Involvement of the thioredoxin system in multiple diseases: A focus on mechanisms of action in autophagy and ferroptosis (Review)

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Abstract. The thioredoxin (Trx) system comprises four core components: Trx-interacting protein (TXNIP), Trx, Trx reductase (TrxR) and NADPH. TrxR utilizes NADPH to reduce Trx, reducing target proteins through its conserved thiol groups, thereby maintaining cellular redox balance. TXNIP inhibits Trx activity by forming a disulfide exchange reaction with Trx. Beyond its role in redox regulation, the Trx system interacts with various cellular regulators and participates in intracellular signaling networks. The Trx system exhibits dual regulatory roles in autophagy, with Trx primarily exerting an inhibitory effect on ferroptosis and apoptosis, whereas TXNIP promotes these processes. Multiple molecular mechanisms are implicated in these regulatory functions. Furthermore, the Trx system mediates cross-regulation between autophagy and ferroptosis, as well as autophagy and apoptosis, thereby influencing cellular responses to stress conditions. The present review examines the structural components of the Trx system and the cellular translocation of TXNIP. Additionally, it explores the involvement of the Trx system in various diseases, including neurodegenerative disorders, cardiovascular diseases and cancer, highlighting its potential as a therapeutic target. By analyzing the molecular mechanisms through which the Trx system modulates cell death pathways, including ferroptosis, autophagy and apoptosis, the present review may provide novel research perspectives and theoretical foundations for developing disease treatment strategies.

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Abbreviations: Trx, thioredoxin; TXNIP, thioredoxin-interacting protein; TrxR, thioredoxin reductase; GPX, glutathione peroxidase; ASK1, apoptosis signal-regulated kinase 1; MAPK, mitogen-activated protein kinase; GLUT1, glucose transporter 1; ERS, endoplasmic reticulum stress; ROS, reactive oxygen species; NLRP3, NOD-like receptor family pyrin domain-containing 3; PPAR, peroxisome proliferator-activated receptor; Keap1, Kelch-like ECH-associated protein 1; PD, Parkinson's disease; CML, chronic myeloid leukaemia; AMPK, AMP-activated protein kinase; NF-κB, nuclear factor κB; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; HCC, hepatocellular carcinoma; FoxO1, forkhead box O1; LC3, microtubule-associated protein light chain 3; LAMPs, lysosome-associated membrane proteins; PINK1, PTEN-induced kinase 1; α-syn, α-synuclein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DR, diabetic retinopathy; LECs, lens epithelial cells; ACR, acrylamide; AGE, advanced glycation end-product; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, protein kinase B; MGO, methylglyoxal; TFEB, transcription factor EB; JNK, c-Jun N-terminal kinase

Key words: Trx system, ferroptosis, autophagy, apoptosis, biological structure

Contents

1. Introduction

The thioredoxin (Trx) system constitutes a pivotal intracellular antioxidant defense network that plays an essential role in maintaining cellular redox homeostasis and modulating signaling cascades, impacting numerous cellular processes such as proliferation, differentiation and apoptosis (1-3). Recent advances in redox biology have highlighted the Trx

system's involvement not only in redox regulation (4-6) but also in the modulation of complex cell death pathways (4,7-9). Despite considerable progress, comprehensive reviews elucidating the mechanistic underpinnings of Trx's role in programmed cell death remain scarce, particularly in relation to autophagy and ferroptosis. Autophagy, an intracellular degradation process, is a well-recognized double-edged sword, wherein it can both mitigate oxidative stress damage by removing oxidized biomolecules and promote cell death under certain conditions (10). Ferroptosis, a recently identified form of iron-dependent programmed cell death, has garnered increasing attention due to its pathophysiological relevance in a variety of diseases, including neurodegeneration, cancer and ischemic organ injury (11,12). Autophagy and ferroptosis are distinct yet intimately linked cell death modalities, with redox status playing a crucial role in their regulation (13,14). The precise mechanisms through which the Trx system influences these processes, however, are not fully elucidated, highlighting a significant area for further investigation. This review aims to provide an overview of recent findings on the regulatory roles of the Trx system in cell death pathways (Fig. 1), with a particular focus on its interactions with autophagy and ferroptosis, across various disease contexts. By integrating the latest research, we aim to provide a conceptual framework for future studies and therapeutic strategies targeting Trx-mediated regulation of cell death.

2. Trx system

The Trx system consists of Trx-interacting protein (TXNIP), Trx, Trx reductase (TrxR) and NADPH, which serve an important role in growth promotion, apoptosis, inflammation regulation, antioxidant defense and maintenance of redox state homeostasis (15). In a study by Laurent *et al* (16) in 1964, Trx was isolated from *Escherichia coli*. Three different Trx isoforms were found in mammalian cells, categorized as Trx1, Trx2 and Trx3 (17). Trx1, a 105-amino-acid redox protein with a molecular mass of 12 kDa, is an important component of the Trx system and is mainly localized in the cytoplasm and nucleus (10,18). Trx2 is present in mitochondria, whereas Trx3 is found only in germ cells (17).

Trx exhibits broad phylogenetic conservation spanning prokaryotic to eukaryotic systems. Trx has different isoforms in different organisms with distinct subcellular localization patterns, including cytoplasmic, mitochondrial, endoplasmic reticular, membranous and extracellular distributions. Notably, these various isoforms have different functions (5). Structural analyses have revealed conserved architecture across family members, comprising three α-helical elements encircling a central four-stranded β-sheet core, with higher eukaryotes demonstrating supplementary secondary structure elements (19). In *Homo sapiens*, the molecular configuration manifests as a quintuple β-sheet assembly interspersed with four α-helical domains (20). Evolutionary preservation is notably observed in the catalytic domain, characterized by a Cys-Gly-Pro-Cys sequence maintaining redox function across taxa (18). Trx undergoes a redox reaction through cysteine residues in its active site. It has been shown that active site cysteines form disulfide bonds in the oxidized state, while in the reduced state they exist as thiols (19). Trx reduces disulfide bonds in target proteins through this redox exchange, thereby regulating their activity and function (21). This shift is important for its catalytic function. The process of electron transfer through the reversible transformation of active site sulfhydryl-disulfide (-SH/-S-S-) is the core mechanism of the Trx system (21).

Biological structure of Trx1 and Trx2. In addition to the two catalytic cysteine residues (Cys32 and Cys35) in the catalytic site, human Trx1 contains three key non-catalytic cysteine residues: Cys62, Cys69 and Cys73. Cys62 and Cys69 are amenable to S-nitrosylation, whereas Cys73 undergoes multiple modifications, including S-nitrosylation and glutathionylation (22,23). Given that all these cysteine residues are subject to post-translational modifications, Trx1 exhibits diverse functional roles.

