Context-dependent targeting of thioredoxin reductase 1 in cancer: a mechanistic review

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Targeting the cytosolic selenoprotein thioredoxin reductase 1 (TrxR1, also named TXNRD1) has emerged as a promising strategy to exploit redox vulnerabilities in cancer. However, both preclinical observations and recent mechanistic studies indicate that TrxR1 inhibition can have context-dependent outcomes. This article synthesizes a mechanistic framework linking cytosolic redox buffering, proteostasis, receptor tyrosine kinase (RTK) signaling, and immune surveillance with treatment responses. It highlights the dual functional roles of the TrxR1-substrate TXNL1 (also named TRP32), discusses intracellular transcriptional crosstalk shaping treatment sensitivity, and outlines potential combination strategies with RTK modulators. Magy Onkol 70:128-135, 2026

Keywords: *thioredoxin reductase, redox biology, TXNL1, selenoprotein, combinational therapy*

A citoszolikus tioredoxin-reduktáz 1 (TrxR1, más néven TXNRD1) szelenofehérje gátlása ígéretes tumorterápiás stratégia a redox rendszerek érzékenységének kiaknázására. Mind a preklinikai megfigyelések, mind a legújabb, működéssel összefüggő vizsgálatok azt mutatják, hogy a TrxR1 gátlásának a daganat típusától vagy mikrokörnyezetétől függő eredményei lehetnek. A jelen publikáció egy olyan működési mechanizmust bemutató keretet szeretne nyújtani, amely a citoszolikus redox pufferelést, a proteosztázist, a receptor-tirozinkináz (RTK) jelátvitelt és az immunrendszer-felügyelet lehetséges hatásait kapcsolja össze a kezelési válaszokkal. Kiemeli a TXNL1 (más néven TRP32) TrxR1-szubsztrát kettős funkcionális szerepét, tárgyalja a kezelési érzékenységet befolyásoló intracelluláris transzkripciós kölcsönhatásokat, és felvázolja az RTK-modulátorokkal történő lehetséges kombinációs stratégiák szerepét.

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Kulcsszavak: tioredoxin-reduktáz, redoxbiológia, TXNL1, szelenofehérje, kombinációs terápia

INTRODUCTION

Redox signaling in cancer and therapy

Reactive oxygen species (ROS) and redox circuits are integral to carcinogenesis and anticancer treatment response (1–8). Cancer cells maintain elevated oxidative pressure while preserving redox homeostasis through adaptive systems including the thioredoxin and glutathione pathways – the only two disulfide reducing enzyme systems in human cells (9–11). Many cytotoxic and targeted anticancer regimens shift this balance, either deliberately or as collateral, aggravating oxidative stress and reconfiguring redox sensitive signaling (4, 5, 12–14). Consequently, the thioredoxin system — with the cytosolic selenoprotein TrxR1 as a central NADPH-dependent reductase — has become a focus for precision redox therapeutics (1, 15–19).

Therapeutic promise and paradox

Selective inhibition of TrxR1, e.g., with TRi-1 which is the most specific inhibitor of the enzyme yet described (15, 20, 21), has demonstrated broad anticancer activity by collapsing cytosolic redox buffering, intensifying oxidative/proteotoxic stress, and rewiring signaling via important transcription factors including NRF2, NF-κB, and STAT3; nonetheless, context-dependent deleterious outcomes have also been observed. The actual outcome of TrxR1 inhibition in cancer treatment is likely related to cell-specific pathways and signaling events within the tumor microenvironment as well as systemically. Specifically, the reliance on the thioredoxin vs. glutathione system, the extent of enzyme inactivation, resulting oxidative stress vs. antioxidant capacity, and specific redox modulated signaling pathways of the cell – possibly shifting responses from adaptive NRF2-mediated survival to irreversible oxidative stress and cell death when compensatory mechanisms are overwhelmed. This, in turn, may explain why in some models, expansion of regulatory T cells and thus suppression of immune-mediated cancer control can become the main result of TrxR1 targeting rather than the intended anticancer effect (22). This paradox highlights the need for mechanistic criteria to distinguish and predict outcome in terms of beneficial or harmful effects of TrxR1 inhibition, where therapeutically harmful outcomes would involve immune suppression and impaired tumor growth inhibition. This emphasizes the need of considering immune-competent animal models as essential tools to uncover treatment strategies that may shift TrxR1 targeting responses toward the intended therapeutic efficacy.

