity of Srx for individual Prx and the role of individual components of *Srx-Prx system* in tumor progression and metastasis. This enhanced understanding of molecular aspects of Srx-Prx interaction and its role in cell signal transduction will help in defining *Srx-Prx system* as a future therapeutic target in human cancer.

Keywords

Sulfiredoxin; Peroxiredoxin; Redox signaling; Tumorigenesis; Oncogene

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Conflict of Interest Statement

None

Introduction

Redox signaling is an essential component of various cellular processes that maintain physiological homeostasis in eukaryotes as well as prokaryotes. The intracellular activity regulated by the reactive oxygen/nitrogen species (ROS[1]/RNS) includes (but is not limited to) growth factor such as EGF [1] and IGF [2] signaling as well as important energy metabolism and hormonal signaling [3]. ROS/RNS have very short half-life partly due to their highly reactive nature and the presence of antioxidants in host organisms. Abnormal accumulation of ROS/RNA leads to oxidative stress, which is known to cause multiple disorders in human, such as diabetes, Alzheimer's & Parkinson's disease, hepatic diseases, and cancer [4] [5]. Antioxidants are *internal housekeeping* (expressed in intracellular or extracellular compartments of animal tissue) or *external* (part of daily diet or supplements) molecules that get preferentially oxidized under oxidative stress conditions. The biological system expresses multiple antioxidant molecules at intracellular as well as extracellular sites to protect it from oxidative damages. *Thiol-based antioxidants* are major internal housekeeping antioxidant molecules that acts as redox switches to modulate homeostasis [6]. Peroxiredoxins (Prx) as well as Sulfiredoxin (Srx) are part of *thiol-based antioxidant* system.

Prx was first discovered about 27 years ago in yeast [7]. These proteins were given multiple names, for example, '*Protector protein*', '*Thiol-specific antioxidants (TSA)*', '*Thioredoxin-linked thiol peroxidase*' and '*Thioredoxin peroxidase (TPx)*' before they are widely accepted as '*Peroxiredoxin*' [7; 8; 9; 10; 11; 12]. Prx is a class of *thiol-based peroxidases* ubiquitously found in prokaryotes as well as eukaryotes. There are six different isoforms of Prx expressed in human [13]. These Prxs are involved in the regulation of cell proliferation, apoptosis, embryonic development, lipid metabolism, immune response etc. [14]. All human Prxs have the enzymatic cysteine called *peroxidatic cysteine* (C_P) on its N-terminus. Five out of six human Prxs also contain one *resolving cysteine* (C_R) on its C-terminus. Depending on the presence and behavior of *resolving cysteine*, human Prxs are classified into three classes i.e. (i) *typical 2-Cys Prx*s including Prx1-4, (ii) *atypical 2-Cys Prx* i.e. Prx5, and (iii) *1-Cys Prx* i.e. Prx6 [15]. The Prx family of proteins reduces H_2O_2, alkyl hydroperoxides and peroxynitrite into water and other harmless metabolites. In this process, the thiol group of *peroxidatic cysteine* (C_p) is oxidized to *sulfenic acid*, which can be reduced back by *glutaredoxin* (Grx) or *thioredoxin (Trx)-thioredoxin* reductase system [16; 17]. The pKa of most biological cysteine is in the range of 8–9 if not stabilized by other factors, while the pKa of *peroxidatic cysteine* falls in a lower range of 5–6 due to the stabilization by neighboring conserved arginine and threonine residues in Prxs [18]. The lower pKa of Prxs facilitates their ability to scavenge ROS at very low levels [18]. There is no evidence that residues close to the *resolving cysteine* have similar function. Therefore, the higher pKa of resolving cysteine making it more resistant to oxidation compared with the peroxidatic cysteine. Since the rate constant of Prx-thiol oxidation is higher than most of thiol-based

[1]AP-1, Activator Protein-1; EGF, Epidermal growth factor; EMT, Epithelial-mesenchymal transition; ERK, Extracellular-signal-regulated kinases; MAPK, Mitogen-activated protein kinase; Nrf2, Nuclear factor erythroid 2-related factor 2; PRDX, Peroxiredoxin gene; Prx, Peroxiredoxin; PTEN, Phosphatase and tensin homolog; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; Srx, Sulfiredoxin; TGF-β1, Transforming growth factor beta 1; TLR, Toll-like receptor; TPA, 12-O-tetradecanoylphorbol-13-acetate; Trx, Thioredoxin; TRAIL, Tumor necrosis factor–related apoptosis-inducing ligand.

proteins, Prxs are approximately 10^5–10^7 times more efficient than other *thiol-based antioxidants* such as GSH, Thioredoxin, GAPDH, PTP1B etc [19]. Higher rate constant indicates the ability of Prx to reduce the ROS present even in minute amounts that cannot be eliminated by other antioxidants. Depending on the levels of oxidative stress and amount of Prxs present in the system, the *peroxidatic cysteine* can be over-oxidized to *sulfinic* or *sulfonic acid*, leading to the loss of their antioxidant activity [20]. This hyperoxidation of Prx is present in majority of eukaryotes and few prokaryotes such as cyanobacteria [21]. It is important to clarify that in some older literature the hyperoxidation of Prx was reviewed as unique to eukaryotes. However, the latest research have indicated occurrence of Prx hyperoxidation in prokaryotes too [21]. The hyperoxidation of Prxs helps them to function as molecular chaperone, adding additional role in protein folding besides their function as antioxidants [22]. However, the molecular basis of Prxs to function as chaperone is yet to be determined. More research needs to be carried out to identify proteins whose folding is assisted by Prx. Results of such research will further help to identify different signaling pathways that are modulated by the chaperone function of Prx. Classification of signaling pathways regulated by chaperone as well as antioxidant functions of Prx will help to design better targeting strategy against Prx in tumor cells. The chaperone function of Prxs was used to be considered only to eukaryotes, however, similar activity is also detected in the Prx homolog of prokaryotes such as *Helicobacter pylori* [23]. Experts were wondering for long time about existence of any enzyme having potential to reduce hyperoxidized Prx until Srx was identified in *Saccharomyces cerevisiae* [24] and later found to be conserved in higher eukaryotes and few species of cyanobacteria. Rate constants from two independent studies indicates that the reduction of oxidized Prx by Trx (rate constant 10^6 $M^{-1}s^{-1}$) is much faster than the rate of reduction of hyperoxidized Prx by Srx (rate constant approximately 2 $M^{-1}s^{-1}$) [25; 26]. Therefore, reduction of hyperoxidized Prx by Srx can be considered as a rate limiting step in reduction of hyperoxidized Prx. Closest prokaryotic counterpart of Srx is a functionally unrelated protein called ‘ParB’ in bacteria, which carries out function of chromosome partitioning [27]. *Oncogenic suppressive activity* or ‘Osa’ protein is probably a connecting link between ParB and Srx. Osa contains both DNAse [18] of ParB as well as ATPase domain of Srx [28]. In normal human tissues, Srx is present in kidney, lungs, and pancreas [29]. Srx is mainly a cytosolic protein that can be translocated into mitochondria under oxidative stress conditions [30]. In this manner, Prx along with Srx play an important role in the management of mitochondria redox balance.

