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MINI REVIEW

PRX5 as a Redox Regulator of STAT3 Signaling in Cancer Stem Cells

Eui-Hwan Choi*

Department of Biotechnology, Korea National University of Transportation, Chungju-si, Chungbuk, Republic of Korea
*Corresponding Author: Eui-Hwan Choi. Email: ehchoi@ut.ac.kr

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ABSTRACT: Peroxiredoxin 5 (PRX5) is an atypical 2-Cys peroxiredoxin distributed across mitochondria, peroxisomes, cytosol, and nucleus. Unlike other PRX isoforms, PRX5 acts not only as a reactive oxygen species (ROS) scavenger but also as a redox-dependent regulator of oncogenic signaling. Cancer stem cells (CSCs) maintain low intracellular ROS to preserve self-renewal and drug resistance, and PRX5 has emerged as a key mediator of this redox control. This review examines the. PRX5-ROS-Signal Transducer and Activator of Transcription 3 (STAT3) axis in CSC biology. We present mechanistic evidence demonstrating that PRX5-mediated redox balance protects STAT3 from oxidative inactivation and proteasomal degradation, sustaining its transcriptional activity and the stable expression of Octamer-binding transcription factor4 (OCT4), SRY-box transcription factor 2 (SOX2), and NANOG, with particular relevance to colorectal cancer. We further discuss how this axis integrates with oncogenic networks and represents a targetable vulnerability. Collectively, the evidence supports PRX5 as a prognostic biomarker and therapeutic target for disrupting CSC maintenance.

KEYWORDS: Cancer stem cell; reactive oxygen species; signal transducer and activator of transcription 3

1 Introduction

Reactive oxygen species (ROS) serve as critical signaling mediators under tightly controlled conditions, regulating cellular proliferation, differentiation, and stress responses [1,2]. Cancer cells use redox adaptability by maintaining ROS at levels that support oncogenic signaling without causing cell death [3,4]. Within this redox-adapted environment, cancer stem cells (CSCs) represent a stable subpopulation characterized by self-renewal capacity and resistance to conventional therapies, features that depend on the maintenance of low intracellular ROS [5–7].

Among the antioxidant systems that regulate CSC redox homeostasis, the peroxiredoxin (PRX) family plays a key role [8]. Peroxiredoxin 5 (PRX5) is distinguished from other PRX isoforms by its atypical 2-Cys catalytic mechanism and its broad subcellular distribution, including mitochondria, peroxisomes, cytosol, and nucleus [9,10]. Importantly, accumulating evidence, including recent integrative analyses of redox biology, cancer stemness, and STAT3 signaling, indicates that PRX5 directly modulates redox-sensitive oncogenic signaling, most notably the Signal Transducer and Activator of Transcription 3 (STAT3) pathway [11]. STAT3 is a key transcriptional regulator of CSC maintenance, governing the expression of pluripotency factors such as Octamer-binding transcription factor 4 (OCT4), SRY-box transcription factor 2 (SOX2), and NANOG [11–13]. Because STAT3 activity is highly sensitive to oxidative modifications, its continuous activation in CSCs requires a tightly controlled redox environment. Accordingly, PRX5-mediated ROS regulation acts as a critical mechanism for maintaining STAT3 signaling stability [14,15].

In this review, we synthesize recent mechanistic, experimental, and clinical evidence supporting a functional role for PRX5 in maintaining STAT3 activity in CSC biology. We show how PRX5-driven redox regulation stabilizes STAT3 signaling, integrates with other oncogenic networks, and contributes to therapeutic resistance, with particular emphasis on colorectal cancer. Finally, we discuss the potential of targeting PRX5-dependent redox homeostasis as a strategy to selectively disrupt CSC maintenance and improve treatment outcomes.

2 The Peroxiredoxin Family and PRX5 Biology

2.1 Classification and Catalytic Diversity of the PRX Family

The PRX family is a conserved group of thiol-dependent peroxidases that protect cells from oxidative damage and participate in redox signaling by reducing hydrogen peroxide, organic hydroperoxides, and peroxynitrite [16,17]. Mammalian PRXs (PRX1-6) are classified by the cysteine chemistry of their catalytic cycles into typical 2-Cys (PRX1-4), atypical 2-Cys (PRX5), and 1-Cys (PRX6) subgroups (Fig. 1; Table 1). In typical 2-Cys PRXs a peroxidatic cysteine (CP) forms a sulfenic acid that is resolved by a resolving cysteine (CR) on a partner subunit to create an intermolecular disulfide [18,19]. By contrast, PRX5, as an atypical 2-Cys enzyme, forms an intramolecular disulfide between CP (Cys47) and CR (Cys151) on the same polypeptide. PRX activity is dynamically regulated by hyperoxidation of the peroxidatic cysteine, which transiently inactivates peroxidase activity to allow localized ROS signaling [20,21]. Although many PRXs are broadly and constitutively expressed, PRX5 stands out for its diverse subcellular distribution: mitochondria, peroxisomes, cytosol, and nucleus, resulting from alternative transcription/translation starts and targeting signals [22]. Emerging evidence links PRX5 expression and redox buffering capacity to cancer progression, where its selective regulation of ROS contributes to signaling pathways that support cancer stem cell phenotypes [22,23].