Trx1 can be proteolytically cleaved by monocytes *in vivo* into a truncated form, Trx80, which exhibits distinct functional properties compared with Trx1 (24,25). Structurally, Trx1 comprises only a Trx-fold domain containing an active CXXC motif, whereas Trx2 includes an N-terminal zinc-finger domain with two additional CXXC motifs alongside the Trx-fold domain. This structural difference renders Trx2 more complex than Trx1 (26).

Biological structure of TrxR. As the central enzymatic constituent of the Trx system, TrxR is classified within the pyridine nucleotide-disulfide oxidoreductase family (27). TrxR is a dimer with an N-terminal structural domain that contains the FAD cofactor, which is responsible for accepting electrons from NADPH, and a C-terminal structural domain that contains the conserved selenocysteine (Sec) active site, which is the end-site for electron transfer (28). During catalysis, electrons from NADPH are transferred to FAD and subsequently relayed through a Cys59-Cys64 disulfide bridge to the Sec residue within the C-terminal domain. This electron flux culminates in the reduction of oxidized Trx ($Trx\text{-}S_2$) to its dithiol state [$Trx\text{-}(SH)_2$], a biochemical process important for sustaining cellular redox equilibrium (28). Due to the high reactivity of Sec residues and the accessible position of the C-terminal active site, TrxR has broad substrate specificity (29).

Human TrxR is a selenoprotein (27). Selenium deficiency leads to impaired TrxR activity, which disturbs cellular redox homeostasis and is closely associated with the pathogenesis of multiple disorders, such as cancer and inflammatory diseases (30,31). Three isoforms of TrxR exist in humans-TrxR1, TrxR2 and TrxR3-which are encoded by the TXNRD1, TXNRD2 and TXNRD3 genes, respectively (32,33). TrxR1 is localized in the cytoplasm and nucleus, TrxR2 in the mitochondria and TrxR3 in testicular tissue (34).

Biological structure of NADPH. NADPH, a key coenzyme, comprises three structural components: i) A reduced nicotinamide ring carrying two hydrogen atoms, which serves as an electron carrier; ii) an adenine nucleotide linked to nicotinamide mononucleotide via a pyrophosphate bond; and iii) a 2'-phosphate group that confers specificity in enzyme binding, for example to TrxR (35). In the Trx system, NADPH acts as the primary electron donor, transferring electrons to $Trx\text{-}S_2$

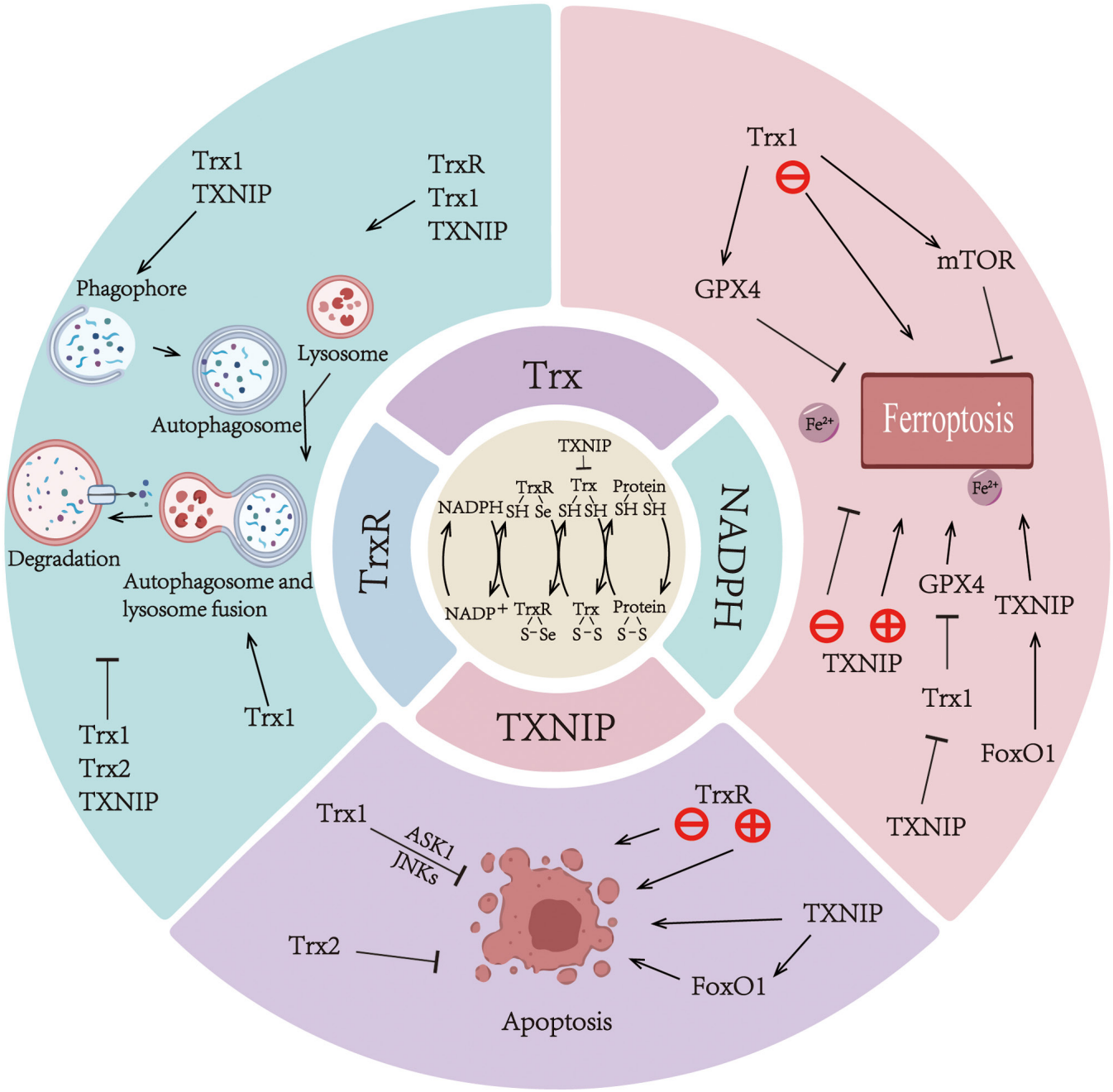

Figure 1. Trx system in the regulation of cell death. Trx, thioredoxin; TXNIP, thioredoxin-interacting protein; TrxR, thioredoxin reductase; NADPH, nicotinamide adenine dinucleotide phosphate; GPX4, glutathione peroxidase 4; FoxO1, forkhead box O1; ASK1, apoptosis signal-regulated kinase 1; JNKs, c-Jun N-terminal kinases; mTOR, mechanistic target of rapamycin.

via TrxR, thereby driving its reduction to the active form [Trx-$(SH)_2$] (36).

