European Journal of Immunology Clinical·Basic·Translational

HIGHLIGHTS

Basic

REVIEW

The thioredoxin system: Balancing redox responses in immune cells and tumors

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The thioredoxin (TRX) system is an important contributor to cellular redox balance and regulates cell growth, apoptosis, gene expression, and antioxidant defense in nearly all living cells. Oxidative stress, the imbalance between reactive oxygen species (ROS) and antioxidants, can lead to cell death and tissue damage, thereby contributing to aging and to the development of several diseases, including cardiovascular and allergic diseases, diabetes, and neurological disorders. Targeting its activity is also considered as a promising strategy in the treatment of cancer. Over the past years, immunologists have established an essential function of TRX for activation, proliferation, and responses in T cells, B cells, and macrophages. Upon activation, immune cells rearrange their redox system and activate the TRX pathway to promote proliferation through sustainment of nucleotide biosynthesis, and to support inflammatory responses in myeloid cells by allowing NF-κB and NLRP3 inflammasome responses. Consequently, targeting the TRX system may therapeutically be exploited to inhibit immune responses in inflammatory conditions. In this review, we summarize recent insights revealing key roles of the TRX pathway in immune cells in health and disease, and lessons learnt for cancer therapy.

Keywords: cancer · cellular redox · immunoregulation · ROS · TRX system

Introduction

Reactive oxygen species (ROS) are highly reactive molecules that contain oxygen, such as hydrogen peroxide and superoxide among others. In addition to exogenous sources (*e.g.* pollutants, radiation, etc), ROS can also arise endogenously by mitochondrial respiratory chain and by the action of NADPH oxidase (NOX) [1]. Despite their essential role in killing pathogens and regulating cell proliferation and differentiation, exacerbated ROS can induce damage to DNA, proteins, and lipids, thereby contributing to aging and cell death [1–3]. Aerobic organisms are equipped with a sophisticated network of antioxidant proteins that maintain reduction-oxidation (redox) homeostasis [4–6]. Tilting of this redox balance towards oxidation, which is known as "oxidative stress", has been associated with multiple pathologies, such as cardiovascular diseases [7], cancer [8], diabetes [9], asthma [10], neurological disorders [11], and aging [1].

The thioredoxin (TRX) system is one of the major cellular antioxidant pathways that control redox homeostasis. This system comprises NADPH, TRX reductase (TRXR, encoded by *TXNRD*), TRX (encoded by *TXN*) itself, and the negative regulator TRX-interacting protein (TXNIP, also known as vitamin D3 upregulated protein 1; encoded by the *TXNIP* gene). TXNIP binds to reduced TRX via intermolecular disulfide interactions and blocks its activity. TRXR is a selenoenzyme that has the unique capacity to utilize reducing equivalents from NADPH generated by the pentose phosphate pathway (PPP) to keep TRX in its reduced state (Fig. 1A). Three different TRXR isoforms have been described in mammals, which differ in their subcellular localization and tissue-specific expression: TRXR1 is found in the cytoplasm, TRXR2 is

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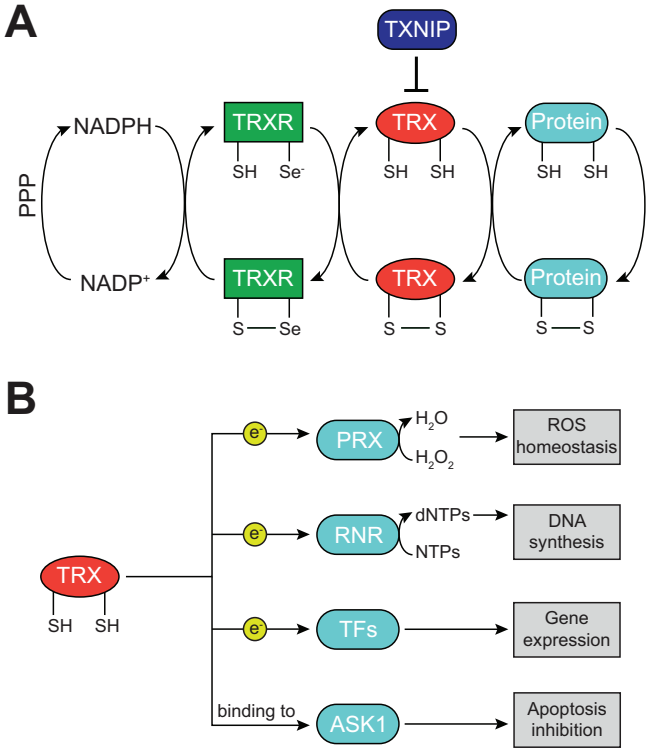