Scope of this article

Here, we integrate recent experimental rationales and results to propose a mechanistic decision model governing TrxR1-targeted therapy. In this model, we emphasize key specific concepts that need to be considered, including: (i) TXNL1-dependent proteostasis and signaling; (ii) RTK–phosphatase axes coupled to TrxR1; and (iii) the interface with antitumoral immunity.

TRXR1 IN CELLULAR REDOX CONTROL AND SIGNALING

Selenoprotein biochemistry and TrxR1

Selenoproteins are a unique family of proteins containing the rare and highly reactive amino acid selenocysteine (Sec, U) (23–25). They are usually redox active enzymes, several

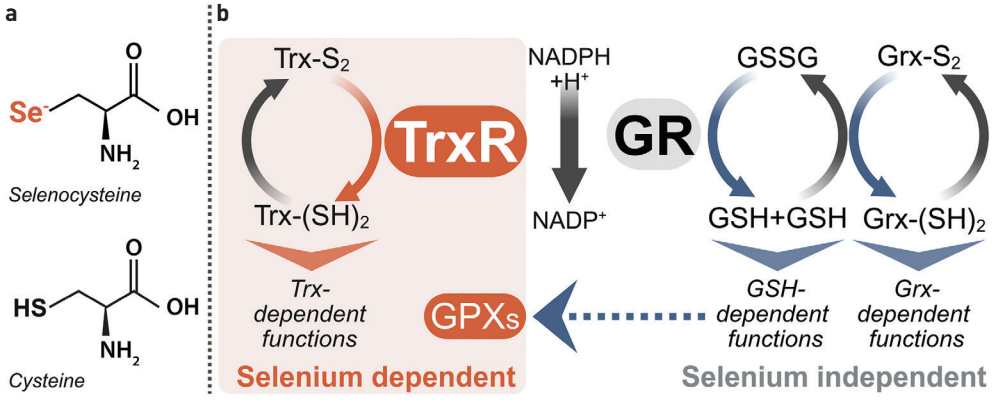


FIGURE 1. Selenium-dependent redox mechanisms. a) Structure of Sec compared to Cys. b) Schematic representation of major reductive enzyme pathways in human cells. Selenium-dependent thioredoxin reductase (TrxR) reduces thioredoxin (Trx) using NADPH as electron donor, consequently, Trx reduces its many downstream targets including ribonucleotide reductase, peroxiredoxins, etc. Glutathione reductase (GR) also uses NADPH to reduce glutathione disulfide (GSSG) to two molecules of glutathione (GSH). GSH subsequently supports many cellular functions and enzymes, including glutathione S-transferases, glutaredoxins (Grxs) and selenium-dependent glutathione peroxidases (GPXs). The thioredoxin and glutathione systems – while showing overlapping functions – interact and complement each other. Selenium-dependent enzymes of the pathways are highlighted in orange.

of them belonging to the two major redox enzyme systems in humans (the thioredoxin and glutathione systems), employing Sec as their catalytic residue. Sec is the Se-for-S substituted analog of the more common cysteine (Cys, C) residue *(Figure 1a),* making it chemically more reactive than Cys (26–28). Intriguingly, Sec is uniquely incorporated during the translation of selenoproteins at the site of a specific in-frame UGA codon, hence redefining this termination codon to a sense codon, using an intricate translation machinery that in essence expands the genetic code (29–32). The human genome encodes for 25 selenoproteins (25), including isoforms of TrxR (cytosolic TrxR1, mitochondrial TrxR2 and testis-specific TGR), being the central enzymes of the thioredoxin system; and several glutathione peroxidases (GPXs) with major roles as glutathione-driven antioxidant enzymes *(Figure 1b).* The unique Sec chemistry (26–28) underpins the high catalytic reactivity of TrxR1 toward oxidized thioredoxin and other disulfide substrates, enabling reductive pathways supporting the activities of peroxiredoxins (33–35), ribonucleotide reductase (36) and protection of cysteine-dependent enzymes (e.g., PTPs) (37, 38), as well as the facile inhibition of TrxR1 by electrophiles targeting the exposed Sec residue in the enzyme (1, 15, 39–42). Selenium-dependent and -independent redox mechanisms are summarized in *Figure 1.*

Network position

By sustaining thioredoxin functions, TrxR1 indirectly regulates RTK signaling through protection/reactivation of protein tyrosine phosphatases; it thereby modulates phosphorylation cascades downstream of EGF, FGF, PDGF, and insulin, with consequences for proliferation and immune evasion (e.g., via STAT3 → PD-L1) (37, 38, 43–48). Hence, altering TrxR1 activity reverberates across metabolic (49–52), proteostatic (53–55), and transcriptional (47, 56–59) cellular pathways.