2.2 Structural Features and Multicompartmental Localization of PRX5

PRX5 is structurally distinct within the PRX family. As an atypical 2-Cys enzyme, it resolves the sulfenic intermediate via an intramolecular disulfide between Cys47 and Cys151, a configuration that favors monomeric or dimeric states rather than the large oligomers seen for some typical 2-Cys PRXs (Fig. 1; Table 1) [19–22]. Its multicompartmental localization is encoded by an N-terminal mitochondrial targeting sequence and a C-terminal peroxisomal targeting signal, and is further diversified by alternative splicing and use of downstream start codons that generate isoforms targeted to specific organelles [24,25]. Functionally, PRX5 acts both as a peroxide scavenger and as a redox chaperone. It contributes to mitochondrial and peroxisomal redox homeostasis, mitigates ER oxidative stress during protein folding, and thereby limits activation of pro-apoptotic unfolded protein responses in stressed or malignant cells [26]. PRX5 activity is regulated at multiple levels: transcriptional induction via Nrf2/ARE, and post-translational modifications such as S-nitrosylation, phosphorylation, and acetylation that alter substrate specificity, interactions, or stability [27,28]. Notably, PRX5 shows relative resistance to hyperoxidative inactivation compared with some other PRXs, allowing continued peroxidase activity under higher oxidative loads [27]. This biochemical resilience, along with its organelle-specific localization, enables PRX5 to buffer ROS in ways that preserve redox-sensitive signaling proteins, thereby supporting metabolic stability and stemness programs in cancer environments [29,30]. Importantly, understanding the compartment-specific functions of PRX5 presents methodological challenges, as its distribution across mitochondria, peroxisomes, and the nucleus requires precise subcellular fractionation and high-resolution imaging to avoid confusing its antioxidant effects with a single organelle [31].

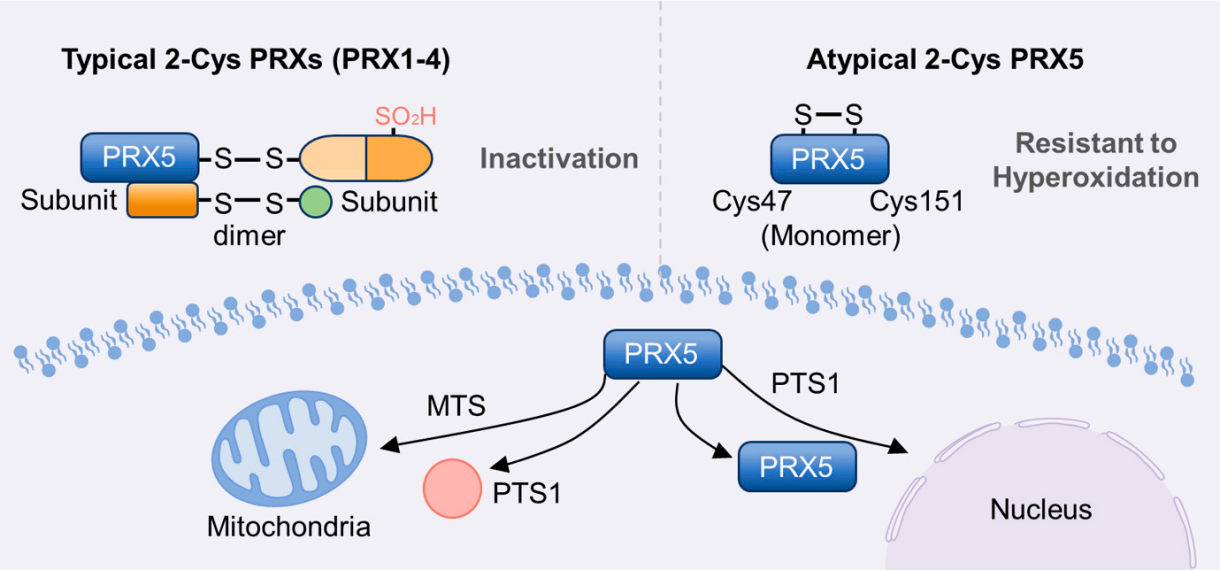

Figure 1: Schematic representation of the human PRX family, highlighting isoform classification, catalytic mechanisms, and subcellular localization. Mammalian PRXs are categorized into typical 2-Cys (PRX1–4), atypical 2-Cys (PRX5), and 1-Cys (PRX6) subgroups based on the number and positioning of catalytic cysteine residues. Unlike typical 2-Cys PRXs, which form intermolecular disulfide bonds, PRX5 utilizes an intramolecular disulfide bond, conferring distinct structural and functional properties. Abbreviations: SO_2H, sulfinic acid (hyperoxidized inactive form); MTS, mitochondrial targeting sequence; PTS1, peroxisomal targeting signal 1 (Fig. 1 is our original work and was prepared using Microsoft PowerPoint 2021).

Table 1: Comparison of human Peroxiredoxin (PRX) isoforms [18,31].

PRX Isoform	Gene Symbol	Protein Length (aa)	PRX Class	Catalytic Cys	Subcellular Localization	Major Functions	Cancer-Related Implications
PRX1	PRDX1	~199	Typical 2-Cys	Cys52/Cys173	Cytosol, Nucleus	H_2O_2 detoxification, redox signaling, chaperone activity	Frequently overexpressed in solid tumors; promotes proliferation, survival, therapy resistance
PRX2	PRDX2	~198	Typical 2-Cys	Cys51/Cys172	Cytosol	Redox buffering, modulation of growth factor signaling	Regulates ROS-dependent signaling; linked to leukemia and breast cancer progression
PRX3	PRDX3	~256	Typical 2-Cys	Cys108/Cys229	Mitochondria	Mitochondrial ROS control, oxidative stress protection	Supports mitochondrial function in cancer cells; associated with metabolic reprogramming
PRX4	PRDX4	~271	Typical 2-Cys	Cys124/Cys245	Endoplasmic Reticulum, Secretory Pathway	Protein folding, ER redox homeostasis	Implicated in tumor growth and metastasis via ER stress modulation