Figure 1. The components of the TRX system and its cellular functions. (A) The pentose phosphate pathway (PPP) produces NADPH, which acts as the most upstream electron donor of the thioredoxin (TRX) system. NADPH keeps TRX reductase (TRXR) in its reduced state, which in turn provides reducing equivalents to TRX. Reduced TRX can ultimately donate electrons to several cellular proteins. The activity of the TRX system is regulated by TRX-interacting protein (TXNIP), which binds to TRX and inhibits its function (S, sulfur atom in cysteine; Se, selenium atom in selenocysteine). (B) Cellular functions of reduced TRX. By donation of electrons (e^-), TRX supports the functionality of cellular peroxiredoxins (PRX), which scavenge hydrogen peroxide (H_2O_2); of ribonucleotide reductase (RNR), which generates 2'-deoxyribonucleotides (dNTPs) for DNA synthesis; and of numerous transcription factors (TFs), thus regulating gene expression. Furthermore, by binding to ASK1 and inhibiting its activity, reduced TRX prevents apoptosis.

localized in mitochondria, and TRXR3 is specifically expressed in testis. Similarly, the two TRX isoforms TRX1 and TRX2 are localized in the cytoplasm and mitochondria, respectively. This specific expression pattern of the components of the TRX system builds up a robust antioxidant system that ubiquitously maintains redox homeostasis [4, 5, 12].

The TRX system regulates several processes, including gene expression, antioxidant response, apoptosis, and cell proliferation [13]. For instance, TRX modulates the activity of various transcription factors such as NF-κB, REF1, and HIF1α [14–16]; it donates reducing equivalents to the antioxidant enzymes peroxiredoxins (PRX) and methionine sulfoxide reductases [17, 18]; it sustains nucleotide biosynthesis by ribonucleotide reductase (RNR) [19]; and it regulates apoptosis by suppressing ASK1 activity [20] (Fig. 1B).

The glutathione (GSH)/glutaredoxin (GRX) system, similarly to the TRX system, utilizes electrons from NADPH and shuttles them to glutathione reductase (GSR), which regenerates reduced GSH from it oxidized form (GSSG). In addition to directly maintain redox balance [21, 22], GSH can in turn provide reducing equivalents to glutaredoxins (GRX) [23]. TRX and GRX shuttle electrons to numerous shared substrates and therefore possess overlapping bioactivities [23]. To which extent, however, TRX and GRX can compensate for each other *in vivo* is poorly understood and may vary in distinct cell types and environmental conditions.

Over the past decade, by studying conditional knockouts of critical components of these redox systems, immunologists have established their cell-autonomous roles in development and function of lymphocytes and myeloid cells. These studies implicate how a dysregulated control of the cellular redox state may contribute to immune dysfunction and disease [4]. In this Review, we summarize recent insights revealing the role of the cytosolic TRX system in immune cells and discuss potential therapeutic strategies in pathological conditions.

Immunoregulation by TRX1 and TRXR1

TRX1-TRXR1 system: An accelerator of T cell proliferation

T cells undergo massive proliferation during thymic development and upon antigen encounter in secondary lymphoid organs. T cell activation is accompanied by the upregulation of cellular redox regulators, including the components of the TRX system TRX1 and TRXR1 [24, 25] (Fig. 2A). Genetic deletion of *Txnrd1* in mice, which encodes the key enzyme that recycles oxidized TRX1 into its reduced form, results in impaired expansion of activated T cells during viral infections and other immune responses [25]. Mechanistically, the TRX1 system donates reducing equivalents to RNR, which ultimately reduces ribonucleotides into the corresponding 2'-deoxyribonucleotides (dNTPs) during DNA biosynthesis at the last step of the PPP [25] (Fig. 2B and C). Although the GSH system can also provide reducing power to RNR and compensate for the absence of TRX1 in other cell types, GRX1 expression is extremely low and not upregulated upon T cell activation [25] (Fig. 2B). Of note, despite the antioxidant function of TRX1, *Txnrd1*-deficient T cells do not display increased levels of ROS [25]. Consistent with the key function of the TRX1 system in T cells, a recent in vivo CRISPR-Cas9 mutagenesis screen identified *Txnrd1* as a positive regulator of the antitumor response of $CD8^+$ T cells [26], and another report showed that overexpression of Trx1 improves the antitumor function of T cells [27]. By contrast, the TRX1-TRXR1 system is largely dispensable for homeostatic maintenance of naïve T cells [25], likely due to their modest requirement of dNTP biosynthesis through the PPP [28].