The Srx-Prx axis can be explored as therapeutic target as well as therapeutic tools depending on their role in particular pathological condition. For example, individual Prx isoforms can be considered as good therapeutic targets in lung cancer [31], glioblastoma [32], colorectal cancer [33], prostate cancer [34] etc. where they protect tumor cells. It is important to evaluate the *risk-benefit ratio* of targeting the individual members of Srx-Prx axis as they also have protective role in normal (non-tumor) tissue. The Srx null mice have normal phenotype under laboratory conditions [33]. Prx3 knockout mice also born and mature normally [35]. Prx4 knockout mice have mild prostate atrophy [36]. Prx1 & Prx2 knockout mice are reported to have some issue with erythropoiesis [37; 38]. Hence, majority of proteins in Srx-Prx axis can be knocked-out without any life threatening issue. Considering the risk associated with cancer, it is worth exploring a target that can prolong the lives of

patients by few extra years. Hence, benefits associated with targeting Srx or individual Prx outweighs the risk associated with it and Srx-Prx system can be considered a therapeutic target in cancer. On the other hand, individual Prx isoforms can be explored as therapeutic or diagnostic tools in Parkinson's disease, Alzheimer's disease, and diabetic complications [39; 40; 41]. These differential properties of individual components of the *Srx-Prx system* draw our attention towards differences in molecular properties of individual Prx isoforms that gives them ability to play such diverse roles. Improved understanding of these molecular differences will help us in therapeutic intervention of the *Srx-Prx system*.

Enzymatic roles of Srx

Human Srx has a length of 137 amino acids [42]. Srx is present in mammals, birds and multiple (*not all*) other eukaryotic organisms and few prokaryotes [43]. It is an exclusive enzyme that acts as an antioxidant to reduce sulfinic acid form of *typical 2-Cys Prx* [44]. Biteau B *et al* (2003) identified how ATP-bound yeast Srx in the presence of Mg^{2+} approaches the hyperoxidized Prx, phosphorylates it and form thiosulfinate intermediate, which can be further reduced by other thiol reducing enzymes [24]. Yeast Srx has two cysteines where the first cysteine (Cys^{48}) helps the enzymatic cysteine (Cys^{84}) by recycling the thiosulfinate intermediate [45]. However, human Srx have only one cysteine i.e. Cys^{99} (a homologue of Cys^{84} of yeast). Therefore, it needs an external source of thiol such as thioredoxin (Trx) or Glutathione (GSH) to reduce the thiosulfinate intermediate [45; 46]. The evolution of an ATP consuming process to reactivate Prx after deactivation of its peroxidase function by H_2O_2 have given a unique advantage to host organism where H^2O^2 and Srx acts as an *On-Off switch* for chaperone and peroxidase function of various Prxs. The excess of H_2O_2 enhances the chaperone function and reduces the peroxidase function of Prx whereas excess of Srx reverses this process [47]. Figure 1 depicts the mechanism by which Srx performs aforementioned antioxidant function. The Prx structure in this figure is designed to give rough idea about the positions of individual cysteines in a *typical 2-Cys Prx*. The C-terminal *resolving cysteine* is shown in C-terminal arm and the other cysteine in Prx indicates the N-terminal *peroxidatic cysteine*.

Another important action of Srx involves the deglutathionylation of several substrates in eukaryotes [42]. Most of the Prx-independent and few Prx-dependent functions of Srx is mediated by this mechanism. Figure 2 depicts role of Srx in deglutathionylation process. Srx can regulate the chaperone function of Prx1 by controlling its levels of glutathionylation. The glutathionylation of Cys^{83} of Prx1 favors formation of dimer over decamer, resulting in the loss of chaperone activity [48]. Although it is a general consensus that Prx-reducing activity of Srx is more important than its deglutathionylation function, more mechanistic studies are required to assess individual contribution of Prx reduction and deglutathionylation processes in regulating the chaperone function of Prx1 or another *typical 2-Cys Prx*. There is no evidence of tissue specific predominance of one function of Srx over the other. However, there is a great scope for exploration of Srx deglutathionylation function in more details and lack of extensive biochemical studies in this field may be a possible reason behind difficulty in ranking the importance of antioxidant Vs deglutathionylation functions of Srx. Unlike the antioxidant function of Srx that is exclusive to Prx, the deglutathionylation carried out by Srx seems not substrate specific. S100A4, Actin and

PTP1B are examples of substrates other than Prx whose glutathionylation levels can be regulated by Srx [22; 49]. There may be other intracellular targets of Srx that can be deglutathionylated by Srx. Identification of such substrates will help to identify different mechanisms by which Srx regulates cell signaling.

The molecular characteristics of the Srx-Prx interaction and the substrate specificity of Srx

The Cys^{99} of human Srx is not involved in the Srx-Prx binding but it is directly involved in antioxidant as well as deglutathionylation functions of Srx [44; 47; 50]. Amino acids adjacent to Cys^{99} i.e. Gly^{97}, Gly^{98}, His^{100} & Arg^{101} are considered to be supportive and are also important for the enzymatic activity of Srx [51]. Pro^{52}, Leu^{82}, Phe^{96}, Val^{118}, Val^{127} and Tyr^{128} are amino acids that form a hydrophobic pocket in Srx that acts as the interface for Srx-Prx interaction [51; 52]. The hydrophobic pocket formed by the active site of Srx forms a depression that wraps around the slightly protruding active site of Prx [51]. This model of the Srx-Prx interaction is illustrated in figure 3.

The Prx family of proteins is one of the most abundant and most efficacious antioxidants in human body. The classification of Prx is based mainly on presence and behavior of the *resolving cysteine* in different Prx isoforms [15]. Individual Prx isoforms also contains few cysteines other than *peroxidatic* and *resolving cysteine* that may play some regulatory role in particular protein. For example, Cys^{83} of Prx1 mediates formation of decameric complex of Prx1 that differentiates the functions of Prx1 from Prx2 [53]. Despite of 78% sequence similarity, one individual cysteine (Cys^{83}) of Prx1 plays such an important role which increases the efficiency of Prx1 to act as a chaperone [53]. Another report has indicated that the Cys^{83}- Cys^{83} disulfide bond formation is not essential for rat Prx1 as it can form decameric structure through hydrophobic interactions and *van der Waals* bonds [54]. Glutathionylation of Cys^{83} has been reported to negatively affect the chaperone function of Prx1 [48]. However, how the glutathionylation impacts the chaperone activity of *typical 2-Cys Prx* remains to be understood. The number of amino acids between the *peroxidatic* and *resolving cysteine* is critical for the formation of the Prx dimer. All human *typical 2-Cys Prx* have 121 amino acids between the *peroxidatic* and *resolving cysteine*, whereas in *atypical 2-Cys Prx* it is reduced to only 104 amino acid [44]. Another highly conserved feature is the distance of two cysteines from the GGLG motif, which is located between the peroxidatic and resolving cysteines and is 42 amino acids downstream of the peroxidatic cysteine. The YF motif is another feature that localized between the resolving cysteine and the N-terminus, and is 20 amino acids downstream of the resolving cysteine. GGLG and YF motif bestows these Prx with unique ability to get hyperoxidized by H_2O_2 [55]. The YF motif interacts with the GGLG motif, which causes steric hindrance for the interaction between *peroxidatic cysteine* of oxidized Prx and *resolving cysteine* of other monomer. This allows the 2^{nd} H_2O_2 molecule to react with the *peroxidatic cysteine* of the first Prx monomer in a timely manner, resulting in the formation of hyperoxidized Prx [56]. The hyperoxidation of *typical 2-Cys Prx* adds an extra chaperone function to these Prx [22]. In the absence of the GGLG and YF motifs, Prx will not become hyperoxidized, thus they are important for the chaperone function of Prx [55]. There are no reports indicating the involvement of the