Pharmacological inhibition

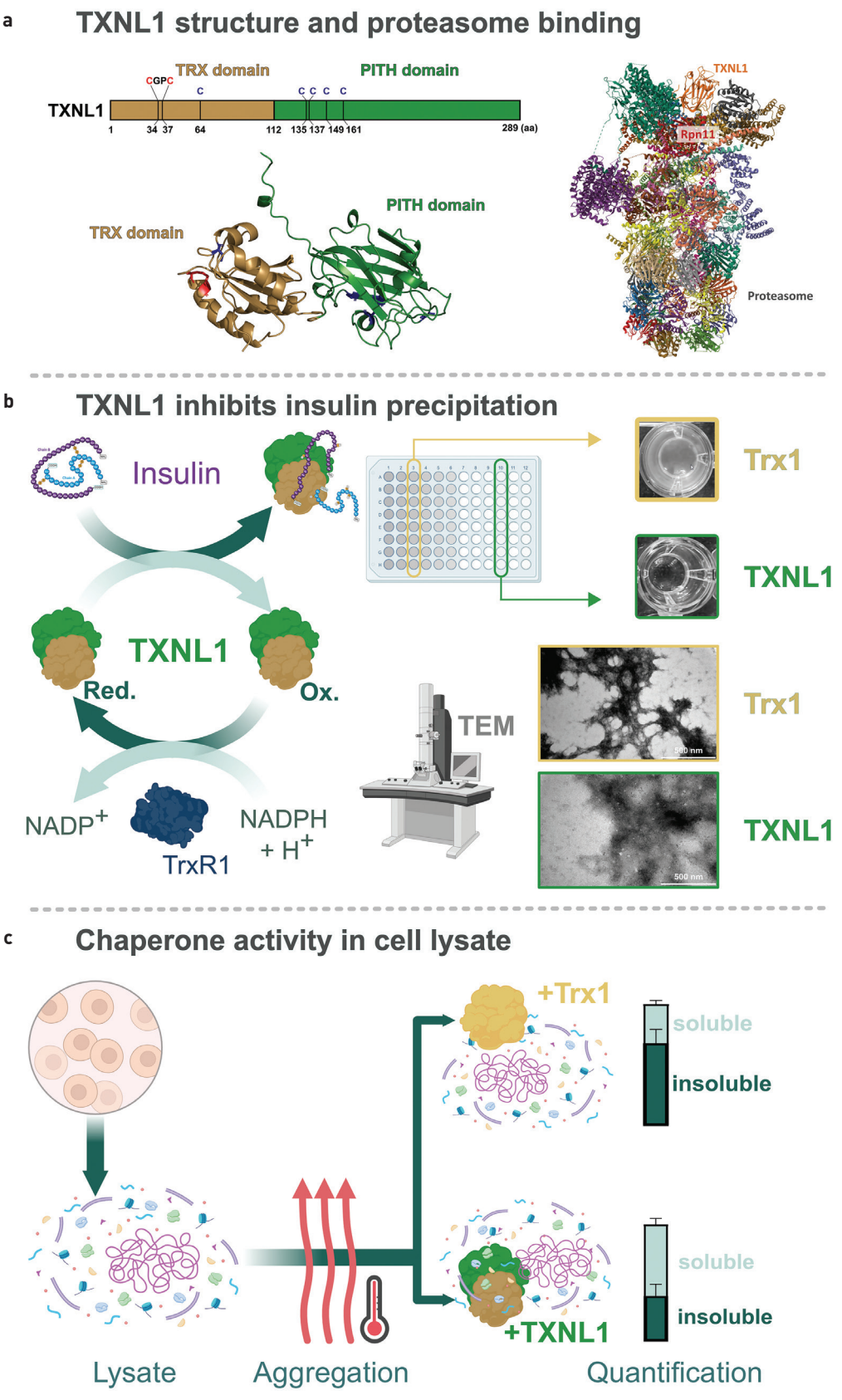
Overcoming species differences in the complex synthesis machinery of selenoprotein expression, methods for synthetic or recombinant selenoprotein production have been developed that facilitate in-depth studies of their catalytic functions (60–65). This also enabled a high-throughput screening campaign leading to the discovery of TRi-1 (15, 66), today known as the most selective TrxR1 inhibitor (21). Importantly, auranofin (Ridaura®) is also a well-known TrxR1 inhibitor (67) but it is less selective than TRi-1 (21); however, auranofin is an already FDA approved gold(I) compound inhibiting TrxR1, and efficiently activates NRF2, the key transcription factor driving cellular defense against oxidative stress (21, 42, 56, 68–70). Both compounds trigger oxidative and proteotoxic stress yet differ in off target spectra and mitochondrial impacts (15, 21). These distinctions are valuable for mechanistic dissection and forthcoming drug combination designs.

