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REVIEW ARTICLE

# The role of thioredoxin system in cancer: strategy for cancer therapy

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## Abstract

**Purpose** Cancer, a major public health problem, exhibits significant redox alteration. Thioredoxin (Trx) system, including Trx and Trx reductase (TrxR), as well as Trx-interacting protein (TXNIP) play important roles in controlling the cellular redox balance in cancer cells. In most cancers, Trx and TrxR are usually overexpressed and TXNIP is underexpressed. In recent years, some agents targeting Trx, TrxR, and TXNIP were used to explore a therapy approach for cancer patients.

**Methods** A systematic search of PMC and the PubMed Database was conducted to summarize the potential of Trx system inhibitors for cancer treatment.

**Results** In this article, we first summarize the functions of Trx, TrxR, and TXNIP in cancers. We also review some small molecule inhibitors of Trx/TrxR and D-allose (TXNIP inducer) and discuss their antitumor mechanisms. We highlight the combined inhibition of Trx system and GSH system in cancer therapy. We expect that a highly specific and selective antitumor agent with no cytotoxicity on human normal cells could be developed in the future.

**Conclusion** In conclusion, Trx system may be very promising for clinical therapy of cancer in the future.

**Keywords** Cancer · Redox · Thioredoxin system · Inhibitor · Combined therapy

## Cancer and redox alteration

Cancer is currently one of high fatal diseases worldwide. Among the cancer-causing factors, oxidative stress is the most important and well-studied one that results in tumor development and progression. Cellular metabolism, especially mitochondrial metabolism, will produce reactive oxygen species (ROS). Normal cells need to maintain a redox homeostasis via keeping a balance between the generation of ROS and their scavenging by intracellular antioxidant systems. Modest ROS levels play specific roles in the regulation of many cellular processes, including gene expression, cell proliferation, and signal transduction [1]. Cancer cells usually exhibit increased ROS levels due to the high metabolic rate and unlimited proliferation compared to normal cells. Extortionate ROS levels can cause damage to key cellular components, such as lipids, proteins, and nucleic acids, and ultimately lead to cell death [2]. The elevated ROS content is essential for maintaining tumor phenotypes, but also renders cancer cells high susceptibility to oxidative stress [3]. To maintain the balance of redox environment, cancer cells also increase their antioxidant capacity to scavenge the increased ROS levels. The redox alteration is the fatal weakness of cancer cells, and could be utilized to clinically treat cancer [4, 5]. Therefore, modulating cellular redox signaling may be a potential strategy for cancer treatment [6–9].

## Thioredoxin system

Thioredoxin (Trx) was first characterized in *Escherichia coli* in 1964 by Laurent et al. [10]. Trx, a 12 kDa multifunctional protein with a conserved redox catalytic site (–Cys–Gly–Pro–Cys–) [11], is identified in all organisms from microbe to human. The two redox-active cysteine residues render Trx a vital role to maintain the cellular environment in a reduced state. Trx system is composed of Trx,

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thioredoxin reductase (TrxR), and coenzyme α-nicotinamide adenine dinucleotide phosphate (NADPH), as well as Trx-interacting protein. Mammalian TrxR, a selenoenzyme, maintains the intracellular redox balance via catalyzing electron transport from NADPH to the oxidized/inactive form of Trx (Trx-S2) and reduces it to an reduced/active form (Trx-$(SH)_2$) [12] and various other substrates [13]. Reduced Trx can reduce many substrates by transferring corresponding reducing equivalents.

## Structures of Trx and TrxR

There are two major isoforms of Trx identified in mammalian cells, cytosolic Trx-1 and mitochondrial Trx-2 [14]. Human Trx-1 has two cysteine residues (Cys32 and Cys35) in its active site and three additional structural cysteine residues (Cys62, Cys69, and Cys73). These three structural cysteine residues, especially Cys62 and Cys69, can form an extra disulfide in Trx-1. Increasing evidence has shown that the extra disulfide formed between structural cysteine residues is important for the regulation of Trx-1 activity [15]. Unlike Trx-1, Trx-2 has only two cysteine residues in its active site. Compared to Trx-1, Trx-2 is expressed with an additional N-terminal 58 amino acid sequence, which mediates the import to the mitochondria and is finally cleaved.

TrxRs are homodimeric proteins and the member of flavoprotein family. Two major isoforms of TrxRs have been identified in mammals: a cytosolic (TrxR1) and a mitochondrial (TrxR2) [16]. Although the cellular localization is different, TrxR1 and TrxR2 share a similar structure. Mammalian TrxRs have a first conserved NADPH-binding site N-terminal redox-active center (–Cys–Val–Asn–Val–Gly–Cys–) which is located in the FAD-binding domain [17], and a second redox-active center (–Gly–Cys–Sec–Gly–) which is located at C-terminal elongation [18]. The unique selenocysteine residue (Sec) is essential for catalysis due to its high reaction [19] and is a suitable target for the development of selective enzyme inhibitors. Human TrxR has an interface domain between FAD-binding domain and C-terminal elongation. As a mitochondrion-localized protein, TrxR2 has an additional N-terminal mitochondrial targeting sequence [20]. For a functional enzyme, TrxR must form a head-to-tail dimer in which the C-terminal redox center of one subunit is adjacent to the N-terminal redox center of the other subunit [21]. The dimeric TrxR transfers reducing equivalents through FAD from NADPH to the disulfide in N-terminal redox-active center of the same subunit, reducing the disulfide to a dithiol pair. Then, the reducing equivalents move to C-terminal active site of the other subunit and reduce it to a selenol–thiol pair. The fully reduced TrxR enzyme transfer reducing equivalents to its substrates, including not only the native substrate oxidized Trx but also glutaredoxin 2 (Grx2), protein disulfide isomerase (PDI), and other small molecules [22].

## Functions of Trx and TrxR

Trx-1 can be found in the cytoplasm, the nucleus, and the extracellular environment [23]. Intracellular Trx-1 mainly localizes in the cytoplasm. In the cytoplasm, Trx-1 system functions as a redox regulator and protects cells from damage caused by oxidative stress, by directly scavenging ROS and controlling a cellular redox balance [24]. Trx-1 also acts as a hydrogen donor for the reduction of the enzyme ribonucleotide reductase in the DNA synthesis [10]. In the biosynthesis process of nucleotide, metabolomic results indicate that TrxR1 is essential for the last step by donating reducing equivalents to ribonucleotide reductase [25]. Trx-1 can suppress apoptosis signal-regulating kinase 1 (ASK1)-dependent apoptosis by binding to its N-terminus and inhibiting its kinase activity [26]. Trx-1 can be induced the nuclear import through karyopherin-α by several factors, including oxidative stress [27]. In the nucleus, Trx-1 has been shown to regulate gene expression via interacting with several transcription factors, such as hypoxia-inducible factor-1α (HIF-1α), redox factor-1 (Ref-1), nuclear factor kappa B (NF-κB), p53, and activator protein-1 (AP-1) [28–31], and increasing the DNA-binding activity of these transcription factors [32]. In the extracellular compartments, Trx-1 has been reported to exhibit both cytokine-like and chemokine-like activity [33].

Trx-2 is highly expressed in the mitochondria of metabolically active tissues, such as the brain, liver, and heart [34]. Trx-2 is more stable than Trx-1, since it does not contain other structural cysteine residues in its amino acid sequence except for the two in the active site [35]. Mitochondrial Trx system is composed of Trx-2, Trx2 reductase (TrxR2), NADPH, and peroxiredoxin-3 (Prx3) [20, 36]. A previous research has showed that Trx-2 system appears to have a more important role in preventing mitochondrial dysfunction than the mitochondrial glutathione in endothelial cells [37]. Along with TrxR2 and Prx3, Trx-2 plays a critical role for scavenging ROS to maintain a reducing status in the mitochondrial matrix [38]. A recent study has reported that Trx-2 regulates the quality control of mitochondria during liver ischaemia/reperfusion injury [39]. Trx-2 maintains cardiac function via inhibiting the generation of mitochondrial ROS and the activity of ASK1 [34]. Trx-2 depletion alters mitochondrial respiratory function and induces cardiomyocyte hypertrophy, although it has no effects on mitochondrial biogenesis [40]. The deficiency of Trx-2 results in an increase of oxidative stress and dysfunction of oxidative phosphorylation, and finally causes early onset neurodegeneration [41]. Lack of functional TrxR2 leads to embryonic death, because TrxR is essential for hematopoiesis, heart development, and

heart function [42]. TrxR2 plays important roles to maintain the mitochondrial redox homeostasis and integrity [43]. Folda et al. have demonstrated that mitochondrial Trx system also acts as a regulator of cyclophilin D, the mitochondrial isoform of the cyclophilin family, which is involved in the regulation of the mitochondrial permeability transition pore [44].