Table 1: *Cont.*

PRX Isoform	Gene Symbol	Protein Length (aa)	PRX Class	Catalytic Cys	Subcellular Localization	Major Functions	Cancer-Related Implications
PRX5	PRDX5	~214	Atypical 2-Cys	Cys48/Cys152	Mitochondria, Cytosol, Peroxisome, Nucleus	Broad-spectrum peroxidase activity; H_2O_2, peroxynitrite, lipid peroxide detoxification	Regulates ROS–STAT signaling; linked to cancer stem cell maintenance and therapy resistance
PRX6	PRDX6	~224	1-Cys	Cys47	Cytosol, Lysosome	Phospholipase A_2 activity, lipid peroxide reduction	Promotes invasion and metastasis; involved in oxidative stress adaptation

Note: PRX1, Peroxiredoxin-1; PRX2, Peroxiredoxin-2; PRX3, Peroxiredoxin-3; PRX4, Peroxiredoxin-4; PRX5, Peroxiredoxin-5; PRX6, Peroxiredoxin-6; CYS, Cysteine.

3 ROS Biology and Cancer Stem Cell Redox Homeostasis

3.1 Sources, Antioxidant Defense Systems, and Dual Signaling Roles of ROS

ROS, representing a diverse array of oxygen-derived chemical species such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and the highly deleterious hydroxyl radical (OH), are primarily generated as obligate by-products of mitochondrial aerobic metabolism during the electron transport chain (ETC) activity, but are also actively produced by specialized enzyme complexes such as NADPH oxidases (NOXs), peroxisomal oxidases, and xanthine oxidase in response to various extracellular stimuli [32,33]. To mitigate the risk of indiscriminate oxidative damage, eukaryotic cells employ a hierarchical and compartmentalized antioxidant defense network consisting of non-enzymatic molecules like glutathione (GSH) and ascorbic acid, alongside an intricate array of scavenging enzymes, including superoxide dismutases (SODs) for O_2^- dismutation, catalases, and particularly the thiol-dependent peroxidases such as glutathione peroxidases (GPXs) and the PRX family [34,35]. In current redox biology, ROS are recognized as critical signaling regulators that exhibit a profound functional contrast; while physiological, low-to-moderate levels of H_2O_2 serve as transient second messengers that specifically oxidize conserved cysteine residues to modulate the activity of phosphatases and kinases within the MAPK/ERK, PI3K/Akt/mTOR, and STAT3 pathways, an uncompensated flow in ROS leads to oxidative distress, characterized by lipid peroxidation, protein carbonylation, and genomic instability that ultimately culminate in apoptosis or cellular senescence [36,37].

3.2 PRX5-Mediated Redox Control in the CSC Compartment

This delicate redox balance is especially vital in the biology of CSCs, a strong subpopulation that exploits specialized antioxidant programs to maintain a low-ROS state, which is essential for preserving their self-renewal capacity and preventing premature differentiation or exhaustion [38]. Recent research suggests that the upregulation of PRX5 within the CSC compartment is not merely a survival mechanism but a strategic molecular adaptation that effectively buffers 'protumorigenic' ROS levels to sustain the activation of the STAT3 signaling axis, thereby ensuring the transcriptional stability of core pluripotency factors such as OCT4, SOX2, and NANOG [39,40]. By preventing the ROS-induced degradation of these stemness determinants, PRX5 reinforces the aggressive phenotypic characteristics of CRC cells, highlighting the critical role of redox-mediated signaling in orchestrating the interplay between metabolic adaptation and the maintenance of the CSC hierarchy, which ultimately drives tumor heterogeneity and therapeutic resistance [41]. Accurately quantifying intracellular ROS remains a significant technical challenge. This is

because conventional fluorescent probes, such as DCFDA, are subject to issues like photo-oxidation, poor organelle specificity, and overlapping emission spectra [42,43].

3.3 Defining Features, Identification, and Signaling Networks of CSCs

CSCs represent a functionally distinct and highly strong subpopulation within the heterogeneous tumor bulk, defined by their hallmark capacities for self-renewal, multi-lineage differentiation, and the initiation of secondary tumors even from a single cell [41]. These primitive cells are typically identified and isolated based on the expression of specific cell surface markers such as CD133, CD44, CD24, and EpCAM, or through functional assays including the side population method based on Hoechst 33342 dye efflux and the gold-standard tumorsphere formation assay, which evaluates anchorage-independent growth under serum-free conditions [44,45]. The maintenance of this undifferentiated state is strictly governed by an intricate network of evolutionarily conserved signaling cascades, most notably the Wnt/β-catenin, Notch, and Hedgehog pathways, along with the STAT3 signaling, which collectively orchestrate the expression of core pluripotency transcription factors like OCT4, SOX2, and NANOG to reinforce the stemness phenotype (Fig. 2) [46]. Recent advances in metabolic profiling have highlighted that CSCs possess a metabolic plasticity that favors a quiescent state with a preferential confidence on oxidative phosphorylation or glycolysis depending on the microenvironment, yet a key hallmark across various malignancies is their tight regulation of low intracellular ROS levels to protect their genomic integrity and prevent premature differentiation. CSCs maintain this unique redox balance by upregulating strong antioxidant systems, with PRX5 acting as a vital buffer to protect key cancer-driving proteins from oxidation [47,48]. In CRC models, PRX5 scavenges ROS to keep STAT3 active and moving into the nucleus, creating a safe environment for CSCs to survive and grow even during treatment or oxidative stress [48].