In addition to its role in the Trx system, NADPH provides reducing power to enzymes such as glutathione reductase and glutathione peroxidase (GPX), enabling the regeneration of antioxidant molecules (37,38). It also serves as a key coenzyme in fatty acid and cholesterol synthesis (39). The NADPH/$NADP^+$ ratio regulates cell proliferation, apoptosis and inflammatory responses through the modulation of Trx, nuclear factor E2-related factor 2 and other pathways (40).

Biological structure of TXNIP. TXNIP is an α-arrestin family member encoded by the TXNIP locus (41). Originally designated vitamin D3 upregulated protein 1 following identification in HL-60 promyelocytic cells under 1,25-dihydroxyvitamin D3 treatment (42), TXNIP was subsequently characterized as Trx-binding protein-2 through yeast two-hybrid screening (43). Structural characterization revealed two conserved PPxY motifs that serve as docking platforms for WW domains of E3 ubiquitin ligases, enabling targeted ubiquitination-mediated proteolysis (44). TXNIP is able to bind to Trx through a disulfide bond exchange mechanism, forming a disulfide bond of TXNIP Cys247-Trx Cys32. This binding results in a structural rearrangement of TXNIP, unlike other α-arrestin family proteins (44). This interaction may explain the negative regulatory effect of TXNIP on Trx activity.

Translocation of TXNIP. The functional dynamics of TXNIP are intrinsically linked to its subcellular compartmentalization. Under basal conditions, TXNIP predominantly localizes to nuclear compartments and exhibits restricted cytoplasmic translocation (45). Oxidative challenge induces atomic export of TXNIP to membranous or mitochondrial domains (45). Mechanistically, TXNIP functions as a Trx1 antagonist, suppressing its redox-regulatory capacity through direct binding (46). Cytosolic TXNIP-Trx1 complexes dissociate the Trx1-apoptosis signal-regulated kinase 1 (ASK1) interaction, triggering the p38 mitogen-activated protein kinase (MAPK) cascade activation, thereby potentiating oxidative stress responses, cellular damage, apoptotic execution and senescence pathways (46-48). Under oxidative stress conditions, mitochondrial-localized TXNIP further engages Trx2 via analogous binding, liberating Trx2-conjugated ASK1 to initiate apoptosis through ASK1 activation (49).

TXNIP is also transcriptionally regulated in a cell type-specific manner by nuclear receptors such as peroxisome proliferator-activated receptor (PPAR), farnesol X receptor, vitamin D receptor and glucocorticoid receptor (50).

TXNIP translocation has been observed under high-glucose conditions. Elevated intracellular glucose induces TXNIP translocation to the cytoplasmic membrane, where it promotes the endocytosis of glucose transporter 1 (GLUT1), reduces GLUT1 expression and consequently decreases GLUT1 abundance on the cell membrane, thereby reducing glucose uptake into the cell (51). Nephrotic syndrome is characterized by notable proteinuria or albuminuria. Albuminuria can induce endoplasmic reticulum stress (ERS), during which TXNIP translocates from the nucleus to mitochondria, promoting mitochondrial reactive oxygen species (ROS) production and activating NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasomes (52). Beyond these mechanisms, TXNIP demonstrates mitochondrial translocation in hyperuricemic inflammation, where its interaction with NLRP3 induces inflammasome assembly and subsequent pro-inflammatory cytokine secretion (53). Furthermore, under high-glucose conditions, elevated levels of translocated TXNIP in retinal Müller cells suggest that the TXNIP-Drp1-Parkin axis may be involved in mediating mitophagy in retinal cells under diabetic conditions (54).

TXNIP serves multifaceted roles in cancer metastasis, closely linked to its subcellular localization and disease context. In renal cancer, nuclear TXNIP in tumor-supporting endothelial cells is associated with elevated ROS and favorable prognosis, whereas cytoplasmic TXNIP is associated with abnormal angiogenesis, necrosis and recurrence (55). Functionally, TXNIP may promote or suppress metastasis depending on cancer type and cellular metabolism. For example, TXNIP upregulation enhances migration in hepatocellular carcinoma (HCC) by increasing ROS levels (56). By contrast, decreased TXNIP expression is associated with enhanced migration, invasion and metastatic potential in colorectal cancer, cervical cancer, melanoma and pancreatic cancer (56).

Furthermore, TXNIP shows context-dependent subcellular localization and expression changes under conditions such as high-glucose exposure, proteinuria-induced ERS, and uric acid-mediated inflammation, which in turn modulate oxidative stress, inflammation and cell fate (51-53). These disease-specific localization and expression patterns not only offer mechanistic insights but also highlight promising avenues for therapeutic targeting. Modulating TXNIP or its associated pathways may serve as a novel strategy for treating tumor metastasis and a broad spectrum of other diseases (56).

3. Mechanisms of the Trx system involved in ferroptosis in different diseases

Ferroptosis constitutes a distinctive cell death modality characterized by iron-dependent lipid peroxidation (57). A recent study has revealed the three key processes in the pathogenesis of ferroptosis following cerebral ischemia: Iron deposition, the accumulation of lipid peroxides and inhibition of the anti-ferroptosis pathway, with the GPX4-mediated antioxidant system serving a central role (58). As a selenoprotein, GPX4 catalyzes the reduction of lipid hydroperoxides, establishing its enzymatic centrality in ferroptosis regulation (59). This cell death paradigm manifests distinct ultrastructural features, including mitochondrial volume reduction with cristae diminution and elevated membrane electron density, while the nuclear architecture remains unaltered. Concomitant biochemical alterations involve progressive accumulation of lipid peroxides and the elevation of ROS (60). The resultant oxidative milieu leads to protein modification and lipid peroxidation, resulting in cellular dysfunction, which is associated with numerous diseases (61).

Linkage between Trx1, TrxR and ferroptosis. Trx1 functions as an antioxidant factor, maintaining redox homeostasis and regulating ferroptosis across diverse pathological conditions. Kelch-like ECH-associated protein 1 (Keap1) serves as an important regulatory component in cellular redox homeostasis (62,63). The cited pharmacological study has demonstrated that curdione modulates redox complexes by disrupting Keap1-Trx1 interactions while enhancing Trx1-GPX4 binding, thereby attenuating post-infarction ferroptosis through Keap1/Trx1/GPX4 axis regulation (64). Complementary mechanistic evidence has emerged from neurodegenerative research: In Parkinson's disease (PD) models characterized by substantia nigra dopaminergic neuron loss, Trx1 exerts ferroptosis inhibition via the modulation of GPX4 activity and glutathione (GSH) (65).