## Trx system in cancers

### The expression of Trx system in multiple cancers

Increased levels of Trx or TrxR have been detected in multiple therioma tissues. The expression of Trx-1 is gradually increasing with the progression of prostate cancer [45]. The mRNA expression of both Trx-1 and TrxR1 is markedly increased in breast cancer patient tissues compared with paired normal breast cells from the same patient [46]. The high mRNA and protein levels of TrxR1 expression in meningioma tissues from the histopathological samples of 29 patients were detected using qRT-PCR and immunostaining, which is involved in the malignant progression of meningiomas [47]. Compared with 8 samples of normal colonic mucosa and 12 colorectal adenomatous polyps, Trx-1 expression was significantly increased in 12 primary colorectal cancers and 7 metastatic colorectal cancer [48]. In tongue squamous cell carcinoma tissues, expressions of Trx and TrxR1 were significantly elevated in 65 patients compared with the 10 normal oral mucous samples [49]. Analogously, TrxR1 expression was also markedly upregulated in oral squamous cell carcinoma [50]. In addition, the levels of Trx-2, superoxide dismutase 2 (SOD2) and glutaredoxin 2 were increased in oral squamous cell carcinoma, which protects mitochondria from oxidative stress [51]. Trx-1 expression was also incremental in colorectal cancer tissues compared to the paired non-cancerous tissues [52]. The mRNA and protein levels of TrxR2 were also upregulated in non-small cell lung carcinomas (NSCLC) tissues [53]. Soini et al. reported that the expression of Trx and TrxR was significantly increased in 89 NSCLC patients with 3 and 8 cases negative, respectively [54]. Besides solid cancers, the expression of Trx and TrxR is also increased in lymphomas and leukemias [55, 56]. However, another group reported that Trx was underexpressed in both acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) patients [57]. Interestingly, both mRNA and protein levels of Trx-1 also increased in leiomyomas, a benign tumour, compared to the matched adjacent myometrium [58] (Table 1).

### The function of Trx system in cancers

The increased levels of oxidative stress may be a cause to induce the expression of the Trx system. The concentration of Trx could be a useful clinical marker for some cancers [59–61]. Trx system is essential for the survival and growth of cancer cells by reducing the sensitivity to cancer treatment intervention and inhibiting apoptosis [62]. Trx-1 knockdown with shRNA impeded the growth of prostate cancer cells [45]. Elevated levels of Trx have been linked to the resistance to chemotherapy drugs, such as docetaxel and cisplatin [63, 64]. Trx mediates the resistance to endocrine therapy by ROS-mediated dysregulation of estrogen-dependent and estrogen-independent redox-sensitive signaling pathways in breast cancer, although the mechanism of action is not well

**Table 1** The expression of Trx system in some tumors

| Tumor type | Expression of Trx system | References |
|---|---|---|
| Prostate cancer | ↑ mRNA of Trx-1 | [45] |
| Breast cancer | ↑ mRNA of Trx-1 and TrxR1 | [46] |
| Meningioma | ↑ mRNA and protein of TrxR1 | [47] |
| Primary and metastatic colorectal cancer | ↑ protein of Trx-1 | [48] |
| Tongue squamous cell carcinoma | ↑ protein of Trx and TrxR1 | [49] |
| Oral squamous cell carcinoma | ↑ protein of TrxR1 and Trx-2 | [50, 51] |
| Colorectal cancer | ↑ protein of Trx-1 | [52] |
| Non-small cell lung carcinomas | ↑ mRNA and protein of TrxR2 | [53, 54] |
| Leukemia | ↑ protein of Trx and TrxR | [55, 56] |
| Leiomyomas | ↑ mRNA and protein of Trx-1 | [58] |
| Aggressive invasive mammary carcinomas and advanced malignant melanomas | ↑ protein of Trx-1 in nucleus and cytoplasm | [73] |
| Breast cancer | ↓ mRNA of TXNIP | [157] |
| Hepatoma | ↓ mRNA and protein of TXNIP | [158] |
| Esophageal adenocarcinoma | ↓ protein of TXNIP | [159] |
| Pancreatic ductal adenocarcinoma | ↓ protein of TXNIP | [160] |

known [65]. Trx-1 overexpression promotes the growth and survival, and mediates the chemoresistance of diffuse large B-cell lymphoma [66]. Trx-1 can also induce drug resistance in ovarian cancer cells via increasing the transcriptional activity of FOXO1 [67]. Trx-1 can promote the activation of Akt, an intracellular prosurvival signal pathway, and induce the growth of neuroblastoma cells; furthermore, Akt expression was much higher in metastatic than primary tumors [68]. Furthermore, Trx-1 upregulates HIF-1α expression, leading to angiogenesis in tumor tissues and drug resistance [69]. Increasing expression of Trx-1 could enhance the activity of HIF-1α under hypoxic conditions, which is independent of TrxR status [70]. TrxR1-deficient DT cells, a malignant mouse cell line, were more sensitive to selenite toxicity compared to control cells [71]. Knockdown of TrxR1 also enhanced the cytotoxicity in selenazolidine-treated human lung cancer cells via inducing mitochondrial dysfunction and DNA damage [72].

Trx expression is closely related to cancer development. In vitro assays showed that overexpression of Trx-1 or addition of exogenous Trx-1 enhanced the cell invasion of MDA-MB-231 breast cancer cell lines [46]. In aggressive invasive mammary carcinomas and advanced malignant melanomas, Trx-1 was highly overexpressed in both nucleus and cytoplasm compared to tumours of lesser aggressive nature [73]. Trx-1 overexpression promoted the invasion and metastasis of colorectal cancer by activating the transcription of S100P gene and, in turn, promoting Trx-1 expression and nuclear localization via upregulating p-ERK1/2 and downregulating TXNIP expression [52]. Trx-1 overexpression significantly increased the activity of ribonucleotide reductase and interacted with ribonucleotide reductase large subunit, resulting in enhanced DNA synthesis and cancer malignancy [74]. The immunoreactivity of cytoplasmic and nuclear Trx and TrxR in Grade I–II NSCLC was stronger than grade III tumors, suggesting loss of redox regulation in tumors with low differentiation [54]. In addition, Trx overexpression may predict poor prognosis [49].

Mitochondrial Trx-2 system is also significantly related to the survival of cancer cells. Trx-2 could protect human glioblastoma cells against TNFα-induced apoptosis [75]. In HeLa cells, Trx-2 downregulation by siRNA resulted in increased sensitivity to BG [76]. Suppression of TrxR2 with miR17* transfection inhibited the tumorigenicity of prostate cancer [77]. Downregulation of TrxR2 suppressed the proliferation of NSCLC cells, induced apoptosis, and inhibited cell invasion and migration [53]. Mitochondrial glutaredoxin 2 system can act as a backup for the mitochondrial TrxR2 and reduce Trx-2 to protect HeLa cells from apoptosis induced by auranofin and 4-hydroxynonenal [78].

## Trx system inhibitors and cancers

Both Trx and TrxR can be targeted by a chemotherapeutic reagent, since the inhibition of TrxR will lead to lower levels of reduced Trx in cells, which prevents the redox function of Trx.

### Trx inhibitors

#### PX-12

1-Methylpropyl 2-imidazolyl disulfide (PX-12) has been proposed as a Trx-1 inhibitor with antitumor effects, since it targets the Cys73 of Trx. It has been demonstrated that PX-12 inhibited the growth of lung cancer A549 and Calu-6 cells via arresting the G2/M phase and induced caspase-mediated apoptosis, which was associated with the intracellular increase in ROS levels and depletion of another antioxidant protein glutathione (GSH) [79, 80]. Analogously, PX-12 played the same effects in HeLa cells [81]. PX-12 was also shown to exhibit a potential to inhibit the cell growth and to induce apoptosis in human cultured (HL-60, NB4 and U937) and primary acute myeloid leukemia (AML) cells in a dose-dependent manner, and to enhance the sensitivity of AML cells to arsenic trioxide [82]. Furthermore, inhibition of Trx-1 by PX-12 administration significantly inhibited tumor formation in male Nu/Nu mice injected with LNAI cells [45]. In addition, PX-12 treatment also inhibited the migration and invasion of colorectal cancer by inducing a G2/M phase arrest, reducing NOX1, CDH17, and S100A4 expression, and increasing KLF17 expression [83] (Table 2).