4 The PRX5-ROS-STAT3 Signaling in Cancer Stemness

4.1 Canonical JAK-STAT Activation and Stemness-Associated Transcriptional Programs

The STAT family, particularly STAT3 and STAT5, serves as a central hub for integrating extracellular cytokine and growth factor signals into specific transcriptional programs, with their activation primarily governed by the canonical Janus kinase (JAK)-STAT pathway, where ligand-induced receptor dimerization triggers JAK-mediated tyrosine phosphorylation of STAT monomers, leading to their dimerization via SH2 domain interactions and subsequent nuclear translocation [49]. Once localized within the nucleus, these activated STAT dimers function as potent transcription factors that bind to specific promoter elements to orchestrate the expression of an expansive range of genes essential for cell survival, such as BCL-2 and MCL-1, pro-inflammatory cytokines, and most crucially, the core pluripotency factors including OCT4, SOX2, and NANOG that collectively define and sustain the CSC phenotype [50,51]. Recent studies have highlighted an intricate crosstalk between STAT activation and ROS dynamics, wherein ROS act as signaling molecules that can either facilitate the oxidative inhibition of protein tyrosine phosphatases (PTPs) to prolong STAT3 phosphorylation or, conversely, induce the oxidative degradation of STAT proteins under excessive ROS (Fig. 2) [52]. Within the strong environment of colorectal CSC, this interplay is strategically modulated by the antioxidant enzyme PRX5, which maintains a protective redox rheostat that prevents ROS-induced STAT3 dephosphorylation and proteasomal degradation, thereby establishing a feed-forward loop that enhances STAT3-mediated gene expression [53]. This PRX5-STAT3 signaling axis not only promotes the expansion of the CSC pool but also confers enhanced resistance to apoptosis and environmental stressors, positioning the redox-regulated STAT signaling network as a fundamental driver of tumor progression and a promising target for killing CSCs in aggressive malignancies [54].

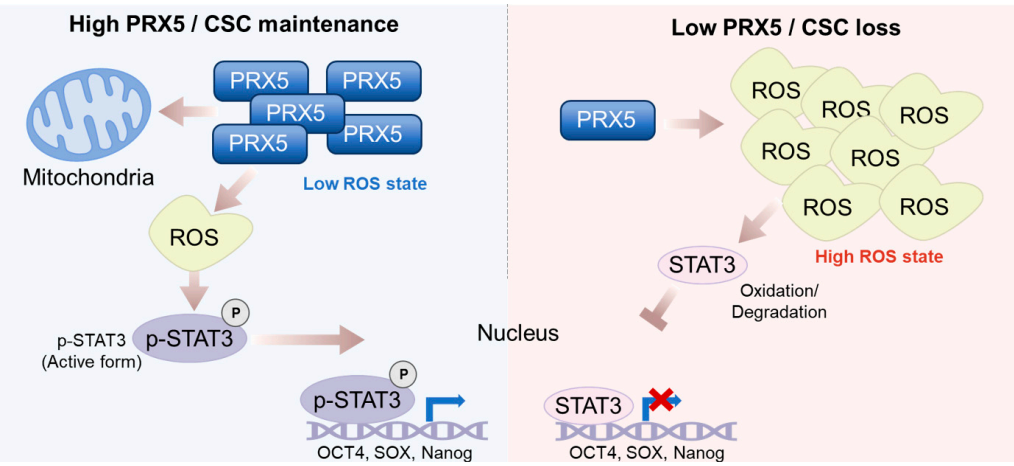

Figure 2: Proposed model illustrating PRX5-mediated redox regulation of STAT3 signaling in cancer cells. Under physiological conditions, PRX5 maintains intracellular ROS at sub-lethal levels, preventing oxidative inactivation of redox-sensitive signaling components. PRX5 limits excessive ROS accumulation, thereby preserving STAT3 phosphorylation, nuclear translocation, and transcriptional activity. In the absence or suppression of PRX5, elevated ROS levels lead to impaired STAT3 signaling through oxidative inactivation and destabilization of STAT3 and/or its regulatory phosphatases. Abbreviations: pY705, STAT3 phosphorylated at tyrosine 705; ROS, reactive oxygen species (Fig. 2 is our original work and was prepared using Microsoft PowerPoint 2021).

4.2 Molecular Evidence for PRX5 as an Upstream Regulator of STAT3

Accumulating molecular and functional evidence supports a direct regulatory role of PRX5 in controlling redox-sensitive STAT3 signaling within CSCs [11,12]. Genetic and biochemical studies consistently demonstrate that PRX5 serves as a critical upstream modulator of intracellular ROS dynamics, thereby shaping the stability and transcriptional activity of STAT3 [55]. At the cellular level, loss-of-function approaches, including shRNA-mediated knockdown and CRISPR/Cas9-driven deletion of PRX5, result in a pronounced accumulation of mitochondrial and cytosolic reactive oxygen species [56]. This ROS elevation is linked to a significant reduction in STAT3 tyrosine phosphorylation and impaired nuclear translocation, indicating that STAT3 activity is highly dependent on PRX5-mediated redox buffering [56,57]. Conversely, enforced PRX5 overexpression markedly attenuates oxidative stress induced by metabolic perturbations or exogenous pro-oxidant stimuli, thereby sustaining STAT3 activation under conditions that would otherwise promote oxidative inactivation [58].