Naïve T cells are quiescent and predominantly rely on oxidative phosphorylation (OXPHOS) for energy generation. By contrast, activated T cells are metabolically more active and utilize the PPP and aerobic glycolysis, a process that converts glucose into lactate despite sufficient oxygen supply, to meet their bioenergetic demands, including the synthesis of nucleotides,

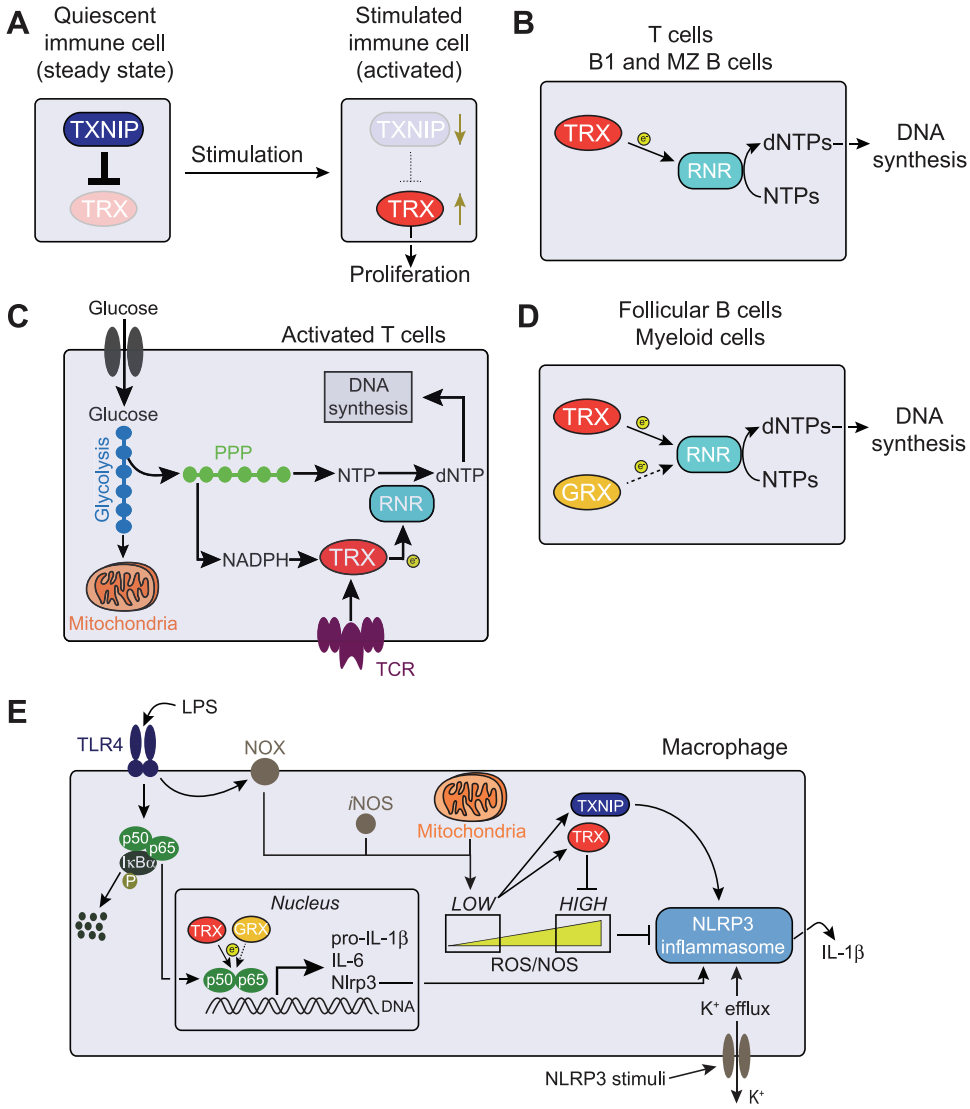

Figure 2. Immunoregulation by the TRX system. (A) Stimulated immune cells activate the thioredoxin (TRX) system by both increasing its transcriptional expression and by repressing its inhibitor thioredoxin-interacting protein (TXNIP), thus promoting proliferation. (**B**) In T cells, B1, and marginal zone (MZ) B cells, the TRX system is the only pathway supporting ribonucleotide reductase (RNR)-mediated reduction (electron [e^-] donation) of ribonucleotides (NTPs) into the corresponding 2'-deoxyribonucleotides (dNTPs) for DNA synthesis. (**C**) T cell stimulation reprogram cellular metabolism towards increased glycolysis and pentose phosphate pathway (PPP), which generates NADPH and building blocks for DNA synthesis. Concomitantly, upregulated TRX shuttles electrons from NADPH to RNR for dNTP production. (**D**) In follicular B cells and myeloid cells, both the TRX and the glutaredoxin (GRX) system can sustain DNA biosynthesis, although GRX-dependent reaction is less efficient (dotted arrow). (**E**) TRX system-dependent redox regulation of NLRP3 inflammasome activation. Lipopolysaccharide (LPS) binding to Toll-like receptor 4 (TLR4) leads to phosphorylation (P) and consequent proteolysis of the NF-κB inhibitor IκB-α. This results in the release and translocation of NF-κB p50 and p65 to the nucleus for transcription of genes encoding pro-inflammatory cytokines (e.g. pro-IL-1β and IL-6) and NLRP3 itself. TRX, and partially also GRX, positively regulates the binding of NF-κB to target DNA, promoting transcriptional activity of target genes. NADPH oxidase (NOX) and mitochondrial metabolism generate reactive oxygen species (ROS), and nitric oxide (NO) synthase (iNOS) produces NO. Low ROS levels releases TRX from TXNIP-mediated inhibition, which then leads to NLRP3 inflammasome activation and IL-1β secretion. This is achieved by both TRX scavenging excessive ROS that would otherwise prevent inflammasome formation and by TXNIP potentially interacting with NLRP3 and enhancing IL-1β production.