#### PMX464

4-Benzothiazole-substituted quinol (PMX464) is reported as a putative Trx-1 inhibitor [84]. PMX464 could bind covalently to Trx through Michael addition of the cyclohexadienone ring [85]. Acting as an electrophilic dual-Michael acceptor, PMX464 targeted and alkylated all the five cysteines in Trx-1, including the Cys32 and Cys35 in the active site of Trx-1, and subsequently induced significant redox alterations in cancer cells [86, 87]. A previous research reported that PMX464 inhibited Trx-1 function without altering its expression, and decreased the proliferation and survival of colorectal cancer HT29 cells [88] (Table 2).

#### SAHA

Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, has striking anticancer effects. SAHA exhibited a potential to inhibit the phenotypes of gastric cancer

**Table 2** Some Trx inhibitors and the antitumor mechanisms

| Inhibitor | Tumor type | Mechanisms | References |
|---|---|---|---|
| PX12 | Lung cancer (A549 and Calu-6 cells), cervical carcinoma (HeLa cells) | Increasing in ROS levels and depletion of GSH, arresting the G2/M phase, inducing caspase-mediated apoptosis | [79–81] |
| | Acute myeloid leukemia (HL-60, NB4, U937 and primary cells) | Inhibiting the growth, inducing apoptosis and enhance the sensitivity to arsenic trioxide | [82] |
| | Prostate cancer | Inhibiting tumor formation | [45] |
| | Colorectal cancer (DLD-1 and SW620 cells) | Inhibiting the growth, migration, and invasion by inducing a G2/M phase arrest of the cell cycle, reducing NOX1, CDH17, and S100A4 expression, and increasing KLF17 expression | [83] |
| PMX464 | Colorectal cancer (HT29 cells) | Decreasing the proliferation and survival | [88] |
| SAHA | Gastric cancer (MGC-803 and MKN28) | Inhibit the proliferation, migration and invasion | [89] |
| | Mesothelioma (Phi and ROB cells) | Increasing oxidative stress and decreasing levels of Trx-1 | [90] |
| | Cervical carcinoma (HeLa cells) | Decreasing Trx-1 and inducing cell death and mitochondrial dysfunction | [91] |
| | Prostate carcinoma (LNCaP cells) and bladder carcinoma (T24 cells) | Increasing TXNIP and decreasing Trx-1 | [93] |
| | Lung cancer cells | Increasing the level of miR-129-5p, decreasing Trx-1 expression, activating ASK1/JNK or ASK1/p38 | [94] |

cells, including proliferation, migration, and invasion [89]. The anticancer effects of SAHA may attribute to its activity to decrease the levels of Trx-1 and further increase oxidative stress in various cancer cells [90, 91]. Importantly, treatment with the SAHA increased the levels of thioredoxin-interacting protein (TXNIP, endogenous Trx-1 inhibitor), decreased the activity of Trx-1, and switched the reduced Trx-1 toward oxidized one [92]. This is consistent with the study in prostate carcinoma and bladder carcinoma [93]. SAHA increased the level of miR-129-5p, binding to 3′-untranslated region of Trx-1 and downregulating its expression, which further resulted in the activation of ASK1/JNK or ASK1/p38 pathway in lung cancer cells [94] (Table 2).

## TrxR inhibitors

Most TrxR inhibitors are electrophiles or proelectrophiles, and inhibit the enzyme activity via binding to the surface-exposed and highly reactive Sec residue of the enzyme [95]. We will discuss several types of TrxR inhibitors.

### Gold-containing compounds

Gold-containing compounds, including gold(I) and gold(III) compounds, are indicated to exert strong cytotoxicity and potent inhibitory effect on tumor cells [96]. Gold-containing drugs and widely used in clinical medicine against tumors and have been validated as potent TrxR inhibitors.

Among the gold(I) compounds, auranofin is the most commonly used one. Auranofin, an oral gold-containing triethylphosphine first used in the treatment of rheumatoid arthritis [97], has been previously reported to inhibit cytosolic and mitochondrial TrxR [98]. After treatment with auranofin, cell migration and clonogenic activity of MDA-MB-231 cells were inhibited with increased ROS levels [46]. Auranofin also increased the radiosensitivity of breast cancer cells by inducing ROS overproduction [99]. Auranofin could kill primary chronic lymphocytic leukemia (CLL) cultured and primary cells with deletion of chromosome 11q or 17p by increasing intracellular ROS levels and inducing a lethal endoplasmic reticulum stress response [100]. The anticancer effects of auranofin, including inhibition of MAPK (JNK and p38 MAPK) phosphorylation, and caspase-3 cleavage and thereby PARP-1 dissociation, can be abolished by the treatment of Trx mimetic peptides [101] (Table 3). Unfortunately, it has been reported that auranofin showed some side effects, such as proteinuria and diarrhea, during clinic treatment for cancers [102].

Apart from auranofin, several other gold(I) compounds possessing different oxidation states of gold have recently been evaluated and confirmed to be effective to inhibit TrxR. Gold(I) carbene complexes showed potent and selective inhibition properties of TrxR [103], which led to extensive oxidation of Trx-1 and Trx-2 in particular in cancer cell lines [104]. Gold(I)–NHC complex (e.g., MC3, a potent inhibitor of TrxR) disturbed the cellular redox homeostasis and resulted in increased ROS levels, induced the apoptosis of pancreatic ductal adenocarcinoma cells via blocking the interaction between Trx-1 and ASK1, and subsequently activated p38-MAPK signaling [105]. Gold(I) phosphine complexes inhibited the growth of cervical carcinoma HeLa cells through cell cycle arrest, mitochondrial membrane depolarisation, and increased production of ROS [106] (Table 3).

**Table 3** Some TrxR inhibitors and the antitumor mechanisms

| Inhibitor | Inhibitor | Tumor type | Mechanisms | References |
|---|---|---|---|---|
| Gold-containing compounds | Auranofin | Breast cancer cells (MDA-MB-231 cells) | Inhibiting cell migration and clonogenic activity, increasing ROS levels | [46] |
| | | Breast cancer (4T1 and EMT6 cells) | Increasing the radiosensitivity | [99] |
| | | Chronic lymphocytic leukemia | Increasing intracellular ROS levels and inducing a lethal endoplasmic reticulum stress response | [100] |
| | Gold(I) carbene complex | Human ovarian cancer cells | Inducing oxidation of Trx-1 and Trx-2 | [104] |
| | Gold(I) MC3 complex | Pancreatic ductal adenocarcinoma | Increasing ROS levels, blocking the interaction between Trx-1 and ASK1, inducing apoptosis through ASK1/p38-MAPK | [105] |
| | Gold(I)–phosphine complex | Cervical carcinoma (HeLa cells) | Causing cell cycle arrest and mitochondrial membrane depolarization, increasing ROS production | [106] |
| | Gold(III)-dithiocarbamato complex | Human cervical carcinoma (HeLa cells) | Generating ROS, and activating ERK1/2 for a long time | [108] |
| | | Prostate cancer | Promoting mitochondrial membrane permeabilization Cyt-c release and ROS generation, activating caspase, decreasing Bax/Bcl-2 ratio and p-EGFR | [109] |
| | Gold(III)–porphyrin complex | Lung cancer (A549 cells) | Inhibiting TrxR, decreasing Trx-1, disturbing redox status, and inducing ROS and ultimate cell death | [110] |
| Platinum-containing complexes | Platinum complexes containing 2-benzimidazole [4,5-f]-[1,10] phenanthroline | Melanoma cancer (A375 cells) | Inducing G2/M arrest, increasing ROS levels, triggering DNA damage, activating p38MAPK, and inactivating AKT and ERK | [115] |
| | Mon-Pt-2 | Various tumor cell lines (BEL-7404, SK-OV-3, A549, A549/DDP, HepG-2 and HCT-116) | Inducing intracellular ROS, mitochondrial dysfunction, and ER stress, ultimately inducing apoptosis and autophagy | [116] |
| | Platinum(II) tacrine complex | Ovarian cancer (SK-OV3/DDP cells) | Inducing mitochondrial dysfunction, activating the p53 signaling pathway and inhibiting the telomerase activity | [117] |