4.2.1 Mechanistic Pathways of STAT3 Protection

Mechanistically, PRX5 preserves STAT3 signaling through multiple main pathways. First, by limiting excessive ROS accumulation, PRX5 prevents the oxidative modification and functional inhibition of PTPs, such as SHP-2, which are essential for maintaining controlled STAT3 phosphorylation dynamics [59]. Second, PRX5 directly shields the redox-sensitive cysteine residues of STAT3 (notably Cys259, Cys687, and Cys712) from H_2O_2-driven sulfenylation and intermolecular disulfide formation, oxidative modifications that would otherwise impair DNA-binding activity. Although direct biochemical evidence for ROS-driven proteasomal turnover of STAT3 in PRX5-deficient CSCs (e.g., CHX-chase or ubiquitination assays) remains to be established, oxidative cysteine modification has been reported to destabilize STAT3 dimers and reduce nuclear retention [59,60]. These protective mechanisms collectively establish a permissive redox environment that stabilizes STAT3 signaling in CSCs.

Importantly, the multicompartmental distribution of PRX5 enables spatially distinct modes of STAT3 protection. Mitochondrial PRX5, directed by its N-terminal targeting sequence, scavenges matrix-derived H_2O_2 and preserves the Ser727-phosphorylated mitochondrial STAT3 pool that supports oxidative phosphorylation and metabolic adaptation in CSCs [29,55]. Peroxisomal PRX5 restricts the diffusion of peroxisome-generated H_2O_2 into the cytosol, indirectly stabilizing cytosolic JAK-STAT3 phosphorylation cascades [25,31]. Nuclear PRX5, in turn, shields nuclear STAT3 dimers from cysteine oxidation that would otherwise disrupt promoter occupancy at OCT4, SOX2, and NANOG loci [60]. This compartment-specific redox buffering provides a unified framework in which a single antioxidant enzyme couples organelle-level oxidant flux to nuclear stemness transcription.

4.2.2 Functional Consequences for Stemness Programs

Functionally, disruption of PRX5 expression leads to a marked suppression of STAT3-dependent transcriptional programs [61]. PRX5-deficient cells exhibit reduced expression of core pluripotency-associated transcription factors, including OCT4, SOX2, and NANOG, accompanied by reduced tumorsphere formation efficiency and clonogenic potential [14]. Importantly, these phenotypic defects can be partially rescued by adding ROS scavengers or by ectopic activation of STAT3, providing strong causal evidence that PRX5 operates upstream of STAT3 through redox-dependent mechanisms [12]. Interpretation of PRX5 loss-of-function data requires caution because PRX5 operates within a redundant antioxidant network. Compensatory upregulation of other peroxiredoxins or glutathione peroxidases may mask the effects of PRX5 deficiency, requiring combinatorial knockdown strategies and extensive profiling [62].

Direct biochemical validation of STAT3 protein turnover under PRX5 loss is currenDirect biochemical validation of STAT3 protein turnover under PRX5 loss is currently lacking and represents an important future direction. Beyond conventional cycloheximide (CHX) chase assays, complementary orthogonal approaches can provide more direct and quantitative evidence for the ROS- and PRX5-dependent regulation of STAT3 stability. These include pulse-chase analysis using ^{35}S-methionine or click-chemistry-compatible amino acid analogs (e.g., L-azidohomoalanine, AHA), as well as tandem ubiquitin-binding entity (TUBE)-based enrichment of polyubiquitinated STAT3. Additionally, denaturing immunoprecipitation coupled with K48-linkage-specific ubiquitin detection, or SNAP-tag- and HaloTag-based live-cell pulse-chase imaging could be utilized [63]. Furthermore, proteasome inhibitor (MG132) rescue experiments will be essential to causally link PRX5-mediated redox buffering to STAT3 proteostasis in CSCs.

4.3 In Vivo and Clinical Validation of the PRX5-ROS-STAT3 Signaling Pathway

In vivo studies confirm that the PRX5-ROS-STAT3 signaling cascade is critical for tumor growth. Xenograft and limiting dilution transplantation models reveal that PRX5-high cancer cells display enhanced tumor-initiating capacity, whereas PRX5-deficient cells show delayed tumor onset and impaired serial transplantation potential, hallmark features of CSC exhaustion [62]. These effects are consistently associated with reduced STAT3 activity and attenuated expression of stemness-related genes within tumor tissues, reinforcing the central role of PRX5 in sustaining CSC-driven tumorigenicity. Clinical and translational analyses provide additional support for this regulatory axis. Transcriptomic profiling and immunohistochemical studies of colorectal cancer specimens demonstrate a strong positive correlation between PRX5 expression, STAT3 activation status, and CSC marker enrichment, particularly within CD133-positive tumor subpopulations [64,65]. Elevated PRX5 levels are frequently associated with advanced tumor stage, poor differentiation, and unfavorable clinical outcomes, suggesting that aberrant activation of the PRX5-STAT3 pathway contributes to disease progression and recurrence [65].

Collectively, these molecular, functional, and clinical observations define PRX5 as a central redox regulator that couples intracellular ROS homeostasis to STAT3-driven transcriptional programs in cancer stem cells [12]. The PRX5-ROS-STAT3 axis therefore represents a mechanistically coherent and pathologically relevant signaling module that supports CSC maintenance and tumor aggressiveness, providing a strong rationale for therapeutic strategies aimed at disrupting redox-dependent STAT3 stabilization.