Ferroptosis is also closely associated with cancer development, progression and suppression. The apoptotic resistance of malignant cells underscores the therapeutic value of non-apoptotic death modalities, with ferroptosis induction emerging as a promising oncological intervention strategy (66-68). Cellular redox homeostasis is jointly maintained by two thiol-dependent antioxidant systems, the GSH and Trx systems, which exhibit redundant functions via inter-system electron transfer capabilities (69). Malignant cells exhibit marked elevation of redox regulators including Trx1 and GSH, creating therapeutic barriers by neutralizing ROS-mediated cytotoxicity and impairing Fenton reaction-driven ferroptosis (34,69). The Fenton process, wherein Fe^{2+} catalyzes H_2O_2 conversion to hydroxyl radicals, initiates lipid peroxidation cascades that can be exploited for targeted tumor ferroptosis induction (70,71).

Trx1 demonstrates marked upregulation across multiple solid malignanciesand is associated with poor cancer prognosis (72). Radiotherapeutic interventions potentiate ferroptosis through ionizing radiation-generated ROS that drive lipid peroxidation cascades (73). Therapeutic synergy is achieved when combining radiotherapy with a Trx1 inhibitor, which enhances tumor-selective ferroptosis induction (74).

Similarly, in chronic myeloid leukaemia (CML), co-inhibition of Trx1 and glutamate-cysteine ligase may serve as a therapeutic strategy for both imatinib-sensitive and drug-resistant patients by triggering ferroptosis (75).

Notably, in other diseases such as PD and myocardial infarction, Trx1 upregulation inhibits ferroptosis to confer cellular protection (64,65). By contrast, in tumors such as CML, Trx1 inhibition promotes ferroptosis, enhancing therapeutic efficacy and overcoming treatment resistance (74,75). Therapeutic induction of ferroptosis through radiotherapy, chemotherapy and immunotherapeutic regimens demonstrates synergistic augmentation of oncological treatment efficacy (68,73,76,77). Overall, Trx1 may negatively regulate ferroptosis; however, ferroptosis exhibits opposite effects in different diseases. This dichotomy likely arises from variations in cell type, metabolic state and pathological microenvironment (78,79).

Furthermore, the diversity and complexity of Trx1 target proteins are highlighted by the identification of 112 Trx1 target proteins in mouse primary cortical neurons, with 77 of these Trx1-interacting proteins being modulated by rapamycin (80). Among these, the mechanistic target of rapamycin (mTOR) is a major downstream target of Trx1, together with AMP-activated protein kinase (AMPK), nuclear factor κB (NF-κB) and histone deacetylase 4 (75). mTOR serves as a regulatory kinase governing cellular proliferation, metabolic programming and survival signaling (81). Oxidative stress promotes direct interactions between Trx1 and mTOR, inducing intermolecular disulfide bond formation within mTOR kinase and thereby leading to its functional inhibition (81,82). Overexpression of Trx1 prevents mTOR oxidation and preserves its catalytic activity, whereas Trx1 knockdown conversely promotes mTOR oxidation and suppresses mTOR signaling (81,83). However, the C1483F mutation in mTOR confers resistance to oxidation-mediated inactivation even under Trx1-deficient conditions (82). Emerging evidence has further demonstrated that exosomal Trx1 derived from hypoxic human stem cells activates mTOR complex 1 (mTORC1) signaling upon cellular internalization, exhibiting anti-ferroptotic and cardioprotective effects against doxorubicin-induced cardiotoxicity (84). These findings collectively establish the Trx1-mTOR axis as an important regulatory mechanism in ferroptosis suppression. Complementary studies have revealed that pharmacological inhibition of TrxR induces ferroptosis in malignant cells, suggesting its therapeutic potential in cancer treatment (85,86).

Summarily, Trx1 inhibits ferroptosis primarily through its antioxidative capacity and regulation of redox-sensitive signaling cascades. In the context of ferroptosis, Trx1 supports GPX4 activity and GSH synthesis, and protects mTOR function under oxidative stress, supporting its role as a negative regulator of lipid peroxidation and cell death. In various tumor settings, inhibition of Trx1-mediated suppression of ferroptosis may enhance the efficacy of anticancer therapies.

Linkage between TXNIP and ferroptosis. TXNIP has been characterized as a ferroptosis-associated gene across multiple pathological contexts, including oncogenesis (87,88), osteonecrosis of the femoral head (89) and hepatic dysfunction (90).

Functionally, TXNIP acts as a tumor suppressor through its downregulation in malignant cells, where it concurrently suppresses proliferation and metastatic potential and promotes apoptotic pathways (91-93).

In HCC models, the protein inhibitor of activated STAT3 potentiates ferroptosis through activation of the TGF-β pathway, which is mechanistically linked to TXNIP transcriptional upregulation (94). Complementary multi-omics investigations by Zheng *et al* (95), employing RNA sequencing and liquid chromatography-tandem mass spectrometry in lung tumor cell populations, revealed TXNIP as a ferroptosis-associated prognostic biomarker. Experimental validation further demonstrated that TXNIP expression was markedly downregulated in lung cancer stem cells and correlated with advanced disease progression (95).

While TXNIP downregulation exhibits ferroptosis-suppressive effects across both neoplastic and non-neoplastic pathologies, disease-specific regulatory mechanisms govern its activity.

In high-fructose-induced nephropathy, carbohydrate-responsive element-binding protein-β-mediated transcriptional activation of TXNIP leads to lipid peroxidation and drives ferroptosis in renal tubular epithelial cells, thereby exacerbating renal injury (96). By contrast, in diabetic retinopathy, 1,8-eudesmol alleviates retinal ferroptosis by suppressing TXNIP expression in a PPAR-γ-dependent manner, thereby reducing oxidative stress and restoring the integrity of the blood-retinal barrier (97). Mechanistically, TXNIP may inhibit both Trx1 and Trx2, disrupting redox homeostasis and promoting ferroptosis. Forkhead box O1 (FoxO1) further exhibits context-dependent regulation by promoting TXNIP transcription and GSH metabolic disruption, thereby inducing satellite cell ferroptosis and contributing to sarcopenia. Notably, TXNIP silencing rescues these ferroptotic phenotypes, alleviating muscle atrophy (98). Furthermore, hypothermic hypoxia-reoxygenation stress elevates TXNIP expression in *ex vivo* liver transplantation models. This ferroptosis cascade is pharmacologically mitigated by dexmedetomidine-argon co-administration, which blocks TXNIP mitochondrial translocation to preserve redox homeostasis (99). These findings position TXNIP as a conserved positive regulator of ferroptosis across multiple diseases.