**Table 3** (continued)

| Inhibitor | Inhibitor | Tumor type | Mechanisms | References |
|---|---|---|---|---|
| Curcumin and its derivatives | Curcumin | Cervical cancer (HaLa cells) | Causing alkylation of both residues in the active site of TrxR1, producing ROS | [118] |
| | Curcumin analogue B5 | Cervical cancer (CaSki and SiHa) | Activating caspases, cleaving PARP, and inducing mitochondrial pathway-mediated apoptosis, activating ASK1-p38/JNK | [119] |
| | Curcumin analogue hexamethoxy-diarylpentadienone | Large cell lung cancer cells (NCI-H460) | Inducing ROS and G2/M cell cycle arrest via michael acceptor-dependent redox intervention | [120] |
| | Mitocurcumin | Lung cancer (A549 cells), prostate cancer (PC-3 cells) | Increasing the mitochondrial ROS, decreasing the mitochondrial GSH levels, increasing Bax/Bcl-2 ratio, cytochrome C release into the cytosol, and caspase-3 activity | [121] |
| Selenium-containing compounds | Selenocystine | Breast cancer (MCF-7 cells) | Inducing ROS-dependent apoptosis and mitochondrial dysfunction, DNA damage-mediated p53 phosphorylation and downregulating phosphorylation of AKT and ERK | [123] |
| | | Lung adenocarcinoma (A549 cells) | Inducing ROS accumulation, DNA damage, and inactivation of Akt and ERK | [124] |
| | Butaselen | Lung cancer (HepG2 and BEL-7402) | Reducing the expression of PD-L1 and further promoting the immune response via the inhibition of STAT3 signal pathway | [125] |
| | | Hepatocellular carcinoma (HepG2, Bel7402 and Huh7) | Inducing G2/M arrest and apoptosis by TrxR/Ref-1 and NF-κB pathway inhibition | [126] |
| | Ethaselen + sodium selenite | Non-small cell lung cancer cells (A549, NCI-H1299 and NCI-1266) | Inhibiting proliferation, inducing G2/M arrest, increasing apoptosis, and decreasing expression of TrxR1, Trx-1, Ref-1 and AP-1, nuclear translocation of Trx-1 | [127] |
| | Selenadiazole derivatives | Melanoma (A375) and cervical carcinoma (HeLa cells) | Enhancing the radiosensitivity by triggering ROS-mediated DNA damage involving inhibition of AKT and MAPKs | [128, 129] |
| DNCB | | Cervical carcinoma (HeLa cells), lung adenocarcinoma (A549 cells) | Activating caspase-3/7 | [133] |
| | | Liver carcinoma (HepG2 cells) | Inducing an increase in the oxidized Trx-1, increasing cytochrome c release and activating caspase | [134] |

**Table 3** (continued)

| Inhibitor | Inhibitor | Tumor type | Mechanisms | References |
|---|---|---|---|---|
| Arsenic-containing compounds | Arsenic trioxide | Acute promyelocytic leukemia | | [135] |
| | | Breast cancer (MCF-7 cells) | Inhibiting cell growth, oxidizing Trx | [136] |
| | As (2-mercaptopyridine N-oxide)3 | Neuroblastoma (SH-SH5Y cells) | Oxidizing all the Cys residues in Trx-1, increasing the ROS levels and triggering cell death process | [15] |
| | Dithiarsinane | Human acute promyelocytic leukemia (HL-60 cells) | Inducing ROS production, activating caspase-3 | [137] |
| | Sodium arsenite | Insulinoma (INS-1 cells) | Activating ASK1, reducing Bax/Bcl-2 ratio, and triggering caspase-3 | [138] |

Gold(III) compounds are another class of gold complexes with strong cytotoxicity and are presently used as antitumor agents. Engman et al. have demonstrated that gold(III) compounds with up to two gold-carbon bonds are usually potential inhibitors of TrxR [107]. Gold(III)–dithiocarbamato complex exhibited enhanced stability due to the presence of the chelating ligands, and could induce cancer cell death through the inhibition of TrxR activity, generation of ROS, and prolonged phosphorylation of ERK1/2 [108]. Gold(III)–dithiocarbamato complex also showed an antitumor activity in prostate cancer cells and xenografts by inducing mitochondrial dysfunction and apoptosis [109]. Using a cancer-targeted delivering nanosystem, gold(III) porphyrin complex showed enhanced inhibition on TrxR, resulting in decreased Trx-1 expression, disturbed redox status, overproduction of ROS, and ultimate death of A549 cells [110]. Importantly, gold(III) containing compounds have a good antitumor activity on cisplatin-resistant cells [97] (Table 3).

## Platinum-containing complexes

Inhibitory activity of platinum-containing complexes on TrxR has been demonstrated to be critical for their antitumor effects [111]. Platinum-containing complexes could irreversibly inhibit the activity of mammalian TrxR [112]. Cisplatin, the first generation of platinum-containing anticancer drug, could inhibit TrxR in dose- and time-dependent manners [113]. Carboplatin, the second generation of platinum-containing anticancer drug, has a better solubility and higher chemical stability and lower side effects than cisplatin. Oxaliplatin, the third generation of platinum-containing anticancer drug, shows notable inhibition on multiple tumors, especially on cisplatin/carboplatin-resistant cancer cells [114]. There are many effective platinum derivatives used in cancer treatment. Acting as a TrxR inhibitor, platinum complexes containing (2-benzimidazole [4,5-f]-[1,10] phenanthroline) ligand could effectively enhance the radiosensitivity in human melanoma A375 cells through induction of G2/M arrest with much lower cytotoxicity toward human normal cells. These complexes also increased intracellular ROS levels, resulted in DNA damage, activated p38MAPK signaling pathways, and inhibited prosurvival Akt and ERK signaling pathways [115]. Wang et al. have described a mono-functional platinum complex, Mon-Pt-2, which mainly accumulates in mitochondria, and stimulates significant TrxR2 inhibition and ROS release, ultimately resulting in apoptosis of various tumor cell lines. Importantly, Mon-Pt-2 exhibits better anticancer activity and lower acute toxicity than cisplatin in a mouse tumor model [116]. A tacrine platinum(II) complex induced the apoptosis of cisplatin-resistant ovarian cancer SK-OV3/DDP cells via inducing mitochondrial dysfunction, activating the p53 signaling

pathway, and inhibiting the telomerase activity by directly targeting the c-myc promoter [117] (Table 3).

### Curcumin and its derivatives

TrxR can be inhibited by many natural products, among of which curcumin has been identified as an effective irreversible inhibitor of TrxR by interacting with the catalytic center of the enzyme. Curcumin, a polyphenol extracted from the plant *Curcuma longa*, has been well known due to its anticancer and antiangiogenic activities. Curcumin irreversibly inhibits TrxR1 by alkylation of both Cys and Sec residues in the catalytically active site; curcumin-modified TrxR1 will strongly induce NADPH oxidase activity to produce ROS, resulting in cancer cell death [118]. A synthetic curcumin analogue, B5, is a potent inhibitor of TrxR that has potential anticancer effects. It activated caspases, cleaved PARP, and induced mitochondrial pathway-mediated apoptosis in cervical cancer cell lines [119]. In addition, B5 treatment resulted in the accumulation of oxidized Trx-1 and subsequently activated ASK1-p38/JNK proapoptotic signal pathway. Another curcumin analogue (hexamethoxy-diarylpentadienone), acting as G2/M cell cycle arrest agents, could more effectively target intracellular TrxR and more easily induce the production of ROS and collapse of the redox buffering system via Michael acceptor-dependent redox intervention [120]. Mitocurcumin, a derivative of curcumin, has been shown to selectively target mitochondria and exhibits much better anticancer effects than curcumin. Jayakumar et al. have demonstrated that mitocurcumin binds to the active site of the TrxR2 with high affinity, decreases its activity, disrupts mitochondrial redox, and, finally, kills cancer cells [121] (Table 3).