fatty acids and amino acids [25, 28]. Metabolic changes and the TRX1 pathway are tightly interconnected in activated T cells: Shift toward increased PPP upon antigen encounter allows the generation of NADPH, which fuels the TRX1 system that ultimately sustains the PPP by donating reducing power to RNR for nucleotide biosynthesis in activated T cells [25] (Fig. 2C).

TRX1-TRXR1 system in B cells and compensatory mechanisms

B cell activation also results in increased mitochondrial activity and glycolysis to fuel the PPP [29]. However, deletion of *Txnrd1* in B cells does not affect development, homeostasis, germinal center reactions, and antibody responses in mice [30], implying that

other compensatory pathways sustain the PPP by providing reducing power to RNR. GRX1 is highly expressed in B cells and indeed fuels dNTP production with reducing equivalents, which may allow proliferation of *Txnrd1*-deficient B cells in the bone marrow and in germinal centers [30]. However, GRX1 is unable to fully sustain rapid expansion, and thus *Txnrd1*-deficient B cells display a partial proliferative delay that may arise from either a less efficient donation of reducing power to RNR or from the time window required to shift from TRX to GRX utilization [30] (Fig. 2D).

In addition to the TRX system, B cell responses can also relinquish on the ROS scavenging enzymes glutathione peroxidase 1 (GPX1) and GPX4, PRX1-PRX4, and NF-E2-related factor 2 (NRF2) [31, 32], indicating that B cells have a more robust and flexible redox system compared to T cells. B cells express NADPH oxidases and show electron leakage from mitochondrial complex I and III upon cell stimulation leading to ROS; Moreover, proper immunoglobulin folding plasma cells also results in ROS cascade from endoplasmic reticulum [31, 33, 34]. Thus, exposure of B cells to high levels of ROS may have evolutionary selected development of redundant pathways allowing to deal with oxidative stress.