TXNIP demonstrates prognostic predictive capacity as a ferroptosis-related biomarker across malignancies. HCC specimens exhibit notable TXNIP downregulation, with diminished expression levels associated with adverse clinical outcomes in HCC progression (100). In lung adenocarcinoma stem cell models, this multifunctional regulator serves dual roles in ferroptosis modulation and prognostic prediction, where reduced expression patterns are associated with three notable clinicopathological parameters: Immunosuppressive tumor microenvironment establishment, advanced tumor, node and metastasis staging, and impaired histodifferentiation status (95). TXNIP is identified as a prognostically notable ferroptosis-associated gene implicated in the pathogenesis of bladder cancer and femoral-head necrosis, offering potential biomarkers for precision medicine applications (89,101).

As a negative regulator of the antioxidant protein Trx1, TXNIP is an important modulator of cellular redox homeostasis (102,103). Experimental evidence has demonstrated that TXNIP inhibits Trx1 activity, thereby promoting ferroptosis. In a neonatal rat model of hypoxic-ischemic injury, hippocampal neuron ferroptosis was shown to be triggered via TXNIP/Trx1/GPX4 pathway activation, which was directly associated with hypoxic-ischemic brain damage severity (104). Similarly, curcumin inhibits ferroptosis by inhibiting the TXNIP/Trx1/GPX4 pathway, thereby attenuating septic lung injury (105).

In summary, TXNIP serves an important regulatory role in ferroptosis across diverse pathological conditions, underscoring its potential as a therapeutic target. Mechanistically, TXNIP antagonizes Trx1 by forming a disulfide bond with its Cys32 residue, leading to Trx1 inactivation and increased ROS levels, thereby facilitating lipid peroxidation and ferroptotic signaling. In addition, TXNIP contributes to ferroptosis by disrupting GSH metabolism and destabilizing redox homeostasis. TXNIP demonstrates notable prognostic associations across multiple malignancies, with expression patterns showing potential utility as a biomarker for cancer diagnosis and prognostic stratification.

4. Mechanisms of the Trx system involved in autophagy in different diseases

The autophagic process comprises four mechanistically distinct phases: Autophagosome nucleation/maturation, cargo sequestration, autolysosomal fusion and lysosomal degradation (106,107). Notably, microtubule-associated protein light chain 3 (LC3) undergoes conjugation with phosphatidylethanolamine during autophagosome biogenesis, leading to the conversion of LC3 to its lipidated form LC3-II, which serves as a principal biomarker for autophagic flux quantification (108-110). Mechanistically, p62 orchestrates selective autophagy execution through ubiquitinated cargo recognition and autophagosomal translocation, ultimately enabling substrate proteolysis (111,112). Lysosome-associated membrane proteins (LAMPs), particularly LAMP1 and LAMP2, are important for maintaining lysosomal acidity and facilitating autophagic flux (113,114). Reduced LAMP2 expression impairs autophagosome clearance through lysosomal dysfunction (115). LAMP2 dysregulation disrupts lysosomal homeostasis, and also impairs the activity of Cathepsin D (CTSD), a key protease for autophagosomal cargo degradation (116,117).

Mitophagy, a selective autophagy subtype, specifically regulates mitochondrial quality control via targeted organelle degradation (118). The PTEN-induced kinase 1 (PINK1)/Parkin axis constitutes an important mitophagy regulatory mechanism. PINK1 selectively accumulates on depolarized mitochondrial membranes, orchestrating Parkin recruitment and activating its E3 ubiquitin-protein ligase activity to initiate ubiquitin-dependent organelle tagging (119). Subsequent recognition of ubiquitinated mitochondria by p62 facilitates autophagosomal engulfment and lysosomal elimination of defective organelles (120). PINK1 and Parkin are also key proteins associated with PD (121).

The mechanisms by which the Trx system regulates autophagy in various diseases are summarized in Table I, highlighting its molecular interactions and bidirectional regulatory effects on autophagy.

Linkage between Trx1 and autophagy. PD develops an abnormal accumulation of α-synuclein (α-syn) (122). Pathological α-syn aggregates exhibit dual neurotoxic effects: Synaptic transmission impairment (123) and autophagic-lysosomal system dysfunction that promotes cytotoxic substrate accumulation (124).

Autophagy-lysosomal pathway impairment induces molecular signatures, including elevated LC3-II expression with concomitant LC3-II/LC3-I ratio upregulation, p62 accumulation and reduced histone D levels (125).

Trx1 enhances α-syn clearance in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD models by modulating autophagic-lysosomal degradation pathways. Furthermore, MPTP exposure upregulates PINK1 and Parkin expression to activate mitophagy. Notably, Trx1 overexpression attenuates this MPTP-induced overaccumulation of damaged mitochondria, demonstrating that Trx1 may restore autophagic flux to eliminate dysfunctional mitochondria (125).

Multiple studies have corroborated the role of Trx1 in enhancing autophagic flux. LC3 accumulation in diabetic retinopathy (DR), accompanied by p62 upregulation, indicates lysosomal dysfunction and subsequent autophagosome accumulation. Trx1 activates autophagy and restores impaired flux by accelerating lysosomal degradation and suppressing excessive autophagosome formation, as demonstrated by autophagic flux assays (126). Furthermore, Trx1 overexpression protects human lens epithelial cells (LECs) from damage by promoting beneficial autophagy under normal conditions while preventing its excessive activation during mild oxidative stress (127). Similarly, Trx upregulation mitigates diabetes-induced hearing loss by preserving cochlear hair cells through TXNIP inhibition and autophagy activation. Elevated LC3-II and reduced p62 expression further support the ameliorating effect of Trx1 on autophagic flux (128).

Cardiac-specific Trx1 expression increases the LC3-II/LC3-I ratio and PPAR-γ coactivator 1-α levels, indicating enhanced mitochondrial autophagy to eliminate dysfunctional mitochondria and mitigate sepsis-induced myocardial dysfunction (129). However, whether autophagic flux is blocked remains yet to be fully elucidated, as the elevated LC3-II/LC3-I ratio may reflect either autophagic activation or impaired flux leading to autophagosome accumulation (130). Further investigation is warranted to clarify these mechanisms.

Evidence indicates that pharmacological inhibition of autophagosome-lysosome fusion with bafilomycin A1, combined with blockade of autophagosome formation using wortmannin, reveals Trx1 primarily regulates autophagy at the initiation stage and promotes its induction (127). This parallels TXNIP-mediated autophagic flux regulation at the initiation phase of autophagy (131).

However, conflicting evidence exists in the literature indicating that Trx1 may negatively regulate autophagy, contradicting the aforementioned findings. Acrylamide (ACR), a neurotoxic chemical, primarily exerts its effects

Table I. Effect of the Trx system on autophagy.