### Selenium-containing compounds

Organic forms of selenium compounds, such as ebselen and selenocystine, are the substrates for TrxR. The metabolism of these selenium-containing compounds will oxidize NADPH and produce ROS via TrxR, oxidize reduced Trx, and then induce apoptosis in vivo. For example, ebselen, a substrate of TrxR1, could target both the Cys497 and Sec498 in the active sites of TrxR1; moreover, high levels of ebselen may kill cells by competing electrons from NADPH and Trx, and further inhibiting the reduction of protein disulfide [122]. Selenocystine, a synergistic inhibitor of TrxR1, enhanced auranofin-induced apoptosis through the induction of ROS-dependent apoptosis with the involvement of mitochondrial dysfunction, DNA damage-mediated p53 phosphorylation, and downregulation of phosphorylated Akt and ERK in human breast cancer MCF-7 cells [123]. Combination of selenocystine and auranofin also enhanced the apoptosis of human lung adenocarcinoma A549 cells in vitro and in vivo by inducing ROS accumulation, DNA damage, and inactivation of Akt and ERK [124] (Table 3).

Butaselen, an organic selenium compound and a novel inhibitor of TrxR, played a role in suppressing tumorigenesis by reducing the expression of PD-L1 and further promoting the immune response via the inhibition of STAT3 signal pathway [125]. Butaselen also induced ROS generation, G2/M arrest, and apoptosis in hepatocellular carcinoma by inhibiting TrxR/Ref-1 and NF-κB pathways [126]. Another organoselenium-containing compound ethaselen combined with low-dosage sodium selenite inhibited cell proliferation, and induced apoptosis in non-small cell lung cancer cells (A549, NCI-H1299, and NCI-1266) via decreasing expression and nuclear translocation of Trx-1, as well as the expression of Ref-1 and AP-1 [127]. Selenadiazole derivatives, potent TrxR inhibitors, enhanced the radiosensitivity of human melanoma and cervical carcinoma cells by triggering excessive ROS-mediated DNA damage involving inhibition of Akt and MAPKs [128, 129]. Selenium nanoparticles further enhanced the anticancer effects of Doxorubicin by progressively inhibiting the activity of TrxR [130] (Table 3).

### DNCB

1-Chloro-2,4-dinitrobenzene (DNCB) is the first identified inhibitor of TrxR. von Nida and Quirk used DNCB to treat successfully a patient with in-transit melanoma metastases [131]. DNCB could result in irreversible inhibition of TrxR by promoting the alkylation of the Cys497 and Sec498 residues, and highly induce NADPH oxidase, which produces excessive ROS [132]. That is why, DNCB shows high cytotoxicity and induces the activation of caspase-3/7 in HeLa cells [133]. Treatment with DNCB significantly induced an increase in the oxidized Trx-1 form in a time-dependent manner and enhanced the antitumor effects of arsenic trioxide (another TrxR inhibitor) in liver carcinoma HepG2 cells [134] (Table 3).

### Arsenic-containing compounds

Arsenic-containing compounds can be employed to treat human diseases. For example, arsenic trioxide can be used to treat acute promyelocytic leukemia [135]. Lu et al. have discovered that arsenic trioxide irreversibly inhibited TrxR by reacting with both N-terminal redox-active dithiol and the C-terminal GCUG active site, and subsequently resulted in Trx oxidation in cultured MCF-7 cells [136]. This inhibition blocked DNA replication and repair, arrested the cell cycle, inhibited the growth of cancer cells, and, finally, induced apoptosis. Other arsenic-containing compounds also induced cell apoptosis via inhibition of TrxR. Arsenic-containing compound (2-mercaptopyridine N-oxide), TrxR1-targeting drugs, oxidized all the Cys residues in Trx-1, which affected

electron transfer from NADPH and TrxR1 to peroxiredoxin 1 (Prx1), increased the ROS levels and triggered cell death process [15]. Another arsenic-containing compound [2-(4-aminophenyl)-1,3,2-dithiarsinane] induced oxidative stress-mediated apoptosis in HL-60 cells by Selectively Targeting TrxR [137]. Sodium arsenite targeted TrxR and induced the death of insulinoma INS-1 cells by activating ASK1, reducing Bax/Bcl-2 ratio and eventually triggering caspase-3-dependent apoptosis [138] (Table 3).

## Combined Trx and GSH inhibition in cancer therapy

Trx/GSH and their system components are the major defenses against oxidative stress in cells [139, 140]. Dysregulation of the Trx and GSH systems may contribute to a broad spectrum of diseases, including cancer, and various infectious and inflammatory disorders [141]. The combination of Trx/GSH system inhibitors plays synergetic antitumor effects in cancer treatment (Fig. 1).

The combined inhibition of GSH and Trx antioxidant pathways leads to a synergistic cancer cell death in vitro and in vivo, demonstrating the importance of these two antioxidants for tumor progression and the potential targets for therapeutic intervention [8]. Mandal et al. have demonstrated that tumor cells from TrxR1$^{-/-}$ mice exhibit normal proliferative, clonogenic, and tumorigenic potential; whereas they are hypersensitive to the GSH synthesis inhibitor buthionine

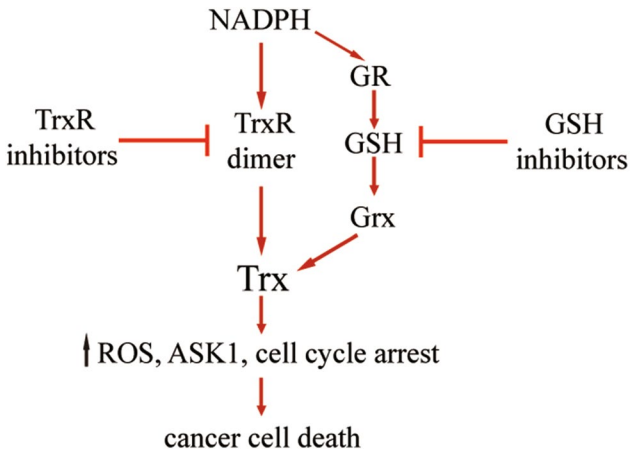


**Fig. 1** The synergetic effects of combined inhibition of Trx and GSH systems. GSH system, acting as a backup system of TrxR, can transform oxidized Trx to reduced Trx when TrxR is inhibited. Dual inhibition of Trx and GSH systems play synergetic antitumor effects in cancer treatment via inducing ROS, arresting cell cycle, and activating ASK1-mediated cancer cell apoptosis. *TrxR* thioredoxin reductase, *Trx* thioredoxin, *Grx* glutaredoxin, *GR* glutathione reductase, *GSH* reduced glutathione, *ROS* reactive oxygen species, *ASK1* apoptosis signal-regulating kinase 1

sulfoximine (a γ-glutamylcysteine synthetase inhibitor) [142], suggesting the potential redundancies between Trx-1 and GSH antioxidant systems. The combined administration of PX-12 and buthionine sulfoximine intensified the death of HeLa cells [81]. Habermann et al. have found that the inhibition of GSH by buthionine sulfoximine or erastin (the cystine/glutamate antiporter inhibitor) synergized with TrxR inhibitor auranofin to induce the death of rhabdomyosarcoma cells [143]. They further found that auranofin acts together with buthionine sulfoximine or erastin to enhanced the activation of BAX/BAK and caspase-3/-7. Combined inhibition of Trx and GSH also enhanced cancer cell clonogenic killing and radiation responses in human breast and pancreatic cancer cells; moreover, combined inhibition of Trx and GSH by auranofin and buthionine sulfoximine prior to irradiation significantly increased the survival of mice with human breast cancer xenografts [144]. Du et al. have recently shown that physiological concentrations of glutathione, NADPH, and glutathione reductase acted as a backup system of TrxR1 when it was inhibited to reduce Trx-1 in vitro and that the reaction was strongly stimulated by glutaredoxin system [145]. They further found that combined inhibition of glutathione by buthionine sulfoximine and TrxR1 activity by aurothioglucose resulted in overoxidation of Trx-1 and decreased viability of HeLa cells. In conclusion, targeting both Trx and GSH systems may be a promising approach for cancer therapy.

Dual disruption of Trx and GSH enhanced the A549 and NCI-H292 lung cancer cell killing and sensitivity to 2-deoxy-D-glucose plus carboplatin [146]. Simultaneous inhibition of Trx and GSH systems induces oxidative stress and clonogenic killing in human head-and-neck squamous cell carcinoma cells (HNSCCs); furthermore, this strategy may be useful in sensitizing HNSCCs to EGFR inhibitors [147]. Combined inhibition of Trx- and GSH-dependent metabolism is necessary to sensitize human breast and prostate cancer cells to 2-deoxy-D-glucose + 17-allylamino-17-demethoxygeldanamycin (an experimental chemotherapeutic agent)-mediated cell killing via enhanced oxidative stress [148]. A recent research showed that dual inhibition of the Trx and GSH systems led to activation of the nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway, resulting in a cut-rate effect of GSH and Trx inhibition and the tolerance of head-and-neck cancer [149]. This study indicates that triple inhibition of the Nrf2/ARE pathway, the Trx system and the GSH system may be applied to clinical treatment of cancer.