Differential requirement of the TRX1-TRXR1 system in B1 and MZ B cells

B cells are generally subdivided into two major subsets which differ in ontogeny, homeostasis, and functionality: B2 and B1 B cells. B2 cells, which are often referred to as "classical" B cells, develop in the bone marrow, produce high-affinity antibodies against foreign antigens and generate immunological memory in secondary lymphoid organs. While B2 cells encompass both follicular and marginal zone (MZ) B cells, the aforementioned features of B2 cells exclusively apply to follicular B cells. MZ B cells functionally differ from follicular B cells and, together with B1 cells, are often referred to as innate-like lymphocytes because of their capacity to rapidly respond to blood-borne antigens and to initiate low-affinity antibody responses [35, 36]. In contrast to follicular B cells, the redox system of innate-like B cells, including both B1 and MZ B cells, is weaker as it has been presented for T cells in the previous chapter. *Txnrd1*-deficient MZ B cells and B1 cells display impaired development, homeostatic maintenance, and antibody responses, since they are unable to engage GRX1 as a compensatory pathway to sustain dNTP production [30] (Fig. 2B). This redox similarity between T cells and innate-like B cells also further applies to their strict requirement of lipid peroxide-scavenging enzyme glutathione peroxidase-4 (GPX4) [32] and of the redox-sensitive organelle "peroxisomes" [37].

Inflammatory role of the TRX1-TRXR1 pathway in dendritic cells and macrophages

In contrast to T cells, the TRX1-TRXR1 pathway is largely dispensable for the development and maintenance of tissue and blood monocytes, dendritic cells, neutrophils, eosinophils, and macrophages in mice due to their flexibility in shifting toward the compensatory GSH/GRX pathway to sustain thiol-based reactions [38]. Despite being dispensable during homeostatic maintenance, the GSH/GRX pathway is unable to fully compensate for the absence of the TRX1 system in a situation of emergency myelopoiesis driven by endotoxin when proliferation of myeloid precursors bursts [38] (Fig. 2D). As described above, this has also been observed for follicular B cells, in which the TRX1 system is dispensable for homeostasis but strictly required during rapid expansion in the germinal centers upon infection.

In the inflammatory phase, M1 macrophages rearrange their metabolism to support production of pro-inflammatory cytokines, lipid mediators, and ROS to kill invading pathogens. A shift toward the PPP generates NADPH, the key electron donor that promotes ROS and nitric oxide (NO) production by NOX enzymes and NO synthase (*i*NOS), respectively [39]. In the resolution phase, however, NADPH donates reducing equivalents to the TRX1-TRXR1 pathway, which in turn scavenges excessive ROS and helps preventing excessive tissue damage after pathogen clearance (Fig. 2E). Consistently, deletion of *Txnrd1* results in ROS overproduction upon TLR stimulation [38]. How exactly NADPH can both promote and inhibit ROS production remains unknown, but it may be explained by highly dynamic metabolic alterations during an immune response, paralleling functional transitions [4, 40].

The transcription factor NF-κB is a key mediator of inflammatory responses that induces the expression of several pro-inflammatory cytokines and chemokines after its translocation into the nucleus [41]. Based on the numerous target genes under control, NF-κB activation is tightly regulated both in the cytoplasm and in the nucleus by distinct mechanisms. TRX1-dependent redox regulation of NF-κB has been previously proposed, although its role in inflammation remains somewhat controversial when considering that both activating and inhibitory roles have been reported. Indeed, while generation of cellular ROS result in NF-κB activation and nuclear translocation, oxidized NF-κB displays impaired DNA-binding activity. Similarly, TRX1 has a dual role: While preventing NF-κB activation by blocking the dissociation and degradation of the IκB-α inhibitor, TRX1 oxidation promotes NF-κB binding to the target DNA by the reduction of cysteine 62 in the p50 subunit of NF-κB [42–44]. Indeed, TLR activation of *Txnrd1*-deficient bone-marrow-derived dendritic cells (BMDCs) results in impaired DNA-binding capacity of the p65 subunit of NF-κB in the nucleus rather than cytoplasmic activation and nuclear translocation [38]. Enhanced NF-kB DNA binding and transcriptional activity may be achieved via structural modifications, such as the reduction of disulfide bonds, of NF-κB itself or other components of the transcriptional complex [38] (Fig. 2E). By contrast, bone-marrow-derived macrophages (BMDMs) express high levels of GRX proteins, which take over the function of TRX1 when *Txnrd1* is genetically deleted, keep nuclear NF-κB p65 reduced, and allow normal transcription of pro-inflammatory target genes

[38]. Dendritic cells, tissue-resident macrophages, and other myeloid cell types express variable levels of GRX proteins *in vivo*. It remains to be investigated which ones rely strictly on the TRX1-TRXR1 system similar to BMDCs, and which ones are more flexible and can use both the TRX1 and GRX pathways similar to BMDM.