A, Trx1

First author, year	Autophagy regulation	Effects on autophagy	Diseases	(Refs.)
Gu, 2024	Positive	Trx1 upregulation improves autophagic flux and promotes clearance of damaged mitochondria by regulating autophagy-lysosomal processes.	Parkinson's disease	(125)
Ren, 2022	Positive	Trx1 activates autophagy and ameliorates impaired autophagic flux.	Diabetic retinopathy	(126)
Hu, 2023	Positive	Trx1 promotes autophagy induction mainly at the initiation stage of autophagy and protects LECs from oxidative damage.	Cataracts	(127)
Ren, 2021	Positive	Trx1 upregulation activates autophagy and improves autophagic flux by inhibiting TXNIP.	Diabetes-induced hearing impairment	(128)
Sánchez-Villamil, 2016	Positive	Trx1 may promote mitochondrial autophagy, but it remains yet to be fully elucidated whether autophagic flux is blocked.	Sepsis-induced myocardial injury	(129)
Nagarajan, 2023	Positive	Trx1 enhances myocardial ischemia-induced autophagy through ATG7 transnitrosylation, thereby playing an important role in mediating protection of the heart.	Myocardial ischemia	(141)
Wang, 2020	Negative	Trx1 antagonizes the induction of autophagy by acrylamide.	Acrylamide-induced neurotoxicity	(132)
Ren, 2018	Negative	Trx1 inhibits autophagy and improves retinal function through the TXNIP/mTOR pathway.	Diabetic retinopathy	(133)

B, Trx2

First author, year	Autophagy regulation	Effects on autophagy	Diseases	(Refs.)
He, 2021	Negative	Trx2 knockdown causes excessive mitochondrial autophagy and accelerates disease progression.	Type 2 diabetes	(143)
Li, 2017	Negative	Trx2 may inhibit ROS-mediated autophagy through the Akt/mTOR and AMPK/mTOR signaling pathways.	Myocardial ischemia/reperfusion injury *in vitro*	(144)
Li, 2017	Negative	Trx2 overexpression reduces cell death via ASK1-dependent mitochondrial apoptosis and inhibits autophagy through the mTOR pathway.	Myocardial ischemia/reperfusion injury *in vivo*	(145)

C, TrxR

First author, year	Autophagy regulation	Effects on autophagy	Diseases	(Refs.)
Lei, 2018	Positive	TrxR inhibitors induce ROS-independent autophagy inhibition and exhibit anticancer effects.	Hepatocellular carcinoma	(147)

Table I. Continued.

C, TrxR

First author, year	Autophagy regulation	Effects on autophagy	Diseases	(Refs.)
Nagakannan, 2016	Positive	TrxR inhibition leads to impaired autophagic flux by interrupting the autophagy-lysosomal degradation pathway, which in turn inhibits autophagy.	Neurodegenerative disease	(148)

D, TXNIP

First author, year	Autophagy regulation	Effects on autophagy	Diseases	(Refs.)
Ren, 2018	Positive	Inhibition of TXNIP may lead to autophagy inhibition and improved retinal function.	Diabetic retinopathy	(133)
Gao, 2020	Positive	TXNIP can stimulate autophagy by interacting with DNA damage-inducible transcript 4 protein, causing an excessive accumulation of autophagosomes.	Myocardial ischemia/reperfusion injury	(154)
Ao, 2021	Positive	TXNIP upregulation positively regulates autophagy and enhances autophagic flux by inactivating PI3K/Akt/mTOR signaling.	Diabetic retinopathy	(155)
Park, 2021	Positive	TXNIP induces autophagy by directly binding to phosphorylated protein kinase AMP-activated catalytic subunit α and regulating mTOR complex 1 and TFEB.	Steatohepatitis	(156)
Huang, 2016	Negative	TXNIP deficiency stimulates autophagy by inhibiting mTOR activation, attenuates diabetes-induced autophagic flux blockage and enhances mitochondrial autophagy.	Diabetic nephropathy	(149)
Huang, 2014	Negative	Silencing TXNIP enhances autophagic flux and reduces autophagosome accumulation.	Diabetic nephropathy	(150)
Du, 2024	Negative	TXNIP knockdown attenuates mTOR activation and restores nuclear translocation of TFEB, thereby stimulating autophagy and ameliorating impaired autophagic flux.	Diabetic nephropathy	(153)

Trx, thioredoxin; TrxR, thioredoxin reductase; TXNIP, thioredoxin-interacting protein; LECs: lens epithelial cells; ROS, reactive oxygen species; TFEB, transcription factor EB; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase.

through ROS elevation. Trx1 overexpression downregulates ATG4B, LC3-II, histone D and LAMP2a, and counteracts ACR-induced autophagy, while Trx1 suppression triggers autophagy (132). Consistent with these findings, Trx1 also suppresses autophagy via the TXNIP/mTOR pathway. DR represents a severe diabetic complication linked to advanced glycation end-product (AGE) accumulation (133). Experimental evidence has demonstrated that Trx upregulation attenuates AGE-mediated neurodegeneration, potentially through TXNIP/mTOR axis suppression and subsequent autophagic inhibition (133). Analogously, in *Streptococcus suis* serotype 2 models, TrxC modulates AGE-induced neurotoxicity via phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (Akt)/mTOR pathway regulation, thereby controlling macrophage autophagic responses (134). *Streptococcus suis* is a common porcine pathogen (135). TrxC is a protein that is widely distributed in microorganisms (134). This evidence indicates that Trx1 exhibits dual regulatory effects on autophagy, influencing either initiation or the autophagy-lysosomal pathway, likely contingent on cellular context and oxidative stress intensity.

Trx1 may undergo autophagic degradation. Methylglyoxal (MGO) accumulation, which promotes AGE formation *in vivo*, induces neuronal autophagy via AMPK/mTOR pathway activation. Inhibition of autophagy through bafilomycin treatment or ATG5 knockdown prevents Trx1 degradation, indicating AMPK-dependent autophagy mediates Trx1 degradation (136). However, in hyperosmotic stress-treated neuronal cells, Trx1 reduction occurs independently of autophagy and AMPK (137), contrasting with MGO-induced AMPK activation and autophagy (137). These discrepancies highlight the need for disease-specific investigation into Trx1 degradation mechanisms.

Autophagy-related proteins ATG4 and ATG7, important for autophagosome formation, are regulated by Trx (138,139). Yeast ATG4 is activated by Trx (140), while Trx1 enhances myocardial ischemia-induced autophagy through ATG7 transnitrosylation (141).