## TXNIP in cancers

As an endogenous inhibitor of Trx, thioredoxin-interacting protein (TXNIP) is broadly regarded as a member of Trx system [150]. TXNIP, also termed as thioredoxin-binding

protein (TBP2) [151], was first identified in 1995 as a gene upregulated in vitamin D3-treated leukemia HL-60 cells [152]. TXNIP inhibits the action and function of Trx-1 via a direct interaction with Trx-1, as well as acts as a competitive inhibitor to remove Trx-1 from ASK1 [153]. Furthermore, the carbohydrate response element in the promoter of *TXNIP* gene mediates the induction of TXNIP expression in a glucose-dependent manner [154], which results in reduced activity of TrxR [155].

### TXNIP expression in cancers

TXNIP is usually underexpressed in some human cancers [156]. TXNIP expression exhibits a notable decrease in MCF-7 cells, which is associated with prognosis in breast cancer [157]. TXNIP expression is also decreased during the process of human hepatic carcinogenesis [158]. A recent study has reported that TXNIP expression is decreased in esophageal adenocarcinoma [159]. In pancreatic ductal adenocarcinoma, TXNIP is negatively regulated by increased miR-224, which binds directly to the 3′-untranslated region of TXNIP and results in HIF1α activation [160] (Table 1).

### The function of TXNIP in cancers

TXNIP functions as a tumor suppressor, since it directly regulates another tumor-suppressor p53 protein by inducing its expression [161]. TXNIP overexpression decreased the interaction between p53 and mouse double minute 2 (MDM2) and further inhibited its ubiquitination degradation [161]. It has been reported that TXNIP deficiency is sufficient to initiate hepatocellular carcinoma [162], whereas overexpression of TXNIP not only inhibits hepatocarcinogenesis by suppressing TNF-α-induced NF-κB activation via association with HDAC1 and HDAC3 [158], but also suppresses the proliferation of hepatocellular carcinoma SMMC7221 cells and triggers apoptosis through inducing generation ROS and activating MAPK pathway [163]. In the neoadjuvant tumors, high levels of TXNIP are considered as an independent marker for improved disease-specific survival [164]. TXNIP has been showed to negatively regulate bladder carcinogenesis via inhibiting the activation of ERK induced by stromal cell-derived factor-1/C-X-C chemokine receptor type 4 signal [165]. Feingold et al. have indicated that constitutive overexpression of TXNIP decreased the proliferation and clonogenicity of esophageal adenocarcinoma cells, and the tumor xenograft growth in murine; furthermore, upregulation of TXNIP by a histone deacetylase inhibitor synergistically increased cisplatin-induced DNA damage and apoptosis [159]. Reactivation of TXNIP induced apoptosis via ASK1-MAPK signal pathway in acute myeloid leukemia [166]. TXNIP overexpression decreases the growth of anaplastic thyroid cancer HTh74 cells and inhibits the glucose uptake. Importantly, overexpression of TXNIP in T238 cells also results in suppressed tumor growth and decreased metastasis in an orthotopic thyroid cancer mouse model (153) [167]. TXNIP downregulation leads to the high proliferative activity and estrogen-induced cell growth of breast cancer cell lines [168]. TXNIP knockout can promote the progress of Helicobacter pylori-induced gastric carcinogenesis in C57BL/6 mice, in part by disrupting cell growth and inhibiting the induction of TNF-α, NF-κB and COX-2 [169]. TXNIP deficiency enhances TGF-β signaling and promotes TGF-β-induced epithelial–mesenchymal transition, suggesting that TXNIP could inhibit tumor progression [170].

### Antitumor effects of D-allose: involvement of TXNIP

D-Allose, a C-3 epimer of D-glucose, is one of rare sugars which exists in small quantities in nature. Accumulating evidence has demonstrated that D-allose is an inducer of TXNIP and exhibits potential antitumor effects in multiple cancers. D-Allose could inhibit the proliferation of leukemia MOLT-4F cells by inhibiting cell cycle progression via induction of TXNIP expression [171]. D-Allose also exerted growth inhibitory effects on head-and-neck cancer cells in vitro and in vivo [172]. D-Allose significantly induced TXNIP expression and decreased the expression of glucose transporters 1 in a dose-dependent manner in hepatocellular carcinoma (HuH-7), Caucasian breast adenocarcinoma (MDA-MB-231), and neuroblastoma (SH-SY5Y), and further inhibited cancer cell growth by G1 cell cycle arrest [173]. G1 cell cycle arrest by upregulated TXNIP in D-allose-treated hepatocellular carcinoma may attribute to the stabilization of cell cycle inhibitor p27 (kip1) [174]. However, a recent research has reported that elevated expression of TXNIP by D-allose induced subsequent G2/M arrest in non-small cell lung cancer [175]. D-Allose enhanced the effects of radiation therapy in 3D cultured head-and-neck cancer HSC-3 cells [176]. D-Allose also enhanced antitumor effect of 5-fluorouracil in hepatocellular carcinoma HuH-7 cells [177]. D-Allose not only exhibits antitumor activity, but also has no side effects on normal human cells [178], suggesting that it may be useful as a potential anticancer agent.

## Concluding remarks and perspectives

Increased levels of Trx and TrxR have been reported in most cancer cells, which are necessary to maintain the tumor phenotypes and characteristics, such as proliferation, invasion, and metastasis. The upregulation of Trx system also renders tumor tissues resistance against chemotherapy and radiotherapy. Thus, Trx system is a promising therapeutic target for cancers. In this review,

we have described the antitumor effects of some inhibitors that target components of the Trx system. Numerous inhibitors of Trx system have been developed and used to explore a better approach for cancer treatment. We also review the function of TXNIP, an endogenous inhibitor of Trx. As summarized above, TXNIP is usually underexpressed in multiple cancers. Overexpression of TXNIP exhibits potential antitumor effects, including regulation on tumor-suppressor p53 protein and induction of apoptosis. D-Allose could exert an antitumor activity, which is involved with upregulation of TXNIP expression. Importantly, D-allose has no known side effects on normal human cells, suggesting that it is a promising agent for cancer treatment.

Increasing studies have provided information regarding the action mechanisms, such as induction of oxidative stress, cell cycle arrest, apoptosis, and inhibition of prosurvival signal pathways, by which these compounds act on the Trx system, but several questions should be answered in the future. First, inhibiting the function of Trx system may inevitably generate cytotoxicity because of the extensive biological action of Trx system, Although cancer cells are much more sensitive to TrxR/Trx inhibitors than normal cells, a common question that how to minimize or overcome the side effects of TrxR/Trx inhibitors on normal cells should be addressed, because the function of Trx system is essential for normal cell survival. Thus, it is a great challenge to develop TrxR/Trx inhibitors as anticancer drugs. Another obvious question is to develop inhibitors with high specificity and selectivity, since some inhibitors currently used in clinical trials are not specific for Trx system. In addition, more advanced delivery approaches should also be developed in the future.

Breaking the interaction of subunit–subunit may be a new strategy for inhibiting TrxR function. TrxR must form a head-to-tail homodimer to act as a functional enzyme. The catalytic mechanisms of TrxR involve that one subunit (N-terminal redox center: –Cys–Val–Asn–Val–Gly–Cys–) obtains electrons from NADPH and transfers them to another subunit (C-terminal redox center: –Gly–Cys–Sec–Gly–), and, finally, passes the reducing equivalents to the disulfide bond of oxidized Trx. Thus, inhibiting the formation of TrxR dimer may depress the enzyme function. Considering that a single molecule may fail to target the large interface of TrxR dimer, a fragment-based approach could be used to link several weak interface-binding molecules together to develop a selective inhibitor.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