TXNL1 AS A SWITCH BETWEEN REDOX BUFFERING AND PROTEOSTASIS STRESS

TXNL1 (thioredoxin-like 1; also named TRP32 for thioredoxin-related protein of 32 kDa) is a cytosolic protein ubiquitously expressed from yeast to mammals (71). The functional roles of TXNL1, however, have yet remained little studied. The protein exhibits two separable functions: (i) a TrxR1-coupled thioredoxin-like redox activity (71–73) which is provided by its N-terminal thioredoxin-fold domain, and (ii) a redox-independent chaperone activity (72), with structural/functional interactions with the proteasome through its C-terminal PITH domain (74–77) *(Figure 2a).* TXNL1 thereby differs from thioredoxin in that it combines redox activity with robust chaperone-like properties. Illustratively, when in vitro assays for Trx-catalyzed reduction of disulfides in insulin are performed, the released A and B chains of insulin will immediately precipitate. However, when such an assay is performed using TXNL1 instead of Trx for reduction of the disulfides in insulin, the chaperone activities of TXNL1 prevent that precipitation from occurring (72) *(Figure 2b)* or provide more potent prevention than seen with Trx1 of aggregation by proteins in cell lysates upon heating *(Figure 2c).* Together with the interactions of TXNL1 with the proteasome (74, 75), these properties suggest that the protein may be a likely culprit as modulator for cellular effects of TrxR1 targeting by TRi-1. Interestingly, TXNL1 is also uniquely downregulated in cells upon treatment with auranofin (21, 78, 79), yet the functional importance of this remains unclear. The different roles of TXNL1 are summarized in *Figure 2.*

Available biochemical evidence indicates that the two activities of TXNL1 are experimentally separable, with

FIGURE 2. Roles of the thioredoxin-fold protein TXNL1. a) TXNL1 has an N-terminal Trx-fold domain and a C-terminal proteasome interacting PITH domain. Active site cysteines responsible for Trx-like redox activity are marked with red. TXNL1 binds to the 19S regulatory particle of the proteasome via interaction with Rpn11 (cryo-EM structure of TXNL1-bound proteasome, PDB: 9BW4; 74). b) TXNL1 is a redox-active enzyme that can reduce the disulfides in insulin and other substrates in a TrxR1-coupled reaction using NADPH. TXNL1 also has chaperone activity that does not require ATP: it makes non-covalent complexes with reduced insulin. Reduced insulin readily precipitates and forms fibrils that are easily visualized by transmission electron microscopy (TEM). Whereas reactions containing Trx1 display protofibrils and globular structures by TEM, TXNL1 keeps reduced insulin in solution, yielding only amorphous, disordered material (72). c) TXNL1 also provides chaperone function towards whole cell lysate proteins by preventing their aggregation during heating. The results reveal that TXNL1 has dual functions, supporting TrxR1-driven redox activities in disulfide reduction reactions, as well as being an ATP-independent chaperone that does not require involvement of its redox activity. Figure panels are based upon our previous publication (72), licensed under CC BY 4.0.


a
TXNL1 structure and proteasome binding
TRX domain
PITH domain
CGPC
C
C C C C
TXNL1
1 34 37 64 112 135 137 149 161 289 (aa)
TRX domain
PITH domain
TXNL1
Rpn11
Proteasome
b
TXNL1 inhibits insulin precipitation
Insulin
TXNL1
Red.
Ox.
NADP+
TrxR1
NADPH
+ H+
TEM
Trx1
TXNL1
Trx1
TXNL1
500 nm
500 nm
c
Chaperone activity in cell lysate
+Trx1
soluble
insoluble
soluble
insoluble
+TXNL1
Lysate
Aggregation
Quantification

the redox activity of the protein conferred by its dithiol/disulfide active site motif in its N-terminal domain, while the chaperone activity is mainly related to its C-terminal domain (72). However, the extent to which these functions are independently regulated also in cells remains unclear. In this context, TrxR1 inhibition is expected to impair TXNL1-dependent redox functions more directly than its intrinsic chaperone activity, although the two functions may remain indirectly coupled within an integrated cellular redox–proteostasis network.