GGLG and/or YF motif for the Srx-Prx interaction. The GGLG and YF motifs were also identified in prokaryotic Prxs too [21]. The chaperone function is gained by formation of higher molecular weight complexes of Prx that looks like a stack or rings in *transmission electron microscopy* and *X-ray crystallography* studies [57]. In some species, hyperoxidation of the *peroxidatic cysteine* is not absolutely necessary for the gain of chaperone function, as their Prx can form similar structure in the absence of hyperoxidation [58]. However, human Prxs have been known to gain chaperone function only after the *peroxidatic cysteine* is hyperoxidized. Also, the loss of C-terminal arm of Prx results in the loss of chaperone function [59]. Even among the *typical 2-Cys Prx*, the susceptibility to hyperoxidation varies. Prx3 is considered more resistant to hyperoxidation than other isoforms [60]. The conservation of amino acids around the *peroxidatic cysteine* probably indicates their importance for the enzymatic activity of Prx or a particular behavior of a Prx isoform. For example, most Prxs have a Proline and a Threonine (occasionally Serine) before the *peroxidatic cysteine*, which results in a P*XXX*T*XX*C motif that may be importance for the enzymatic activity of Prx [61]. In human *typical 2-Cys Prxs*, amino acids around the *peroxidatic cysteine* (i.e. PLDFTFVCPTEI motif) and the *resolving cysteine* (i.e. HGEVCPAXW motif) are highly conserved [62], which may indicate their importance [63]. However, the significance of these amino acids has not been experimentally proved yet and it may be of interest for further studies..

Although all *typical 2-Cys Prx* are generally considered as substrate of Srx, the affinity of Srx to individual Prx is not the same [31]. Data from our lab suggest that the orientation of C-terminal arm of Prx may affect the affinity of Srx for individual Prx (*unpublished*). Srx have highest affinity for Prx4 among all the *typical 2-Cys Prx* [31]. However, it still needs to be studied how this high affinity of interaction affects the kinetics of Prx4 reduction compared to other Prx. Members of the Prx family may have different subcellular localization, and their abundance in different tissues also varies. The interaction between Srx and different isoform of Prx is thus also affected by their subcellular localization. For example, Srx-Prx3 interaction is not significant under low oxidative stress conditions due to mitochondrial location of Prx3, however, this interaction becomes significant under higher oxidative stress conditions where mitochondrial membrane is damaged and hence Srx gets a chance to translocate from cytosol to mitochondria [30]. An alternative explanation of this phenomena is that, Prx3 can get over-oxidized only at higher oxidative stress levels due to its high resistance to over-oxidation [60]. Probably some molecular characteristics of Prx3 do not allow Srx-Prx3 interaction under reduced conditions and interaction is possible only after molecular rearrangements during the oxidation or over-oxidation of Prx3. However, more mechanistic studies are required to clarify whether this is the case, or Srx can bind to Prx3 only in its oxidized/over-oxidized state. All these molecular factors affect the signaling of the Srx-Prx axis. Differential affinity of Srx for individual Prx as well as molecular characteristics of individual Prx allow them to regulate a myriad range of cell signaling.

The Srx-Prx axis in tumorigenesis and cancer progression

The main function of the *Srx-Prx system* is to protect host cells from oxidative damages. This property of the *Srx-Prx system* becomes harmful to host organism when it starts protecting the survival of tumor cells. As per the data from *Oncomine (an online microarray*

database) [64] and other published literature, the *Srx-Prx system* is altered in multiple types of cancer. Table 1 summarizes different types of cancer in which expression of individual members of *Srx-Prx system* is altered. The information in Table 1 indicates changes in mRNA expression. The up-regulation indicates more than 1.5 fold increase in mRNA levels whereas down-regulation indicates more than 1.5 fold decrease in mRNA levels. Apart from table 1, we also notice the alterations at the protein level. The information about expression changes at places other than table 1 are mainly based on studies of their protein levels. The correlation between patient survival and protein expression changes has not been studied. From published data in literature, the Srx-Prx system predominantly functions as activators or enhancers of oncogenic signaling to promote cancer development. There are also studies reporting that members of Prxs repress cancer development by acting as tumor suppressors, suggesting that Prx may function as double-edged sword in tumorigenesis. Therefore, the exact role of individual component of the *Srx-Prx system* in cancer can be complicated, and should be considered under specified context of cancer and cell types..

Srx in cell-signal transduction and tumorigenesis

The expression of Srx is regulated by different factors at both transcriptional and translational levels. Redox signaling is the major component that activates Srx expression. Figure 4 summarizes how the expression of Srx is regulated by redox signaling. Activation of transcription factors, such as *nuclear factor erythroid 2-related factor 2* (Nrf2), induce Srx expression [65]. *Activator Protein-1* (AP-1) also up-regulates Srx expression [66]. c-Jun is a component of AP-1 complex and its activation stimulates Srx expression. *TAM67* is an N-terminal deletion mutant of c-Jun and it acts as a c-Jun antagonist. Therefore, *TAM67* can negatively regulate Srx expression by inhibiting the activity of AP-1 complex [67]. Multiple intracellular as well as extracellular factors such as nitric oxide (NO), cigarette smoke, dietary derived electrophiles and tumor promoters like *12-O-tetradecanoylphorbol-13-acetate* (TPA) that lead to the activation of nrf2 or AP-1 have the potential to stimulate the expression of Srx [67; 68]. In mouse macrophages, treatment with lipopolysaccharide strongly induces Srx expression in an Nrf2 and AP1 dependent manner, and the absence of either significantly affect the levels of Srx induction [69]. Besides aforementioned transcriptional regulation, Srx expression is negatively regulated at translational level by *cAMP-PKA* (*cyclic AMP-Protein kinase A*) through the *elF2 kinase Gcn2* [70].