## References

1. Mikkelsen RB, Wardman P (2003) Biological chemistry of reactive oxygen and nitrogen and radiation-induced signal transduction mechanisms. Oncogene 22(37):5734–5754. https://doi.org/10.1038/sj.onc.1206663
2. Martindale JL, Holbrook NJ (2002) Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol 192(1):1–15. https://doi.org/10.1002/jcp.10119
3. Trachootham D, Alexandre J, Huang P (2009) Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov 8(7):579–591. https://doi.org/10.1038/nrd2803
4. Sabharwal SS, Schumacker PT (2014) Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? Nat Rev Cancer 14(11):709–721. https://doi.org/10.1038/nrc3803
5. Polimeni M, Gazzano E (2014) Is redox signaling a feasible target for overcoming multidrug resistance in cancer chemotherapy? Front Pharmacol 5:286. https://doi.org/10.3389/fphar.2014.00286
6. Sun X, Wang W, Chen J, Cai X, Yang J, Yang Y, Yan H, Cheng X, Ye J, Lu W, Hu C, Sun H, Pu J, Cao P (2017) The natural diterpenoid isoforretin a inhibits thioredoxin-1 and triggers potent ROS-mediated antitumor effects. Cancer Res 77(4):926–936. https://doi.org/10.1158/0008-5472.CAN-16-0987
7. Benhar M, Shytaj IL, Stamler JS, Savarino A (2016) Dual targeting of the thioredoxin and glutathione systems in cancer and HIV. J Clin Invest 126(5):1630–1639. https://doi.org/10.1172/JCI85339
8. Harris IS, Treloar AE, Inoue S, Sasaki M, Gorrini C, Lee KC, Yung KY, Brenner D, Knobbe-Thomsen CB, Cox MA, Elia A, Berger T, Cescon DW, Adeoye A, Brustle A, Molyneux SD, Mason JM, Li WY, Yamamoto K, Wakeham A, Berman HK, Khokha R, Done SJ, Kavanagh TJ, Lam CW, Mak TW (2015) Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Cancer Cell 27(2):211–222. https://doi.org/10.1016/j.ccell.2014.11.019
9. Raj L, Ide T, Gurkar AU, Foley M, Schenone M, Li X, Tolliday NJ, Golub TR, Carr SA, Shamji AF, Stern AM, Mandinova A, Schreiber SL, Lee SW (2011) Selective killing of cancer cells by a small molecule targeting the stress response to ROS. Nature 475(7355):231–234. https://doi.org/10.1038/nature10167
10. Laurent TC, Moore EC, Reichard P (1964) Enzymatic synthesis of deoxyribonucleotides. Iv. Isolation and characterization of thioredoxin, the hydrogen donor from *Escherichia coli* B. J Biol Chem 239:3436–3444
11. Zeng XS, Jia JJ, Kwon Y, Wang SD, Bai J (2014) The role of thioredoxin-1 in suppression of endoplasmic reticulum stress in Parkinson disease. Free Radic Biol Med 67:10–18. https://doi.org/10.1016/j.freeradbiomed.2013.10.013
12. Zeng XS, Geng WS, Chen L, Jia JJ (2018) Thioredoxin as a therapeutic target in cerebral ischemia. Curr Pharm Des. https://doi.org/10.2174/1381612824666180820143853
13. Williams CH, Arscott LD, Muller S, Lennon BW, Ludwig ML, Wang PF, Veine DM, Becker K, Schirmer RH (2000) Thioredoxin reductase two modes of catalysis have evolved. Eur J Biochem 267(20):6110–6117

14. Rybnikova E, Damdimopoulos AE, Gustafsson JA, Spyrou G, Pelto-Huikko M (2000) Expression of novel antioxidant thioredoxin-2 in the rat brain. Eur J Neurosci 12(5):1669–1678
15. Zhang X, Lu J, Ren X, Du Y, Zheng Y, Ioannou PV, Holmgren A (2015) Oxidation of structural cysteine residues in thioredoxin 1 by aromatic arsenicals enhances cancer cell cytotoxicity caused by the inhibition of thioredoxin reductase 1. Free Radic Biol Med 89:192–200. https://doi.org/10.1016/j.freeradbiomed.2015.07.010
16. Scalcon V, Bindoli A, Rigobello MP (2018) Significance of the mitochondrial thioredoxin reductase in cancer cells: an update on role, targets and inhibitors. Free Radic Biol Med 127:62–79. https://doi.org/10.1016/j.freeradbiomed.2018.03.043
17. Zhang B, Zhang J, Peng S, Liu R, Li X, Hou Y, Han X, Fang J (2017) Thioredoxin reductase inhibitors: a patent review. Expert Opin Ther Pat 27(5):547–556. https://doi.org/10.1080/13543776.2017.1272576
18. Zhong L, Arner ES, Holmgren A (2000) Structure and mechanism of mammalian thioredoxin reductase: the active site is a redox-active selenolthiol/selenenylsulfide formed from the conserved cysteine-selenocysteine sequence. Proc Natl Acad Sci USA 97(11):5854–5859. https://doi.org/10.1073/pnas.100114897
19. Mustacich D, Powis G (2000) Thioredoxin reductase. Biochem J 346(Pt 1):1–8
20. Miranda-Vizuete A, Damdimopoulos AE, Pedrajas JR, Gustafsson JA, Spyrou G (1999) Human mitochondrial thioredoxin reductase cDNA cloning, expression and genomic organization. Eur J Biochem 261(2):405–412
21. Zhang J, Li X, Han X, Liu R, Fang J (2017) Targeting the thioredoxin system for cancer therapy. Trends Pharmacol Sci 38(9):794–808. https://doi.org/10.1016/j.tips.2017.06.001
22. Arner ES (2009) Focus on mammalian thioredoxin reductases–important selenoproteins with versatile functions. Biochim Biophys Acta 1790(6):495–526. https://doi.org/10.1016/j.bbagen.2009.01.014
23. Arai RJ, Masutani H, Yodoi J, Debbas V, Laurindo FR, Stern A, Monteiro HP (2006) Nitric oxide induces thioredoxin-1 nuclear translocation: possible association with the p21Ras survival pathway. Biochem Biophys Res Commun 348(4):1254–1260. https://doi.org/10.1016/j.bbrc.2006.07.178
24. Koharyova M, Kolarova M (2008) Oxidative stress and thioredoxin system. Gen Physiol Biophys 27(2):71–84
25. Muri J, Heer S, Matsushita M, Pohlmeier L, Tortola L, Fuhrer T, Conrad M, Zamboni N, Kisielow J, Kopf M (2018) The thioredoxin-1 system is essential for fueling DNA synthesis during T-cell metabolic reprogramming and proliferation. Nat Commun 9(1):1851. https://doi.org/10.1038/s41467-018-04274-w
26. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, Ichijo H (1998) Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J 17(9):2596–2606. https://doi.org/10.1093/emboj/17.9.2596
27. Schroeder P, Popp R, Wiegand B, Altschmied J, Haendeler J (2007) Nuclear redox-signaling is essential for apoptosis inhibition in endothelial cells—important role for nuclear thioredoxin-1. Arterioscler Thromb Vasc Biol 27(11):2325–2331. https://doi.org/10.1161/ATVBAHA.107.149419
28. Zhao L, Li W, Zhou Y, Zhang Y, Huang S, Xu X, Li Z, Guo Q (2015) The overexpression and nuclear translocation of Trx-1 during hypoxia confers on HepG2 cells resistance to DDP, and GL-V9 reverses the resistance by suppressing the Trx-1/Ref-1 axis. Free Radic Biol Med 82:29–41. https://doi.org/10.1016/j.freeradbiomed.2015.01.014
29. Gurusamy N, Malik G, Gorbunov NV, Das DK (2007) Redox activation of Ref-1 potentiates cell survival following myocardial ischemia reperfusion injury. Free Radic Biol Med 43(3):397–407. https://doi.org/10.1016/j.freeradbiomed.2007.04.025
30. Freemerman AJ, Gallegos A, Powis G (1999) Nuclear factor kappaB transactivation is increased but is not involved in the proliferative effects of thioredoxin overexpression in MCF-7 breast cancer cells. Cancer Res 59(16):4090–4094
31. Hirota K, Matsui M, Iwata S, Nishiyama A, Mori K, Yodoi J (1997) AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. Proc Natl Acad Sci USA 94(8):3633–3638
32. Flores LC, Ortiz M, Dube S, Hubbard GB, Lee S, Salmon A, Zhang Y, Ikeno Y (2012) Thioredoxin, oxidative stress, cancer and aging. Longev Healthspan 1:4. https://doi.org/10.1186/2046-2395-1-4
33. Billiet L, Furman C, Larigauderie G, Copin C, Brand K, Fruchart JC, Rouis M (2005) Extracellular human thioredoxin-1 inhibits lipopolysaccharide-induced interleukin-1beta expression in human monocyte-derived macrophages. J Biol Chem 280(48):40310–40318. https://doi.org/10.1074/jbc.M503644200
34. Huang Q, Zhou HJ, Zhang H, Huang Y, Hinojosa-Kirschenbaum F, Fan P, Yao L, Belardinelli L, Tellides G, Giordano FJ, Budas GR, Min W (2015) Thioredoxin-2 inhibits mitochondrial reactive oxygen species generation and apoptosis stress kinase-1 activity to maintain cardiac function. Circulation 131(12):1082–1097. https://doi.org/10.1161/circulationaha.114.012725
35. Tanaka T, Hosoi F, Yamaguchi-Iwai Y, Nakamura H, Masutani H, Ueda S, Nishiyama A, Takeda S, Wada H, Spyrou G, Yodoi J (2002) Thioredoxin-2 (TRX-2) is an essential gene regulating mitochondria-dependent apoptosis. EMBO J 21(7):1695–1703. https://doi.org/10.1093/emboj/21.7.1695
36. Damdimopoulos AE, Miranda-Vizuete A, Pelto-Huikko M, Gustafsson JA, Spyrou G (2002) Human mitochondrial thioredoxin. Involvement in mitochondrial membrane potential and cell death. J Biol Chem 277(36):33249–33257. https://doi.org/10.1074/jbc.m203036200
37. Lowes DA, Galley HF (2011) Mitochondrial protection by the thioredoxin-2 and glutathione systems in an in vitro endothelial model of sepsis. Biochem J 436(1):123–132. https://doi.org/10.1042/BJ20102135
38. Lu J, Holmgren A (2012) Thioredoxin system in cell death progression. Antioxid Redox Signal 17(12):1738–1747. https://doi.org/10.1089/ars.2012.4650
39. Kang JW, Choi HS, Lee SM (2018) Resolvin D1 attenuates liver ischaemia/reperfusion injury through modulating thioredoxin 2-mediated mitochondrial quality control. Br J Pharmacol 175(12):2441–2453. https://doi.org/10.1111/bph.14212
40. Hu C, Zhang H, Qiao Z, Wang Y, Zhang P, Yang D (2018) Loss of thioredoxin 2 alters mitochondrial respiratory function and induces cardiomyocyte hypertrophy. Exp Cell Res 372(1):61–72. https://doi.org/10.1016/j.yexcr.2018.09.010
41. Holzerova E, Danhauser K, Haack TB, Kremer LS, Melcher M, Ingold I, Kobayashi S, Terrile C, Wolf P, Schaper J, Mayatepek E, Baertling F, Friedmann Angeli JP, Conrad M, Strom TM, Meitinger T, Prokisch H, Distelmaier F (2016) Human thioredoxin 2 deficiency impairs mitochondrial redox homeostasis and causes early-onset neurodegeneration. Brain 139(Pt 2):346–354. https://doi.org/10.1093/brain/awv350
42. Conrad M, Jakupoglu C, Moreno SG, Lippl S, Banjac A, Schneider M, Beck H, Hatzopoulos AK, Just U, Sinowatz F, Schmahl W, Chien KR, Wurst W, Bornkamm GW, Brielmeier M (2004) Essential role for mitochondrial thioredoxin reductase in hematopoiesis, heart development, and heart function. Mol Cell Biol 24(21):9414–9423. https://doi.org/10.1128/mcb.24.21.9414-9423.2004
43. Yoshioka J (2015) Thioredoxin reductase 2 (Txnrd2) regulates mitochondrial integrity in the progression of age-related