TXNL1 has been reported to associate with the 26S proteasome through interactions with Rpn11 and to participate in protein quality-control pathways (74). Moreover, TXNL1 depletion causes a moderate accumulation and stabilization of ubiquitinated protein conjugates, supporting its role in proteostasis regulation (77). Thus, under TrxR1 inhibition, one plausible scenario would be that loss of TXNL1-mediated reductive capacity compromises the handling or processing of oxidized or misfolded proteins, whereas the remaining chaperone activity represents a compensatory, but potentially insufficient, buffering mechanism. This may contribute to the accumulation of damaged proteins and subsequent proteotoxic stress, which may have therapeutic effects (80).

We hence posit that TXNL1 abundance or function can potentially determine whether TrxR1 inhibition causes manageable stress (possibly leading to initial cytostasis followed by NRF2 activation) or an overwhelming proteotoxicity (leading to cell death), and that auranofin-induced TXNL1 downregulation might amplify proteasome dysfunction in specific contexts. However, these hypotheses need to be further addressed in appropriate immune-competent models.

RECEPTOR TYROSINE KINASE SIGNALING, PHOSPHATASES, AND REDOX SENSITIVE TRANSCRIPTION FACTOR SIGNALING

Signaling through RTKs is under redox control, with the cellular responses to growth factors, including EGF, PDGF, FGF, or insulin, being shaped by inhibitory cysteine based protein tyrosine phosphatases (PTPs). For their activities, PTPs depend on catalytic Cys residues which are easily oxidized, and typically require TrxR1-driven reductive pathways for reactivation; thus, TrxR1 inhibition can prolong RTK driven phosphorylation or, depending on context, disrupt adaptive signaling and promote cell death (37, 43, 44, 46, 49, 81). Furthermore, many transcription factors, including p53 (82–85), NRF2 (58), NF-κB (86–88), and STAT3 (47, 86), are sensitive to redox modulation through TrxR1 inhibition, with the potential to influence immune functions. This includes modulation of cytokine production by NF-kB signaling (89, 90), PD-L1 regulation through the STAT3 pathway (47, 48), and through immunoregulatory effects of NRF2 (22, 68, 69). TrxR1 inhibition promotes innate immune activation through modulated cGAS–STING signaling (91), inflammasome activation (92, 93), and immunogenic cell death (69), while simultaneously modulating adaptive immunity by altering T-cell function and macrophage polarization in a redox-dependent manner (94).

Many clinical agents (e.g., platinum compounds, nitrosoureas, quinones) also targetTrxR1 (16, 40, 95–97); and RTK inhibitors (imatinib, osimertinib, lapatinib, sorafenib) modulate upstream signaling. Therefore, we suggest that future combinations of RTK inhibitors with specific TrxR1 targeting may possibly uncover synergies, or antagonisms, with regards to the anticancer efficacy of these classes of drugs. So far there have been no trials evaluating specific TrxR1 inhibitors such as TRi-1 in this context, but some reports suggest that addition of auranofin can increase the anticancer efficacy of Akt inhibition in lung or pancreatic cancer (98), and of RTK inhibitors such as trametinib in breast cancer (99), or in combination with IPA-3, a non-ATP competitive p21-activated kinase 1 (PAK1) inhibitor, in EGFR-mutated non-small cell lung cancer cell lines (100).

The dependence of cancer cells on TrxR1, TXNL1 and RTKs, with the potential context-dependent outcomes of combined RTK and TrxR1 inhibition, are schematically summarized in *Figure 3*.

CONCLUSIONS

TrxR1 is a powerful lever in cancer redox biology, but its therapeutic deployment demands context awareness. By integrating TXNL1-mediated proteostasis, RTK/PTP signaling, and immune dynamics, it may become possible to forecast and shape outcomes of TrxR1 inhibition. Such approaches could support rational, biomarker guided combinations — particularly with RTK inhibitors — to transform context dependency into predictable clinical benefit.