5 Experimental and Clinical Evidence Linking PRX5 to CSC Functions and Tumorigenicity

5.1 In Vitro Evidence: Self-Renewal Capacity and Stemness Marker Regulation

A growing body of experimental evidence from *in vitro* and *in vivo* models substantiates the functional importance of PRX5 in the maintenance and expansion of CSC populations [66]. Across multiple CRC cell line models, enforced PRX5 overexpression significantly enhances tumorsphere-forming efficiency and clonogenic growth under serum-free, non-adherent conditions, two widely accepted functional assays for evaluating CSC self-renewal capacity [22]. In contrast, genetic suppression of PRX5 through shRNA-mediated knockdown or CRISPR/Cas9-based deletion consistently results in a marked reduction in sphere number and size, indicating impaired self-renewal and growth independently [67]. At the molecular level, PRX5 depletion is accompanied by a robust downregulation of established CSC-associated surface markers, including CD133, CD44, and EpCAM [14,68]. These transcriptional and phenotypic changes closely mirror the loss of STAT3 signaling activity observed under PRX5-deficient conditions, supporting the functional link between PRX5 expression and CSC identity [7,12]. Importantly, restoration of redox balance using pharmacological antioxidants or forced STAT3 activation partially rescues sphere-forming ability and stemness marker expression, providing functional validation that PRX5-driven CSC phenotypes are mediated through redox-dependent STAT3 signaling.

5.2 In Vivo Tumorigenicity and Serial Transplantation

The tumorigenic role of PRX5 is further supported by *in vivo* xenograft transplantation studies [14,67]. Cancer cells expressing high levels of PRX5 exhibit accelerated tumor initiation and increased tumor burden when implanted into *in vivo* models, even at limiting dilution, a defining feature of enhanced CSC frequency. Conversely, PRX5-deficient cells display delayed tumor onset, reduced tumor incidence, and impaired serial transplantation capacity, indicating a failure to sustain long-term tumor-propagating potential. Histological and molecular analyses of xenograft tumors consistently reveal reduced STAT3 activation and reduced expression of stemness-associated genes in PRX5-depleted tumors, linking *in vivo* tumorigenicity directly to CSC exhaustion [55,69].

5.3 Model System Limitations and Methodological Considerations

While these *in vitro* and *in vivo* findings are convincing, important model system limitations require consideration. Traditional two-dimensional monolayer cultures often fail to recapitulate the complex spatial architecture and oxygen gradients of the *in vivo* TME that are fundamental to CSC redox homeostasis [70]. Although three-dimensional tumor sphere and organoid models better approximate physiological conditions, they remain limited in reproducing interactions with stromal and immune components [71]. Furthermore, immortalized cancer cell lines may not fully capture the intra-tumoral heterogeneity and distinct antioxidant profiles observed in patient-derived primary cells (PDCs) or patient-derived xenografts (PDXs), underscoring the need for validation in these more clinically relevant systems [71,72].

5.4 Clinical Correlations and Prognostic Significance

Clinical and translational evidence further corroborates the pathological significance of PRX5 in human malignancies [73,74]. Transcriptomic analyses of CRC patient cohorts and immunohistochemical staining of tumor specimens demonstrate that PRX5 expression is significantly elevated in tumor tissues compared with adjacent normal mucosa [47,74]. Notably, PRX5 upregulation is enriched within CSC-associated subpopulations, particularly CD133-positive cells, and shows a strong positive correlation with activated STAT3 levels [53]. In a limited number of cohort studies, elevated PRX5 expression has been correlated with advanced TNM stage, poor differentiation, and shorter OS/DFS in univariate analyses [75,76]. However, PRX5 has not yet been established as an independent prognostic factor in multivariate models, and larger, multi-center validation cohorts are required before definitive prognostic claims can be made [75].

Available Kaplan-Meier analyses from individual cohorts suggest a trend toward higher post-treatment recurrence in PRX5-high tumors, although the independent prognostic value of PRX5 remains to be confirmed in adequately powered multivariate studies [76]. Importantly, subgroup analyses suggest that the prognostic impact of PRX5 is most pronounced in tumors characterized by elevated CSC marker expression and active STAT3 signaling, highlighting the specificity of the PRX5-STAT3 axis in driving aggressive disease phenotypes [40,60]. Collectively, these experimental and clinical observations establish PRX5 not merely as a marker of oxidative stress adaptation but as a functional driver of CSC-mediated tumor initiation, progression, and recurrence.

6 Integration of the PRX5-STAT3 with Oncogenic Networks and the Tumor Microenvironment

6.1 Crosstalk with PI3K/AKT, NF-κB, and Wnt/β-Catenin Pathways

The PRX5-mediated redox regulation and the consequent stabilization of the STAT3 signaling axis do not operate in isolation but are connected to cross-amplifying oncogenic pathways, where the antioxidant capacity of PRX5 serves as a critical node for integrating signals from the PI3K/AKT/mTOR, NF-κB, and Wnt/β-catenin cascades [77,78]. Experimental insights suggest that PRX5-induced ROS scavenging effectively prevents the oxidative inhibition of AKT, thereby sustaining AKT activity that synergizes with STAT3 to enhance the promotion of anti-apoptotic genes, while concurrently, the reduction of intracellular ROS by PRX5 modulates the IKK complex activity to facilitate the nuclear translocation of NF-κB, increasing the expression of anti-apoptotic and stemness genes [54,79,80]. This crosstalk extends to the Wnt/β-catenin and Notch pathways, where the PRX5-STAT3 axis maintains the stability of β-catenin and Notch intracellular domain (NICD) by shielding them from ROS-induced ubiquitin-proteasomal degradation, thus creating a robust multi-pathway reinforcement of the CSC phenotype.