Inflammasomes are large cytosolic proteins that trigger IL-1β processing and release [45]. IL-1β is produced as an inactive precursor (pro-IL-1β) after exposure to pathogens or danger signals, and requires a second signal leading to inflammasome assembly to be processed into its active form by caspase-1 [45]. Several mechanisms have been reported to describe NLRP3 inflammasome activation. In addition to potassium (K^+) efflux, which is a common event that is associated with several NLRP3 stimuli, ROS production has been also proposed to promote inflammasome activation [46]. In particular, mitochondrial ROS, oxidized mitochondrial DNA, and compounds that induce mitochondrial outer membrane permeabilization lead to IL-1β production and secretion [47–50]. Paradoxically, despite this NLRP3-promoting function of ROS, a defect of the TRX1 system prevents IL-1β processing by the NLRP3 inflammasome due to impaired scavenging of excessive ROS (such as hydrogen peroxide) that may oxidize and damage other inflammasome components [38, 42] (Fig. 2E). NLRP3 itself and caspase-1 can be oxidized and damaged by exacerbated ROS and NO levels [38, 51–53].

Taken together, TRX1 promotes the production of pro-inflammatory cytokines (e.g., IL-12, IL-6, IL-1β, and TNF-α) by both enhancing NF-κB binding to target DNA in the nucleus and allowing proper NLRP3 inflammasome formation in the cytoplasm.

TXNIP, the inhibitor of the TRX1-TRXR1 pathway

TXNIP as brake of lymphocyte proliferation

TXNIP binds to TRX1 and negatively regulates the activity of the TRX1 system [54]. T cell activation results in rapid TXNIP downregulation, release of TRX1 from inhibition, and donation of electrons to RNR for dNTP production [25, 55] (Fig. 2A). The transcription factor c-Myc mediates TXNIP repression and thereby contributes to the activation of the TRX1 system upon TCR triggering, in addition to promoting T cell metabolic reprogramming [25]. Consequently, absence of TXNIP results in increased proliferation of effector T cells and germinal center B cell in immune responses [55].

Klein Geltink et al. proposed that CD28 signaling (signal 2) leads to the downregulation of TXNIP, which then translates into the engagement of mitochondrial fatty acid oxidation [56]. Muri et al., however, found that TCR triggering alone (anti-CD3; signal 1) is sufficient to potently inhibit TXNIP expression in $CD8^+$ T cells, and that CD28 engagement has only a minor contribution at weak TCR engagement (low concentration of anti-CD3) [55]. This discrepancy may arise from the fact that Klein Geltink et al. only focused on the minor difference between anti-CD3 alone and anti-CD3/anti-CD28 without a comparison to the expression of TXNIP in naïve T cells, thus missing that signal 1 is the main contributor to TXNIP inhibition.

Controversial role of TXNIP in inflammasome activation

TXNIP has originally been suggested as a redox-sensitive ligand of NLRP3 that links ROS production to NLRP3 inflammasome activation in macrophages [57]. A physical interaction of TXNIP and NLRP3 has also been proposed in pancreatic islets, leading to enhanced IL-1β production in type 2 diabetes [57, 58]. However, the requirement of TXNIP in NLRP3 inflammasome activation has been questioned in other studies. *Txnip*-deficient macrophages display indeed normal NLRP3 activation and IL-1β production both *in vitro* and *in vivo* [38, 59]. In conclusion, despite the controversial role of TXNIP in inflammasome activation, the TRX1-TRXR1 pathway is key in the production of IL-1β (Fig. 2E).

The TRX system in cancer and therapeutic approaches

Roles of TRX and TRXR in cancer and therapeutic interventions

Cancer is a complex and heterogeneous disease ranking among the top 10 leading causes of death worldwide. Cancer cells switch metabolism from oxidative phosphorylation to glycolysis (Warburg effect), which fuels the synthesis of anabolic molecules required for accelerated cell proliferation. In addition to metabolic reprogramming, exacerbated ROS production, mainly driven by aberrant electron flow in the mitochondrial electron transport chain and NADPH oxidases, is a hallmark of cancer cells [60]. Rapid cancer cell proliferation induces ROS and oxidation of redox-sensitive signaling pathways (i.e., PI3K/Akt/mTOR and MAPK) and transcription factors (such as NF-kB, HIF-1α, p53) promote cell growth and a pro-tumorigenic state. However, oxidative stress also induces DNA damage, genome instability, and toxic lipid oxidation resulting in senescence, apoptotic, necrotic, or ferroptotic cell death. To counteract oxidative stress and prevent cytotoxicity, cancer cells adapt to elevated ROS levels by upregulation of antioxidant pathways [61–63]. It is therefore not surprising that TRX and TRXR levels are increased in numerous types of solid tumors (i.e. lung [64], colorectal [65], pancreatic [66], gastric [67], breast [68, 69], and prostate [70]) as well as hematopoietic malignancies and correlate with poor prognosis [71–73].