Linkage between Trx2 and autophagy. Multiple experiments have indicated that Trx2 suppresses mitochondrial ROS generation, preserving organelle integrity and function (142). Trx2 knockdown disrupts systemic metabolic homeostasis, exacerbates hyperglycemia and promotes excessive mitochondrial autophagy (143). Specifically, Trx2 deficiency in adipocytes triggers NF-κB-dependent p62 accumulation, which targets damaged mitochondria for excessive autophagy via polyubiquitination (143). Consistent with these findings, *in vivo* and *in vitro* experiments have demonstrated that Trx2 reduces myocardial ischemia-reperfusion injury by inhibiting ROS-mediated autophagy through the Akt/mTOR and AMPK/mTOR signaling pathways (144,145). Collectively, Trx2 exerts dual regulatory effects by suppressing both mitochondrial-specific and general autophagy processes.

Linkage between TrxR and autophagy. TrxR regenerates functional Trx through reductive reactivation, establishing a catalytic cycle that drives iterative redox transitions (146). TrxR inhibitors not only display antitumor effects by inhibiting apoptosis in HCC cells but are also capable of inducing ROS-independent inhibition of autophagy. Pharmacological autophagy inhibition enhances HCC susceptibility to TrxR suppression, positioning TrxR as a promising chemotherapeutic target for HCC management (147). In serum deprivation models, TrxR is associated with lysosomal maturation and regulates the terminal stage of autophagy. Specifically, TrxR inhibition disrupts autophagosome-lysosome fusion, impairing autophagic flux and blocking autophagic degradation (148). This mechanism parallels the role of TrxR as a positive regulator of autophagy in HCC.

Linkage between TXNIP and autophagy. Inhibition of TXNIP enhances autophagy in diabetic nephropathy models. Elevated LC3 and p62 levels in the kidneys of patients with diabetic nephropathy and diabetic rats indicate autophagy dysregulation. TXNIP deficiency stimulates autophagy by inhibiting mTOR activation, alleviates diabetes-induced tubular autophagic flux blockage and promotes tubular mitochondrial autophagy in diabetic rat kidneys (149). Consistently, *in vitro* studies have shown that silencing TXNIP reduces autophagic vesicle accumulation and the expression of LC3-II and p62 in renal tubular cells exposed to high glucose, thereby enhancing autophagic flux and resolving autophagic dysfunction (150). Transcription factor EB (TFEB), a key regulator of autophagy and lysosomal biogenesis (151,152), is negatively regulated by mTOR, which suppresses TFEB nuclear translocation (152). TXNIP knockdown attenuates mTOR activation, restoring TFEB nuclear translocation and stimulating autophagy to improve impaired flux (153).

However, TXNIP may also exert context-dependent pro-autophagic effects. For example, in DR, TXNIP inhibition paradoxically suppresses autophagy (133), highlighting the tissue-specific and disease context-dependent nature of the autophagic regulation of TXNIP. TXNIP positively modulates autophagic activity via complex formation with stress sensor DNA damage-inducible transcript 4 protein (REDD1). This TXNIP-REDD1 interaction amplifies autophagosome biogenesis, resulting in cytoplasmic autophagic vesicle overload that precipitates cardiomyocyte death through excessive autophagy during myocardial ischemia-reperfusion injury (154).

TXNIP-mediated autophagy regulation extends to mTOR pathway inhibition through other mediators under metabolic stress conditions. In DR models, TXNIP upregulation potentiates Müller glial autophagic flux via PI3K/Akt/mTOR signaling suppression (155). Similarly, TXNIP ameliorates steatohepatitis through activation of autophagy and suppression of lipotoxic fatty acid oxidation. Mechanistically, TXNIP induces autophagy by directly binding to phosphorylated protein kinase AMP-activated catalytic subunit α. and regulating mTORC1 and TFEB (156).

Crosstalk between apoptosis and ferroptosis with autophagy. Multiple studies have documented the interplay between autophagy and apoptosis (157,158). In pancreatic islet cells, TXNIP overexpression concurrently drives autophagy and apoptosis, whereas pharmacological autophagy inhibition via 3-methyladenine attenuates TXNIP-induced apoptosis (159). Trx upregulation reduces intracellular ROS levels and suppresses apoptosis by inhibiting autophagy (133).

Autophagy and ferroptosis also exhibit crosstalk in various disease contexts (160). Previous evidence has indicated that TXNIP-mediated autophagy regulates ferroptosis. Specifically, TXNIP suppresses both canonical autophagy and mitochondrial autophagy in patients with diabetes (149). In renal pathology, PINK1/Parkin-driven mitochondrial autophagy protects tubular epithelial cells from ferroptotic death through the ROS/heme oxygenase 1/GPX4 axis (161). In diabetic nephropathy, upregulation of the epigenetic regulator UHRF1 inhibits TXNIP expression, thereby promoting PINK1-mediated mitochondrial autophagy and suppressing ferroptosis (162).

Overall, the regulation of autophagy by TXNIP exhibits a dual nature, capable of either suppressing or promoting autophagy. This dichotomy may arise from several factors: i) TXNIP-mediated regulation of autophagy is context-dependent, varying across different disease settings (163); ii) the function of TXNIP is influenced by its subcellular localization and interactions with distinct intracellular factors, which modulate its effects on autophagy; and iii) this duality may reflect the inherent dual nature of autophagy itself, a process that maintains cellular homeostasis by degrading damaged components but becomes detrimental when excessive.

Furthermore, whether TXNIP possesses a threshold mechanism that governs the initiation or suppression of autophagy remains to be elucidated. Given the complexity of autophagy regulation and the multifaceted role of TXNIP, further investigation into these mechanisms is warranted to elucidate the precise regulatory frameworks governing this relationship.

Notably, the Trx system co-regulates autophagy and other cell death pathways, such as ferroptosis and apoptosis, primarily through four key signaling axes: i) The PINK1/Parkin pathway, linking mitophagy and ferroptosis (161,162); ii) the TXNIP-FoxO1 pathway, linking autophagy to apoptosis (164); iii) the ASK1/c-Jun N-terminal kinase (JNK) pathway, mediating redox-sensitive apoptosis and autophagy (165); and iv) the Trx1/mTOR pathway, linking Trx1 to ferroptosis suppression (81-84). Such crosstalk reflects the key regulatory position of the Trx system in balancing stress signaling and influencing cell survival outcomes.

5. Mechanisms of the Trx system involved in apoptosis in different diseases

Apoptosis, a form of programmed cell death, is executed through tightly regulated gene activation cascades and molecular signaling networks, exerting important regulatory functions in both physiological homeostasis and disease pathogenesis (166).

Trx1 exerts anti-apoptotic effects across various diseases, often involving ASK1 and JNKs (167,168). Specifically, Trx1 inhibition abolishes preconditioning-induced cardioprotection by promoting apoptosis (169). Additionally, Trx1 suppresses apoptosis triggered by ERS (170), which arises from redox environment imbalance and Ca^{2+} homeostasis disruption in the ER. ERS activation, in turn, stimulates excessive ROS production (171). However, the role of Trx1 in apoptosis regulation varies in tumorigenesis. In HCC, Trx1 upregulation inhibits arsenide-induced apoptosis, potentially due to mutations in its active site (172). Similarly, Trx2 has been shown to negatively regulate apoptosis across multiple studies (173,174).