6.2 Metabolic Reprogramming and Bioenergetic Adaptation

Beyond signal transduction, the PRX5-STAT3 regulatory network serves as a metabolic rheostat that intersects with cellular bioenergetics, particularly by orchestrating a shift toward metabolic plasticity characterized by enhanced glucose uptake and glutamine metabolism [81]. PRX5, through its diverse localization in the mitochondria and peroxisomes, preserves mitochondrial membrane integrity and facilitates efficient oxidative phosphorylation even under metabolic stress, while STAT3-driven transcriptional programs upregulate key metabolic enzymes like GLUT1 and GLS1, thereby providing the necessary biosynthetic precursors and ATP to satisfy the high energetic demands of self-renewing CSCs (Fig. 3) [82]. This metabolic adaptation is further exacerbated within the dynamic TME, where PRX5-mediated redox buffering becomes indispensable for CSC survival under conditions of chronic hypoxia

and nutrient deprivation. In the hypoxic TME, PRX5 cooperates with Hypoxia-Inducible Factor 1-alpha (HIF-1α) to alleviate the excessive mitochondrial ROS production that would otherwise trigger mitophagy or apoptosis, while also influencing the secretome of CSCs to promote an immunosuppressive environment (Fig. 3) [83]. Specifically, the PRX5-STAT3 axis facilitates the secretion of cytokines such as IL-10 and TGF-β, which polarize tumor-associated macrophages (TAMs) toward a pro-tumorigenic M2 phenotype and suppress the effector functions of cytotoxic T lymphocytes, thereby establishing an immunosuppressive niche that shields CSCs from immune surveillance (Fig. 3) [84,85]. Consequently, the integration of PRX5 and STAT3 with systemic oncogenic signaling, metabolic reprogramming, and TME-mediated stress responses establishes drug resistance that drives tumor heterogeneity, clinical progression, and therapeutic resistance in aggressive colorectal malignancies, positioning this integrated molecular model as a key driver for developing next-generation multimodal anticancer strategies [86].

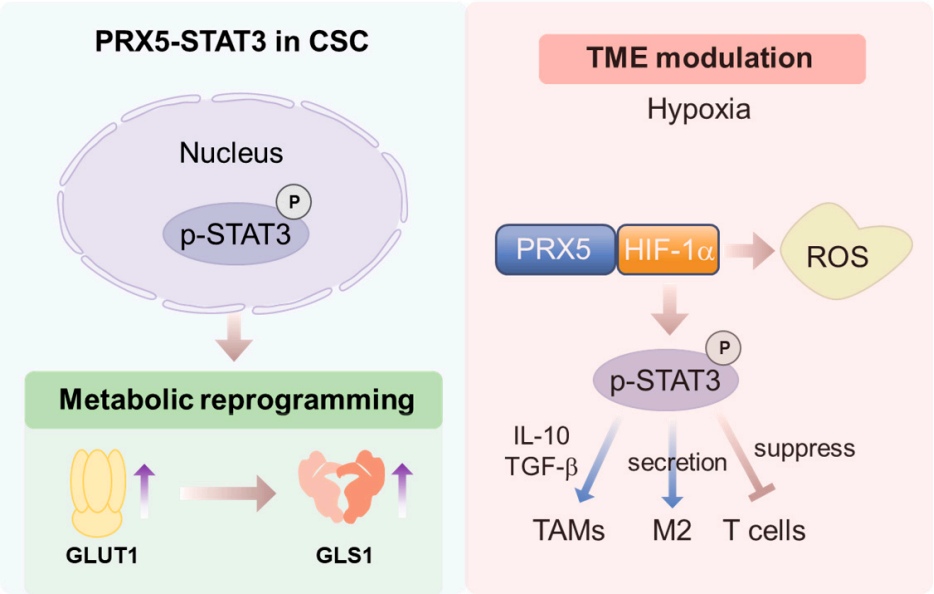

Figure 3: Schematic illustration of the PRX5-STAT3 in CSC maintenance and TME modulation. (**Left**) In CSCs, activated p-STAT3 in the nucleus drives metabolic reprogramming, leading to increased expression levels of GLUT1 and GLS1 (indicated by upward arrows). (**Right**) Under hypoxia, the interaction involving PRX5, HIF-1α, and ROS signaling triggers STAT3 activation. This axis promotes an immunosuppressive tumor microenvironment (TME) by inducing the secretion of IL-10 and TGF-β from TAMs and M2 macrophages, while simultaneously suppressing T cell-mediated immunity (Fig. 3 is our original work and was prepared using Microsoft PowerPoint 2021).

7 Therapeutic Implications and Translational Strategies

7.1 Basis for Targeting the PRX5-STAT3 Signaling Pathway

The identification of PRX5 as a central redox regulator sustaining STAT3 signaling in CSCs provides a compelling therapeutic rationale for targeting this axis in aggressive and refractory cancers [11–13]. Unlike conventional oncogenic drivers, PRX5 occupies a unique upstream position that integrates redox homeostasis with stemness-associated transcriptional programs, making it an attractive vulnerability for selectively destabilizing the CSC compartment [6,40]. One potential therapeutic strategy involves the direct inhibition of PRX5 enzymatic activity. Although no PRX5-selective inhibitor has been clinically advanced, the structurally distinct intramolecular Cys47–Cys151 disulfide of PRX5 provides a rational basis

for designing isoform-specific covalent inhibitors, conceptually analogous to conoidin A and adenanthin previously developed against typical 2-Cys PRXs [55,87]. Such scaffolds may serve as starting points for medicinal-chemistry optimization toward PRX5 selectivity.