Upregulation of the TRX1 system has been associated with each of the six cancer hallmarks proposed by Hanahan and Weinberg [74]. Beyond scavenging ROS, TRX is a driver of

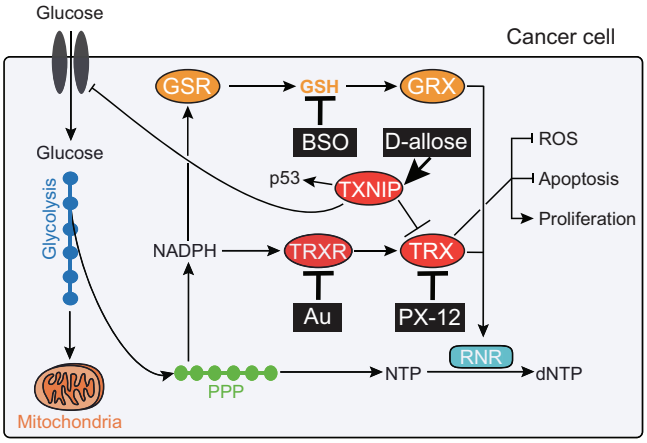

Figure 3. Targeting the TRX system for cancer therapy. Cancer cells adapt to elevated ROS by upregulating cellular antioxidants, including thioredoxin (TRX) and TRX reductase (TRXR), and by downregulating their inhibitor TRX-interacting protein (TXNIP). The chemotherapeutic drugs auranofin (Au) and PX-12, which respectively inhibit TRXR and TRX, lead to oxidative stress, reduced 2'-deoxyribonucleotide (dNTP) biosynthesis and cell death of cancer cells. D-Allose inhibits cancer cell survival and proliferation by boosting TXNIP expression, which results in the induction of the tumor suppressor p53 and in the inhibition of TRX and of glucose transporter 1 (GLUT1)-dependent glucose import. Of note, while blockade of TRX or TRXR alone may be sufficient to inhibit T cell leukemia and lymphomas, additional inhibition of the glutathione (GSH)/glutaredoxin (GRX) pathway by the drug buthionine sulfoximine (BSO) may be required to treat B cell malignancies and other tumors due to their redundant functions (e.g. donation of electrons to ribonucleotide reductase [RNR]). Abbreviations: GSR, glutathione reductase; PPP, pentose phosphate pathway; black rectangular boxes indicate chemotherapeutic drugs.

tumor development, propagation, metastasis, angiogenesis, resistance to chemotherapies [73, 75, 76] by regulating transcription factors (such as p53, NF-κB, and AP1, HIF-1α), signaling pathways (including p38 MAPK, ASK-1, JNK, PTEN), and synthesis of DNA building (i.e. RNR) that are all involved in regulation of cell growth and death. Moreover, extracellular activity of TRX can also promote cell growth [73, 75, 76]. Consequently, inhibiting TRX/TRXR activity is a promising tumor therapy.

Several chemotherapeutic drugs have been developed to target the TRX pathway and act mainly by inducing oxidative stress and apoptosis in tumor cells, as reviewed elsewhere [61, 62, 77]. For instance, the compound 1-methylpropyl 2-imidazolyl disulfide (PX-12) inhibits TRX activity through binding to the cysteine 73 residue of TRX. PX-12 has previously entered clinical trials [62] and has been shown to possess potent antitumor activity against different types of tumors, including lung cancer [78], acute myeloid leukemia [79], and lung colorectal cancer [80] among others. Furthermore, the gold-based compound auranofin, which is FDA-approved for the treatment of rheumatoid arthritis [81], targets primarily TRXR (Fig. 3). Based on its capacity to induce apoptosis, auranofin has been repurposed to treat cancer, such as ovarian cancer [82], breast cancer [83], multiple myeloma [84], and chronic lymphocytic leukemia [85, 86]. Despite the availability of numerous drugs that target the TRX system, and some promising effects in preclinical reports, only few compounds went to clinical trials, and they do not inhibit TRX/TRXR specifically. Novel strategies for development of better and more specific drugs have been summarized in excellent reviews recently [61, 62, 77].