Srx is over-expressed in a variety of cancer and it may promote carcinogenesis in Prx-dependent as well as independent manner [31; 49]. It promotes tumor progression in lung cancer by enhancing intracellular phosphokinase signaling such as *mitogen-activated protein kinase* (MAPK) and AP-1/MMP9 (*Matrix metalloproteinase 9*) signaling in Prx4-dependent manner [31]. It may also enhance cell migration in lung cancer in a Prx-independent manner by interacting with S100A4 (*a calcium binding protein*) and *non-muscle myosin IIA* (NMIIA) [49]. Aberrant expression of Srx in lung squamous cell carcinoma, lung adenocarcinoma, and pancreatic cancer is correlated with poor survival in those patients [71; 72; 73]. Srx protein is also over-expressed in renal cell carcinoma where it is proposed to be a good antibody target that can result in tumor cell death [74]. Srx expression is stimulated by TPA via MAPK/JNK (*c-Jun N-terminal kinase*) pathway in skin carcinogenesis and Srx depletion at least partially protects mice against DMBA(*7,12-dimethylbenz[a]anthracene*)/

TPA-induced skin carcinogenesis [75]. Srx is also necessary for colon carcinogenesis as it is highly over-expressed in colon tumor tissue compared to normal human colon, and Srx null mice are highly resistant to *azoxymethane/dextran sulfate sodium*-induced colon carcinogenesis [33]. Although the importance of Srx in various tumor types is well established, we still need a lot of research to understand the mechanism by which Srx plays its role in tumor progression and metastasis. Considering lung cancer as an example, the antioxidant and deglutathionylation activities of Srx may work in tandem to enhance the chances of tumor promotion and metastasis [31; 49]. However, more studies are required before we can rank their individual contribution towards cancer. Unraveling the mechanistic details of Srx signaling will further help us in designing a better approach to target tumors in which Srx plays an essential role.

Prx1 in cell-signal transduction and tumorigenesis

Prx1 is mainly localized in the cytoplasm, but can also be found in the nuclear [76]. The expression of Prx1 is regulated at both transcriptional as well as post-transcriptional levels. At the transcriptional level, Nrf2 directly activates its expression [77]. *Focal Adhesion Kinase* (FAK) is also reported to be involved in transcriptional regulation of Prx1 [78]. In one study, Prx1 null mice were shown to be prone to spontaneous tumor development [37], suggesting that Prx1 may function as a tumor suppressor However, Prx1 null mice developed in another lab are normal and free of tumor development [79]. The tumor suppressor function of Prx1 may be mediated by its regulation of PTEN levels as indicated in a mouse breast cancer model [80]. Also, PTEN null mouse embryonic fibroblasts are resistant to ROS mediated induction of Prx1/Prx2 expression [81]. Prx1 may also be required for the ROS mediated activation of the K-Ras/ERK pathway that contributes to lung tumorigenesis [82]. Moreover, Prx1 along with Prx4 play essential roles in the regulation of c-Jun and AP-1 mediated promoter activity in lung cancer cells [83], and activation of Prx1 by *histone deacetylase inhibitor FK228* result in induction of apoptosis in esophageal tumor cells [84]. Furthermore, Prx1 helps reactivate DEP-1, a protein tyrosine phosphatase that functions as tumor suppressor,) by reducing the levels of ROS [85]. Aforementioned mechanisms are few example mechanisms by which Prx1 acts as a tumor suppressor.

On the other hand, there are many reports indicating that Prx1 has an essential pro-oncogenic role in cancer. For example, Prx1 promotes the *vascular endothelial growth factor* (VEGF) expression in *Toll-like receptor 4* (TLR4)-dependent manner. This effect of Prx1 enhances angiogenesis and results in an environment favorable for tumor cell proliferation and promotes tumor progression in prostate cancer [86; 87]. Prx1 is over-expressed in esophageal cancer cells and has an auto-immunogenic activity [88]. Prx1 protein is also found aberrantly increased in early stage endometrial cancer where its functional significance is yet to be established [89]. Prx1 induces TRAIL (*tumor necrosis factor–related apoptosis-inducing ligand*) resistance by suppressing the redox-dependent activation of caspase [90]. TRAIL is a biological agent that induces apoptosis of cancer cells and is considered a promising anticancer agent [91]. Down-regulation of Prx1 using RNA interference or chemical agents like dioscin results in the induction of apoptosis in tumor cells [92; 93]. Also, in A549 lung adenocarcinoma cells Prx1 enhances the TGF-β1 induced

epithelial-mesenchymal transition (EMT) by stimulating the expression of snail and slug, two transcription factors that inhibits E-cadherin expression [94]. For this function, the Cys^{51} (peroxidatic cysteine) of Prx1 is essential as replacement of Cys^{51} by Ser nullifies such effects [94]. Another study using murine hepatocytes as well as human esophageal and lung cancer cell lines reports that the TGF-β1 enhances the ROS production by up-regulating the levels of ferritin heavy chain (FHC) and intracellular labile iron pool (LIP) [95]. It can be inferred from these studies that ROS produced by TGF-β1 signaling probably oxidizes the peroxidatic cysteine of Prx1 and this oxidation is essential for role of Prx1 in EMT. Therefore, higher levels of ROS may promote of the progress of EMT. On the other hand, oxidation of Prx1 will reduce the levels of ROS. Whether and how the hyperoxidation of Prx1 and its molecular chaperone activity are involved in the process of EMT are largely unknown. Figure 5 depicts how Prx can perform both tumor suppressor as well as oncogenic functions. However, the factors that determine the dominance of one role over other are yet to be studied in more details. It is possible that Prx1 functions as a tumor suppressor before the transformation of a normal cell to tumor, but after transformation it promotes tumor cell proliferation by protecting them from ROS-induced cell death. Other possible explanations may be related with the *single nucleotide polymorphism* (SNPs) or allelic variants of Prx1 but none of these factors have been investigated in detail in the literature.

Prx2 in cell-signal transduction and tumorigenesis

Prx2 is the 2nd member of the *typical 2-Cys Prxs* that are mainly present in cytosol [76]. It is one of the most efficient H_2O_2 scavenger in cell compared to majority of other antioxidants [96]. In red blood cells (RBCs), the oxidation-reduction cycle of Prx2 correlates with the circadian rhythm, which results in circadian rhythm dependent oligomerization of Prx2 [97]. This oscillation in levels of hyperoxidized Prx2 is not controlled at the transcriptional level since RBCs do not have a nucleus [97], and is not likely controlled by Srx as the oscillations existed in Srx null mice [98]. It is rather controlled by hemoglobin autoxidation and 20S proteasome in RBCs [98]. Extensive methylation of CpG islands in the promoter region of the Prdx2 gene is one of the mechanisms to control Prx2 expression in melanoma [99]. Prx2 expression is also regulated by transcription factor *Hand1/Hand2* [100]. In mouse embryonic fibroblasts, Prx2 is induced by ROS in a PTEN dependent manner [81]. As mentioned earlier, the PTEN activation itself is regulated by Prx1, therefore, it can be assumed that Prx1 may have potential to affect Prx2 expression too. Prx2 is down-regulated in few cancers where Prx1 is up-regulated, but the exact mechanism behind these differential expression is not available yet [101; 102]. Whether or not PTEN is responsible for this relationship between Prx1 and Prx2 expression in those tissues, is still a question. Nitrosylation of Tyr^{193} in the YF motif of Prx2 is an important post-translational modification that plays a critical role in the regulation of disulfide bond formation under oxidative stress conditions [103]. Glutathionylation is another post-translational modification of Prx2, which may affect its localization to extracellular compartment [104]. The extracellular glutathionylated Prx2 induces the TNFα production and leads to oxidative stress dependent inflammatory reaction [104]. In this manner, Prx2 plays a role in cytokine mediated inflammatory signaling. The serum levels of Prx2 in colorectal cancer are correlated with the survival of patients [105]. In human papillomavirus (HPV) related cervical cancer, increased expression of Prx2 is proposed to mediate the carcinogenesis in