7.2 Transcriptional and Post-Transcriptional Suppression of PRX5

Beyond direct enzymatic inhibition, transcriptional and post-transcriptional suppression of PRX5 represents an alternative strategy. Antisense oligonucleotides, siRNA, or CRISPR-mediated CRISPR-based tools could reduce PRX5 expression, thereby lowering the redox buffering capacity of CSCs [88]. Such approaches may be particularly effective when combined with ROS-inducing therapies, as PRX5-depleted CSCs exhibit hypersensitivity to oxidative stress and impaired STAT3-driven stemness programs [89]. Targeting PRX5 also aligns conceptually with emerging pro-oxidant therapeutic paradigms. While traditional antioxidant strategies aim to limit oxidative damage, CSC-directed therapies increasingly exploit oxidative overload to selectively eliminate cancer cells [90]. By analogy with preclinical studies targeting other PRX isoforms, disruption of PRX5-mediated redox buffering is hypothesized to sensitize CSCs to pro-oxidant agents. This CSC-selectivity rationale, based on the lower redox-buffering threshold of CSCs relative to normal stem cells, remains to be experimentally validated, as direct preclinical or clinical data for PRX5-targeted pro-oxidant therapy are currently lacking.

7.3 Combination Therapy and Synergistic Approaches

Combination therapy represents a particularly promising avenue for clinical translation. Co-targeting PRX5 and STAT3 signaling may prevent compensatory redox adaptation and signaling bypass mechanisms that often undermine single-agent therapies [91,92]. Preclinical evidence suggests that PRX5 suppression enhances the efficacy of STAT3 inhibitors and standard chemotherapeutic agents, such as 5-fluorouracil and oxaliplatin, by dismantling the redox-supported survival network of CSCs [93,94]. These findings support the integration of PRX5-targeted approaches into multimodal treatment regimens aimed at preventing tumor recurrence. Despite these promising opportunities, several challenges must be considered. Given the physiological role of PRX5 in normal tissues, systemic inhibition may cause oxidative damage, particularly in organs with high metabolic activity. Therefore, the development of tumor- or CSC-selective delivery strategies, such as nanoparticle-based systems or ligand-directed targeting, is likely to be essential for minimizing side effects [89–91]. In parallel, the identification of robust biomarkers to stratify patients based on PRX5 and STAT3 activity will be critical for successful treatment.

In summary, targeting the PRX5–STAT3 axis represents a novel and effective way for eradicating CSCs and overcoming therapeutic resistance. By disrupting the redox-dependent protection that sustains stemness and survival, PRX5-directed interventions hold significant potential to improve patient survival and reduce relapse in aggressive cancers.

8 Future Perspectives and Research Directions

8.1 Compartment-Specific Functions and Multi-Omics Integration

Despite the significant strides made in elucidating the PRX5-dependent STAT3 maintenance, several fundamental questions remain unresolved, particularly regarding how PRX5 functions across distinct subcellular compartments and its spatiotemporal orchestration of redox signaling within the CSC niche. Future investigations should prioritize the delineation of how PRX5 differentially modulates the redox proteome in the mitochondria versus the nucleus or peroxisomes, as understanding these compartmentalized roles may reveal distinct metabolic or transcriptional vulnerabilities that are currently overlooked [95]. To

achieve this, the integration of cutting-edge multi-omics approaches, including single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, will be indispensable to map PRX5 expression across diverse CSC subpopulations and to identify co-regulated gene modules that drive therapeutic resistance. Furthermore, advanced redox proteomics should be employed to identify the precise cysteine residues on the STAT family and other partners that are protected by PRX5, thereby providing a molecular blueprint for the development of highly selective covalent inhibitors [73]. Transitioning these laboratory findings into clinical practice requires a robust strategy for biomarker development, where the validation of PRX5 levels in liquid biopsies or circulating tumor cells could serve as a non-invasive diagnostic tool to predict tumor recurrence and patient response to pro-oxidant therapies. Moreover, future clinical-oriented research should focus on clarifying the synergistic potential of combining PRX5-targeted agents with immune checkpoint inhibitors, as the PRX5-STAT3 axis significantly influences the immunosuppressive TME.

8.2 Toward Precision Medicine Targeting of PRX5

Ultimately, refining our understanding of the PRX5-mediated antioxidant network through the lens of personalized medicine and high-resolution molecular analysis will be paramount to decouple the protective shields of CSCs and establish PRX5 as a high-value cornerstone in the next generation of precision oncology. To overcome current methodological constraints, such as limited culture system fidelity and imprecise ROS detection, researchers must integrate multi-omic profiling with advanced redox-sensitive imaging. This integration is essential to resolve the spatiotemporal dynamics of the PRX5-STAT3 axis and ensure that preclinical findings are successfully translated into effective therapies [96–98].

9 Conclusion

PRX5 has emerged as a pivotal regulator of redox-dependent oncogenic signaling rather than a mere antioxidant enzyme. By balancing intracellular ROS levels, PRX5 preserves the activity of redox-sensitive pathways, most notably STAT3, thereby maintaining the transcriptional programs that define cancer stem cell identity and function. The PRX5-driven STAT3 activity provides a mechanistic framework that links antioxidant defense, stemness maintenance, and therapeutic resistance, particularly in CRC. The growing body of experimental and clinical evidence reviewed here supports PRX5 as a candidate prognostic biomarker and a promising therapeutic target, pending further validation in independent clinical cohorts. Disrupting PRX5-mediated redox buffering has the potential to destabilize STAT3 signaling, reduce CSC self-renewal, and make tumors more sensitive to conventional and pro-oxidant therapies. Future efforts focused on developing selective PRX5 inhibitors, improving redox-sensitive biomarker strategies, and integrating PRX5 targeting into combination treatment regimens may open new avenues for overcoming CSC-driven recurrence and achieving better clinical outcomes in refractory malignancies.

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