The relationship between TrxR and apoptosis has been markedly investigated in cancer research, where TrxR inhibitors have been shown to induce apoptosis and exert antitumor effects (86,175,176). Beyond pharmacological inhibition, the upregulation of TrxR itself can promote apoptosis in non-neoplastic diseases. For example, selenite alleviates bleomycin-induced idiopathic pulmonary fibrosis by upregulating TrxR, thereby increasing ROS production and promoting apoptosis in mouse lung fibroblasts (177).

TXNIP interacts with NLRP3 to activate inflammatory responses and subsequent pyroptosis (178). Beyond its role in inflammation, TXNIP markedly contributes to apoptosis induction (179). Specifically, TXNIP upregulation activates apoptotic pathways (155) and modulates intracellular ROS generation, which in turn induces oxidative damage and apoptosis (180). Additionally, TXNIP upregulates FoxO1 expression via ROS accumulation and enhances FoxO1 acetylation by inhibiting sirtuin 1 activity, thereby promoting autophagic apoptosis in diabetic cardiomyopathy (164).

In summary, while the role of the Trx system in apoptosis regulation is well-documented, its manifestations across different disease contexts and interactions with other intracellular mechanisms warrant further in-depth investigation. TXNIP promotes apoptosis by disrupting the Trx1-ASK1 and Trx2-ASK1 complexes, leading to ASK1 activation, activation of the p38 MAPK and JNK pathways, and initiation of apoptotic cascades (46,48,49). TXNIP-induced ROS production further amplifies apoptotic signaling and activates inflammasomes (52,180). By contrast, Trx1 protects against apoptosis through ASK1 and JNK inhibition, demonstrating their opposing regulatory roles in cell fate decisions (167,168). Beyond its roles in autophagy, ferroptosis and apoptosis, TXNIP has recently emerged as a modulator of immune responses. Programmed cell death protein 1 (PD-1) and its ligand programmed cell death 1 ligand 1 (PD-L1) are key immune checkpoint regulators that play a pivotal role in modulating immune activity. Combination regimens incorporating PD-1/PD-L1 inhibitors with modalities such as chemotherapy, radiotherapy, complementary immunotherapies or targeted agents have demonstrated enhanced therapeutic efficacy (181). Given its role in shaping the tumor immune microenvironment and promoting inflammasome activation, TXNIP-targeted modulation may enhance responses to immune checkpoint inhibitors such as PD-1/PD-L1 blockade. A recent study suggests that TXNIP depletion could improve T cell-mediated immunity and may serve as a promising combinatorial strategy in immunotherapy, warranting further investigation (182).

6. Challenges and perspectives of targeting the Trx system in neurodegenerative diseases

Synergistic and antagonistic interactions in complex disease networks. The Trx system interacts dynamically with multiple signaling pathways related to oxidative stress, inflammation, apoptosis and cell survival. These interactions include both synergistic and antagonistic effects (183). For example, targeting TXNIP can suppress NLRP3 inflammasome activation, offering a promising anti-inflammatory strategy (184). Furthermore, Trx/GSH system inhibitors have demonstrated synergistic antitumor effects in cancer therapy (185). Therefore,

therapies targeting the Trx system in isolation may be insufficient or potentially imbalanced. Trx-based diagnosis and treatment should preferably be combined with other oxidative stress markers or standard therapies to improve therapeutic efficacy and ensure system-level coordination.

Genetic and environmental influences enabling personalized treatment. The expression and activity of Trx/TXNIP are highly sensitive to environmental stressors, such as glucose, ROS and ERS, and are further modulated by genetic polymorphisms and environmental exposures such as nutrition, metals and toxins. These factors influence individual responses to redox-targeted interventions. Therefore, personalized therapeutic strategies integrating genetic and environmental context may reduce off-target effects and overcome the risk of systemic redox imbalance (183,186).

Spatial and temporal precision in delivery and regulation. Jia *et al* (185) demonstrated that adeno-associated virus-mediated Trx1 overexpression restricted to the hippocampus in APP/PS1 mice improved cognitive function without disrupting systemic redox homeostasis. This may support the notion that region-specific delivery can confine Trx system modulation to affected tissues, helping avoid systemic imbalance. In cancer therapy, Trx-targeted treatments have also been combined with precision delivery systems, such as nanoparticles or exosomes, to selectively target diseased tissues or cell populations (49,63). Additionally, the role of the Trx system may vary across different disease stages; thus, temporal precision and disease-phase specificity may also be important for therapeutic success.

These considerations are important for developing precise and safe Trx-based interventions in complex neurological conditions.

7. Conclusion

Being a central regulator of intracellular redox homeostasis, the Trx system is markedly involved in autophagy, ferroptosis and apoptosis regulation via its electron transfer function and diverse signaling pathways. The present review summarizes the biological structure and function of the Trx system, with a focus on its dual roles in autophagy and ferroptosis, and its complex influence on cell fate across different pathophysiological contexts.

In autophagy regulation, the Trx system exhibits dual functionality, either inhibiting or enhancing autophagy. It modulates autophagy at both the initiation and autophagy-lysosome binding stages, likely contingent on disease-specific environments and cell types. TXNIP, in particular, achieves bidirectional autophagy regulation by engaging with distinct target proteins, such as the metabolic regulators mTOR and AMPK, the stress sensor REDD1, the master transcription factor TFEB, and by influencing the PI3K/Akt/mTOR signaling pathway. Notably, when observing autophagy inhibition, the status of autophagic flux should be carefully assessed to determine if it is blocked.

Regarding ferroptosis, Trx predominantly exerts negative regulation. Trx1 inhibition induces ferroptosis in tumors, offering potential antitumor strategies (86,173,174). Conversely, TXNIP positively regulates ferroptosis across various diseases, including diabetic retinopathy, high-fructose-induced nephropathy, sarcopenia and *ex vivo* liver transplantation models, and serves as a ferroptosis-related gene for cancer diagnosis and prognosis prediction.

In the regulation of apoptosis, Trx and TrxR generally exhibit anti-apoptotic properties, whereas TXNIP and TrxR in non-neoplastic diseases show pro-apoptotic effects. Furthermore, crosstalk between autophagy and ferroptosis, as well as between autophagy and apoptosis, has gained research attention. These interplays reflect cellular adaptive strategies to complex stress conditions, and provide novel therapeutic targets and concepts for disease intervention.

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Authors' contributions

WHW, DLL and SSX were responsible for designing the study. WHW and YDM both contributed to writing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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