cervical tissue [106; 107]. However, more studies are required to establish whether the alteration of Prx2 is a cause or effect of carcinogenesis. Prx2 is the main factor determining the metabolic stress and oxidative stress response of breast cancer cells metastasized to lung [108]. It also regulates the activation of transcription factor STAT3 by transferring the oxidative equivalents to later resulting in the generation of disulfide-linked inactive STAT3 oligomer [96]. Prx2 reduces the chances of metastasis by negatively regulating Src/ERK activation, resulting in increased E-cadherin expression and β-catenin retention [109]. Prx2 overexpression also reduces the chances of TGF-β1 induced EMT and cell migration in colorectal cancer cells [110]. It is interesting to note that the effect of Prx2 on TGF-β1 induced EMT in colorectal cancer cells is exactly opposite to the effect of Prx1 on same signaling pathway in A549 cells, which is discussed earlier in this review and depicted in figure 5. However, it is not clear yet whether these activities are regulated in a tissue-specific manner or they co-exist in same cancer type too.

Prx3 in cell-signal transduction and tumorigenesis

Prx3 is primarily a mitochondrial Prx. The expression of Prx3 is enhanced by SirT1 in partnership with FoxO3a and PGC1α, and the absence of either leads to its down-regulation [111]. SirT1 enhances the complex formation of FoxO3a with PGC1α and this complex regulates the Prx3 as well as multiple other antioxidant protein expressions [111]. Prx3 expression is also regulated by *superoxide dismutase* (SOD) through an unknown mechanism [112]. Prx3 is a downstream target of c-Myc transcription factor and it acts as a major mediator for the regulation of C-Myc functions in cell transformation, tumor progression and apoptosis [113]. In medulloblastoma, Prx3 is a target of MiR-383 (a microRNA), and its expression reduces cell proliferation [114]. In cervical cancer, Prx3 is over-expressed and its levels are correlated with increased rate of cell proliferation [115]. SNP *RS7082598* of PRDX3 gene is correlated with a reduced risk of cervical cancer [116]. In lung squamous cell carcinoma, Prx3 is over-expressed along with increased Srx in an Nrf2 dependent manner, which indicates a potentially important role of the *Srx-Prx3 axis* in these tumors [71]..

Prx4 in cell-signal transduction and tumorigenesis

Prx4 is the 4th member of *typical 2-Cys Prx* family which resides mainly in endoplasmic reticulum (ER). There is also a low molecular weight secretory form of Prx4, which can be found in extracellular matrix and plasma. Although there are few reports about the post-transcriptional regulation of Prx4, how this protein is regulated at the transcriptional level is yet to be studied. Calpain (*a calcium-dependent cysteine protease*) can enhance the expression of Prx4 through post-transcriptional regulation [117].

Besides its regular antioxidant function, Prx4 also mediates the oxidative folding of various endoplasmic reticulum proteins through its chaperone function, which may accomplished through the cooperation of protein disulfide isomerase (PDI) [118]. Data in our lab indicate that Prx4 is susceptible to hyperoxidation at very low levels of oxidative stress (*unpublished*), which may facilitate its molecular chaperone function. Prx4 improves insulin synthesis by enhancing the endoplasmic reticulum folding of insulin and thus improves pancreas β-cell function [119]. In pancreatic cancer, Prx4 is reported to be downregulated

[64]. However, it is not clear whether the Prx4 downregulation is a cause or effect of pancreatic cancer. Expression of Prx4 promotes the metastatic potential of lung adenocarcinoma cells [83]. Prx4 along with Srx increases RAS-RAF-MEK signaling by enhancing intracellular phosphokinase signaling [31]. RAS-RAF-MEK pathway is well known for controlling cancer cell proliferation and metastasis in various types of cancer. Therefore, the ability of Srx-Prx4 system to modulate this pathway indicates their importance in cancer development. The exact mechanism by which Srx or Prx4 carries out regulation of RAS-RAF-MEK pathway still needs to be identified. Theoretically, an ROS dependent mechanism may be involved since Srx restores the antioxidant function of Prx4 [31]. Moreover, Prx4 is a downstream mediator of Srx in lung cancer development, which is demonstrated by the recapitulation of reduced tumor phenotypes in Srx knockdown cells by knockdown of Prx4 (i.e. reduction in anchorage independent colony formation, cell migration, and invasion) [31]. There are other few *typical 2-Cys Prx* isoforms that may have similar effect in other pathological or physiological conditions, but such a strong relationship of Srx and Prx4 in lung cancer has not been reported before. Furthermore, Prx4 is over-expressed in the majority of cancers where Srx is overexpressed (Refer to Table 1) [64]. In prostate cancer, over-expressed Prx4 enhances the rate of cell proliferation [120]. In oral cavity squamous cell carcinoma, expression of Prx4 enhances cancer metastasis [121]. In colorectal cancer, high expression of Prx4 is correlate with poor survival of patients [122]. As mentioned before, Srx is also highly expressed in colon cancer and is required for chemical induced colon carcinogenesis [33]. Therefore, it may be of interest to study the significance of Srx and Prx4 in colon cancer.

Conclusions

Srx is an exclusive enzyme that reduces over-oxidized forms of *typical 2-Cys Prxs*. The Srx-Prx interaction plays critical roles in a variety of physiological as well as pathological conditions involving redox signaling. Molecular characteristics of Srx have been studied in great details as most of the important amino acids that are involved in the Srx-Prx interaction as well as deglutathionylation reaction are already known. However, the molecular structure of Prxs needs to be further explored to identify essential amino that impacts the formation of the Srx-Prx complex. Although some information is available about the cross-talk of the Srx-Prx axis in several signaling pathways, factors that affect these cross-talks are largely unknown and how individual isoform of Prxs contributes to different signaling pathways remains elusive. It is also necessary to differentiate the contribution of the antioxidant function of Prx and its molecular chaperone function in terms of impacting signaling transduction. Prx is clearly shown to play protective role in cardiovascular and neurological diseases. However, its role in cancer is still controversial due to both tumor-suppressor as well as oncogenic roles played by Prx isoforms in different cancer types. Special attention need to be paid to mechanism by which same Prx isoform can play different and sometimes opposite roles in different cancer types. Post-translational modifications of Prx may be one of the mechanisms that contribute to the dual behavior of Prx. Other possible explanations may include the presence of allelic variants or *single nucleotide polymorphism* of the Prx genes. More in-depth mechanistic studies in the future

will help to unravel the interweaved behavior of Prxs and lead to the development of better therapeutic strategies for cancer prevention or treatment.