Dual targeting of the TRX and GSH/GRX system

As both the TRX and the GSH/GRX systems regulate cellular redox homeostasis in cancer cells, the two pathways are functionally overlapping and absence or inefficiency of one system can be compensated by the other. Consistently, genetic deletion and pharmacological inhibition of both the TRX and GSH/GRX pathways *in vitro* and *in vivo* synergistically induce cancer cell death [87, 88]. However, the efficiency of the therapeutic interference with the two redox systems depends on the type of tumor. Although inhibition of the TRX pathway alone could be exploited to inhibit T cell leukemia and lymphomas based on their exclusive utilization of the TRX pathway for proliferation [25], blockade of both the TRX and GSH/GRX systems may be needed to treat B cell lymphoma, myeloid tumors, sarcoma, mammary tumors and possibly others due to redundancy of the two systems [30, 38, 87–89] (Fig. 3). As an additional level of complexity, other cellular antioxidants, including PRX, GPX, and other components of the GSH pathway, are also upregulated in tumor cells and promote tumorigenesis [90–92]. Development of drugs that target the catalytically active selenocysteine group present in TRX and GPX, but not the thiol group of cysteine residues present in many proteins and enzymes that are vital for the function of non-tumor cells will facilitate reaching several goals at once.

Role of TXNIP in cancer

TXNIP acts as a tumor suppressor that is commonly silenced in various human cancers, including breast cancer [93] and hepatocellular carcinoma [94] among others, and exploited by the tumor cells to maintain redox homeostasis [61]. Moreover, in a TRX-independent manner, TXNIP negatively regulates glucose metabolism by inhibiting the expression of glucose transporter 1 (GLUT1) in cancer cells [95], and it can act as tumor suppressor by directly regulating the induction of p53 [96]. D-Allose, a sugar that induces expression of TXNIP, exhibits antitumor effects in several cancers [61] (Fig. 3). In this regard, a recent genetic screen identified TXNIP to possess key metabolic gatekeeper functions in B cell acute lymphoblastic cells and proposed that pharmacological TXNIP agonists, such as D-allose, synergize with glucocorticoids and thus represent a potential therapeutic strategy [97].

In summary, the different components of the TRX system, namely TRX, TRXR, and TXNIP, can all be targeted by chemotherapeutic drugs and offer opportunities for cancer therapy.

Concluding remarks

Recent reports unraveled an essential role of the TRX system for the expansion of effector and memory T cells, and macrophage inflammatory responses. B cells are more flexible and can use both the GSH/GRX and TRX systems for germinal center and antibody responses. Cancer cells upregulate the TRX system to allow rapid growth, alike activated T cells, and avoid damage and death due to oxidative stress. Thus, interference with redox homeostasis is considered the Achilles' heel of cancer cells and targeting the components of the TRX and GRX systems as a promising therapeutical strategy. The main challenge will be to selectively target the TRX system in tumor cells that rely solely on TRX and to target both the TRX and GSH/GRX systems in tumors with redundant antioxidant activity. At the same time, antitumor immunity and successful immune therapy relies on intact TRX function. Further research is required to define the specific functions of the TRX pathway in $CD4^+$ T cell subsets (such as $T_H1/T_H2/T_H17$ cells and T regulatory (T_{reg}) cells), natural killer (NK) cells, and in myeloid cell populations including neutrophils, conventional DCs (cDC1/cDC2), tissue-resident macrophages, and inflammatory versus alternatively activated macrophages. Moreover, it would be of general interest to investigate the expression and function of the TRX system in exhausted T cells (T_{ex}). Since they are known to have reduced proliferative potential and accumulated ROS, T_{ex} cells may potentially display a high TXNIP/TRX ratio. A better understanding may be exploited for therapeutic interventions in cancer and other inflammatory diseases.

Acknowledgments: We appreciate financial support by research grants from Swiss National Science Foundation (SNF 310030B_182829) and ETH Zürich (ETH 23-16-2).

Conflict of interest: The authors declare no commercial or financial conflict of interest.

Author contribution: The authors contributed equally to all aspects of the article.

Data availability statement: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Received: 29/8/2022
Revised: 20/10/2022
Accepted: 24/10/2022
Accepted article online: 25/10/2022