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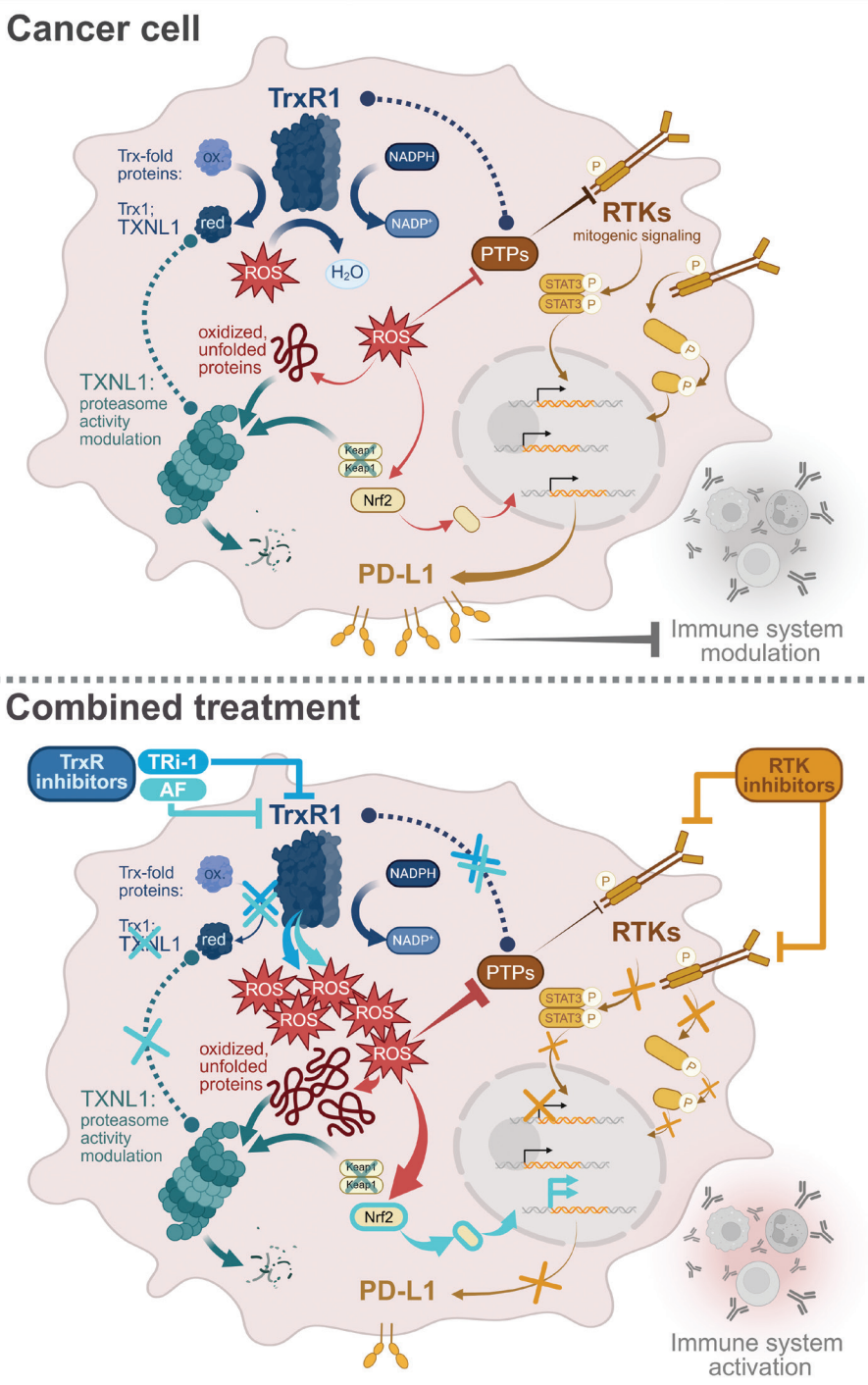

FIGURE 3. TrxR1 inhibition might have context-dependent outcome in cancer therapy and may be combined with RTK inhibition. TrxR1 activity (dark blue) propels both antioxidant systems and TXNL1 functions, its inhibition by TRi-1 (light blue) or auranofin (AF, teal) results in dramatic elevation of cytosolic reactive oxygen species (ROS; red) that challenge the cellular redox systems and induces proteotoxicity, and — in TXNL1-low states — may tilt cells toward lethal collapse. Receptor tyrosine kinase (RTK) activity generates peroxide bursts that inhibit PTPs, and as TrxR1/Trx reactivates PTPs, inhibiting TrxR1 prolongs mitogenic phosphorylation cascades but can also stress proteostasis. RTK signaling also induces activation of STAT3, that as a transcription factor related to TrxR1 function shapes PD-L1 expression and immune modulation. Consequently, co inhibiting RTKs (yellow) together with TrxR1 targeting may transform the signaling dynamics towards cell death, specifically in cancer cells, and furthermore increase the efficacy of the antitumoral immune surveillance.

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