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Highlights

- Specificity of individual Prx signaling is determined by minor molecular changes
- Difference in Srx-individual Prx affinity is defined by their molecular differences
- All enzymatic activities of Srx/Prx collaborates to maintain cellular homeostasis
- Srx-Prx axis regulates carcinogenesis through modulation of cell-signaling pathways
- Srx-Prx axis is a promising therapeutic target in variety of human cancers

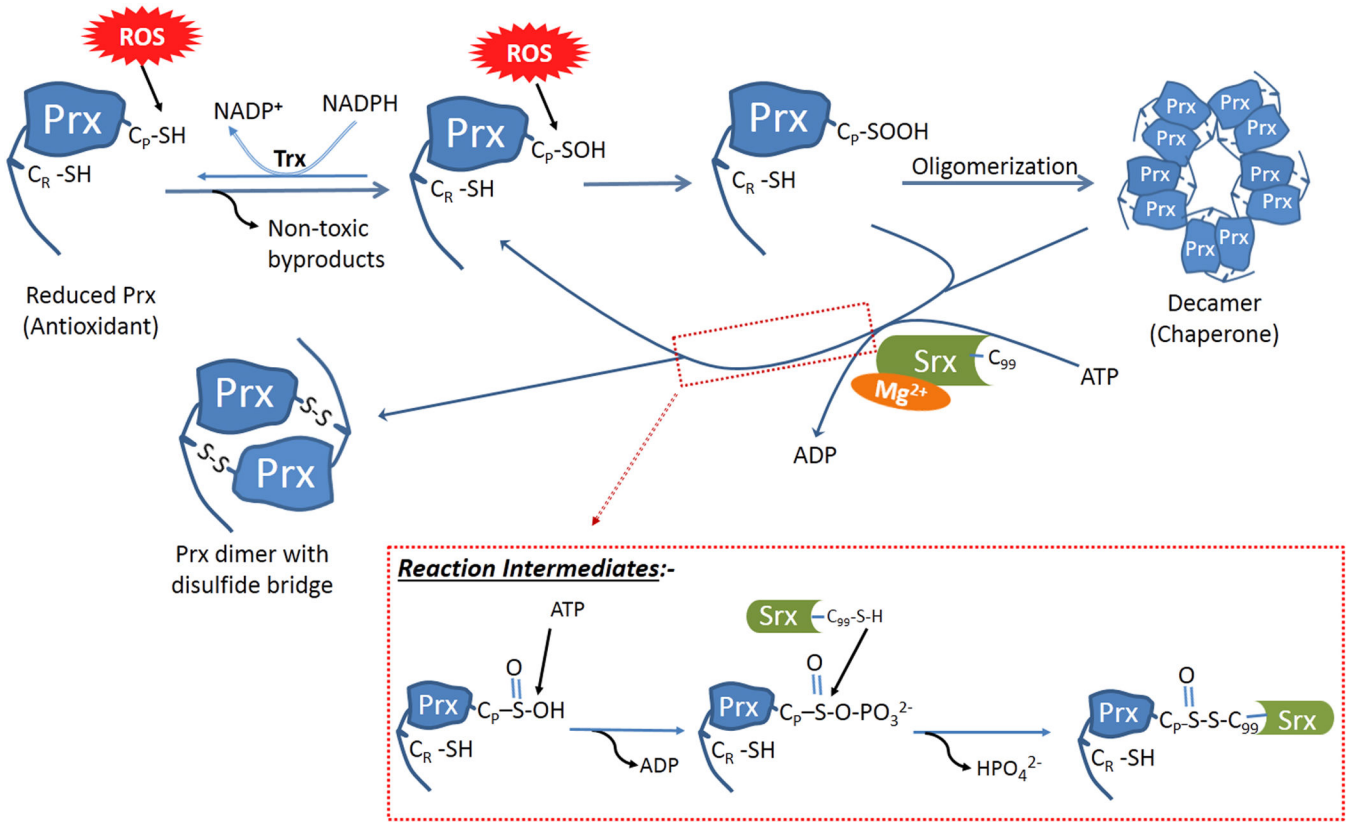

Figure 1.

Sulfiredoxin specifically reduces hyperoxidized form of typical 2-Cys peroxiredoxins and acts as an on-off switch to keep the balance between antioxidant and chaperone function of Prxs.

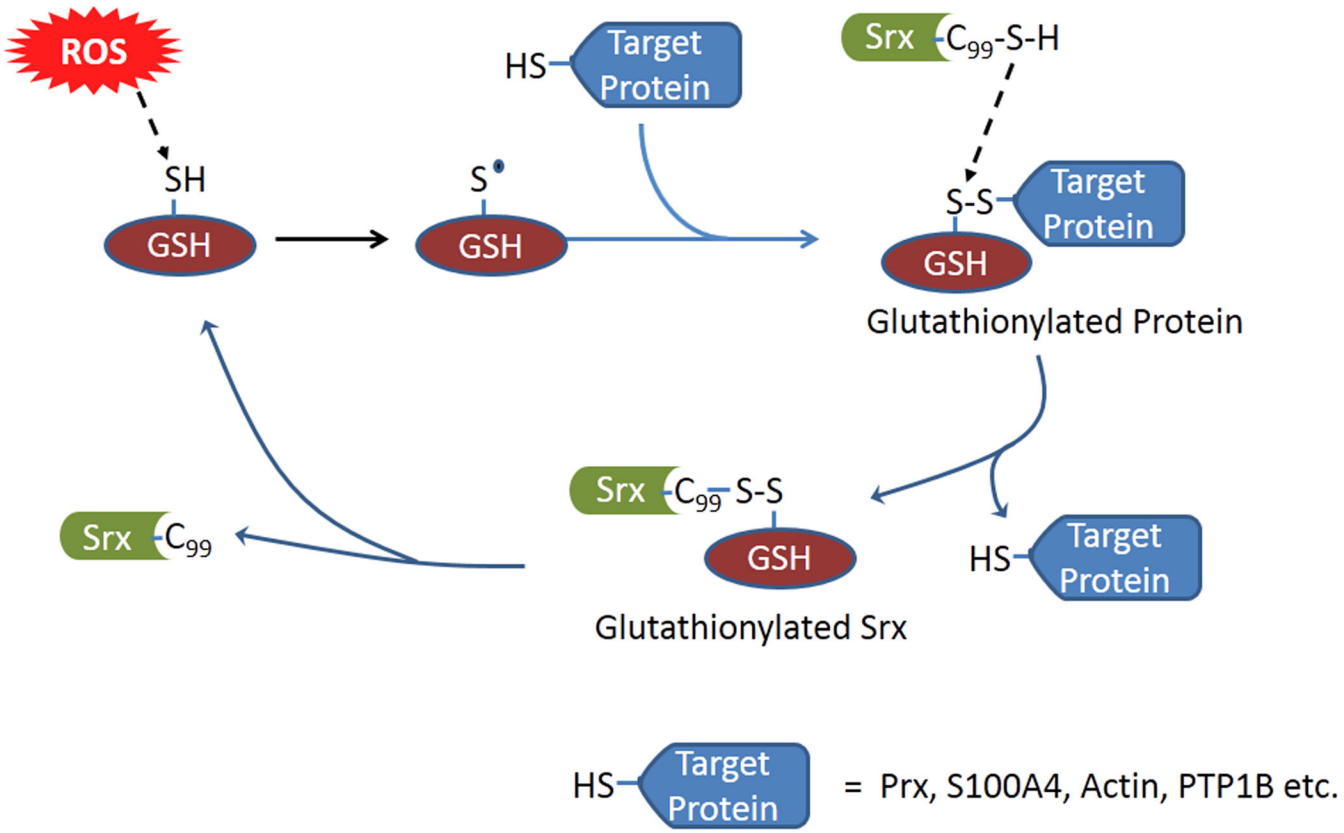

Figure 2.
Sulfiredoxin catalyzes deglutathionylation of a variety of substrates.

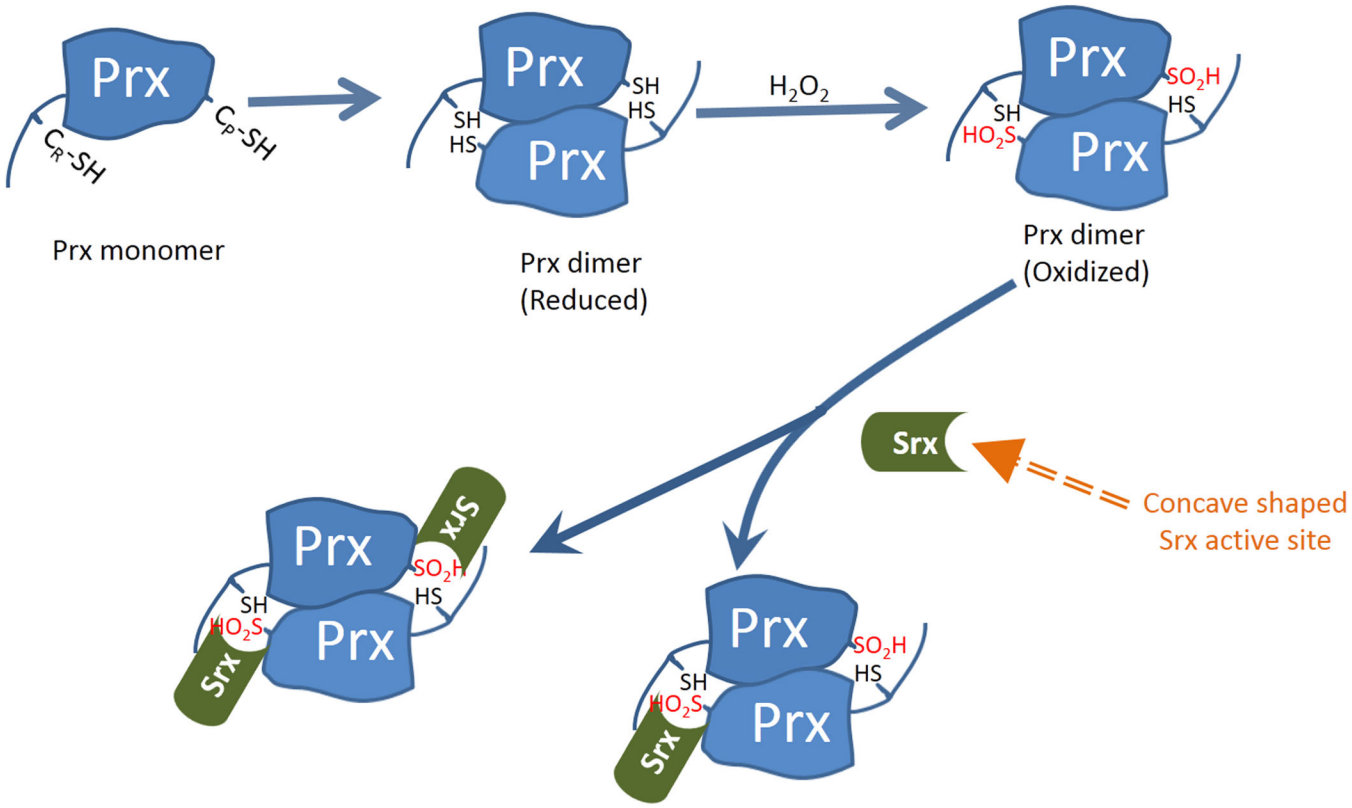

Figure 3.

A *model* of Srx-Prx interaction showing how concave shaped active site of Srx interacts with Prx dimer.

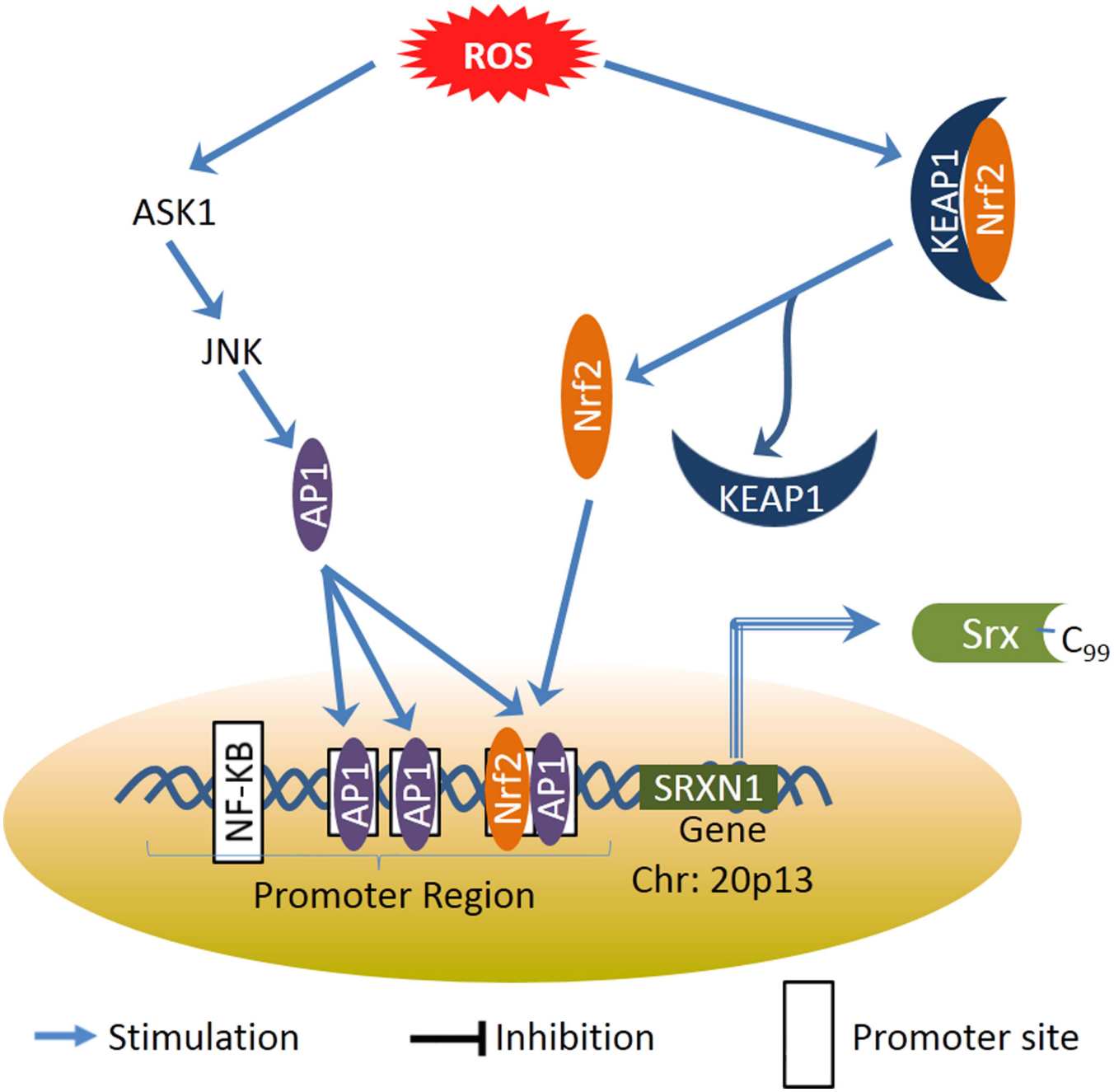

Figure 4.
Oxidative stress stimulates Sulfiredoxin expression by regulating AP-1 and Nrf2 activity.

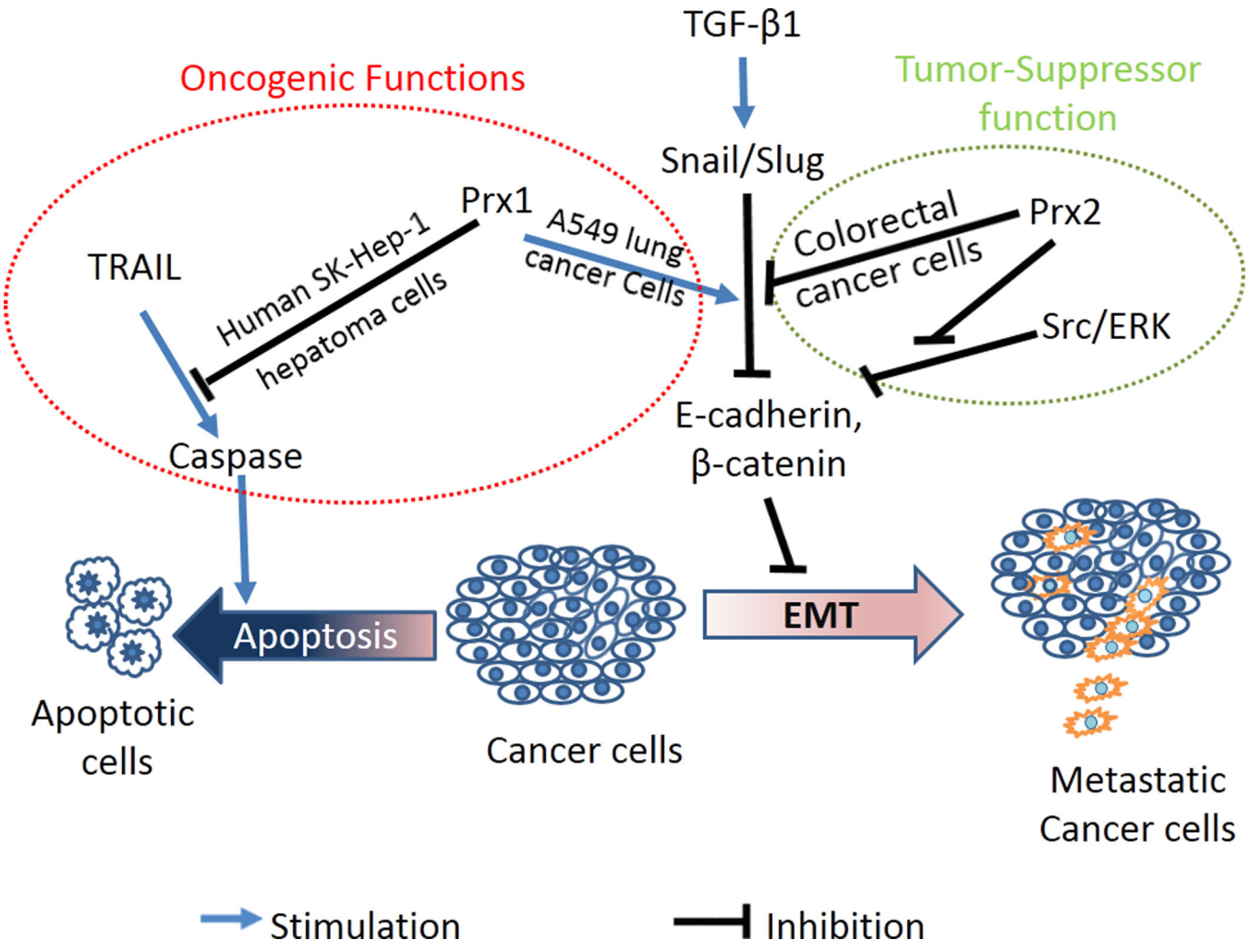

Figure 5.
Peroxiredoxin may act as tumor-suppressor or oncogene depending on the context of tumor type.

Table 1

Expression pattern of *Srx-Prx system* in different cancer types as evident from microarray data available at Oncomine online microarray dataset; Up-regulation is classified as more than 1.5 fold increase in expression compared to normal non-tumor cells; Down-regulation is classified as more than 1.5 fold decrease in expression compared to normal non-tumor cells. Data summarized here is the one that could be confirmed by other independent studies.

Protein	Up-Regulation	Down-regulation
Srx	Breast cancer, Colorectal Cancer, Lung Cancer, Prostate Cancer, Skin cancer	Esophageal Cancer
Prx1	Bladder cancer, Colorectal cancer, Gastric cancer, Leukemia, Liver Cancer, Lymphoma, Breast Cancer, Pancreatic cancer, Sarcoma	Esophageal Cancer, Head & Neck cancer, Myeloma
Prx2	Colorectal cancer, Lung cancer, Lymphoma, Myeloma, Ovarian cancer	Brain & CNS cancer, Esophageal Cancer, Head & Neck cancer, Kidney cancer, Leukemia, Pancreatic cancer, Sarcoma
Prx3	Gastric cancer, Head & Neck cancer, Lymphoma, Prostate Cancer	Bladder cancer, Brain & CNS cancer, Kidney cancer, Leukemia, Pancreatic cancer
Prx4	Bladder cancer, Brain & CNS cancer, Breast cancer, Cervical cancer, Colorectal cancer, Head & Neck cancer, Kidney cancer, Lung cancer, Lymphoma, Melanoma, Prostate Cancer, Sarcoma	Leukemia, Liver cancer, Pancreatic cancer