heart failure. J Am Heart Assoc. https://doi.org/10.1161/jaha.115.002278
44. Folda A, Citta A, Scalcon V, Cali T, Zonta F, Scutari G, Bindoli A, Rigobello MP (2016) Mitochondrial thioredoxin system as a modulator of cyclophilin D redox state. Sci Rep 6:23071. https://doi.org/10.1038/srep23071
45. Samaranayake GJ, Troccoli CI, Huynh M, Lyles RDZ, Kage K, Win A, Lakshmanan V, Kwon D, Ban Y, Chen SX, Zarco ER, Jorda M, Burnstein KL, Rai P (2017) Thioredoxin-1 protects against androgen receptor-induced redox vulnerability in castration-resistant prostate cancer. Nat Commun 8(1):1204. https://doi.org/10.1038/s41467-017-01269-x
46. Bhatia M, McGrath KL, Di Trapani G, Charoentong P, Shah F, King MM, Clarke FM, Tonissen KF (2016) The thioredoxin system in breast cancer cell invasion and migration. Redox Biol 8:68–78. https://doi.org/10.1016/j.redox.2015.12.004
47. Esen H, Feyzioglu B, Erdi F, Keskin F, Kaya B, Demir LS (2015) High thioredoxin reductase 1 expression in meningiomas undergoing malignant progression. Brain Tumor Pathol 32(3):195–201. https://doi.org/10.1007/s10014-015-0212-x
48. Raffel J, Bhattacharyya AK, Gallegos A, Cui H, Einspahr JG, Alberts DS, Powis G (2003) Increased expression of thioredoxin-1 in human colorectal cancer is associated with decreased patient survival. J Lab Clin Med 142(1):46–51. https://doi.org/10.1016/S0022-2143(03)00068-4
49. Zhu X, Huang C, Peng B (2011) Overexpression of thioredoxin system proteins predicts poor prognosis in patients with squamous cell carcinoma of the tongue. Oral Oncol 47(7):609–614. https://doi.org/10.1016/j.oraloncology.2011.05.006
50. Iwasawa S, Yamano Y, Takiguchi Y, Tanzawa H, Tatsumi K, Uzawa K (2011) Upregulation of thioredoxin reductase 1 in human oral squamous cell carcinoma. Oncol Rep 25(3):637–644. https://doi.org/10.3892/or.2010.1131
51. Banerjee S, Mukherjee S, Mitra S, Singhal P (2017) Altered expression of mitochondrial antioxidants in oral squamous cell carcinoma. J Oral Sci 59(3):439–446. https://doi.org/10.2334/josnusd.16-0655
52. Lin F, Zhang P, Zuo Z, Wang F, Bi R, Shang W, Wu A, Ye J, Li S, Sun X, Wu J, Jiang L (2017) Thioredoxin-1 promotes colorectal cancer invasion and metastasis through crosstalk with S100P. Cancer Lett 401:1–10. https://doi.org/10.1016/j.canlet.2017.04.036
53. Bu L, Li W, Ming Z, Shi J, Fang P, Yang S (2017) Inhibition of TrxR2 suppressed NSCLC cell proliferation, metabolism and induced cell apoptosis through decreasing antioxidant activity. Life Sci 178:35–41. https://doi.org/10.1016/j.lfs.2017.04.008
54. Soini Y, Kahlos K, Napankangas U, Kaarteenaho-Wiik R, Saily M, Koistinen P, Paaakko P, Holmgren A, Kinnula VL (2001) Widespread expression of thioredoxin and thioredoxin reductase in non-small cell lung carcinoma. Clin Cancer Res 7(6):1750–1757
55. Shao L, Diccianni MB, Tanaka T, Gribi R, Yu AL, Pullen JD, Camitta BM, Yu J (2001) Thioredoxin expression in primary T-cell acute lymphoblastic leukemia and its therapeutic implication. Cancer Res 61(19):7333–7338
56. Li H, Li M, Wang G, Shao F, Chen W, Xia C, Wang S, Li Y, Zhou G, Liu Z (2016) EM23, a natural sesquiterpene lactone from elephantopus mollis, induces apoptosis in human myeloid leukemia cells through thioredoxin- and reactive oxygen species-mediated signaling pathways. Front Pharmacol 7:77. https://doi.org/10.3389/fphar.2016.00077
57. Kamal AM, El-Hefny NH, Hegab HM, El-Mesallamy HO (2016) Expression of thioredoxin-1 (TXN) and its relation with oxidative DNA damage and treatment outcome in adult AML and ALL: a comparative study. Hematology 21(10):567–575. https://doi.org/10.1080/10245332.2016.1173341
58. Hou P, Zhao L, Li Y, Luo F, Wang S, Song J, Bai J (2014) Comparative expression of thioredoxin-1 in uterine leiomyomas and myometrium. Mol Hum Reprod 20(2):148–154. https://doi.org/10.1093/molehr/gat069
59. Shan W, Zhong W, Zhao R, Oberley TD (2010) Thioredoxin 1 as a subcellular biomarker of redox imbalance in human prostate cancer progression. Free Radic Biol Med 49(12):2078–2087. https://doi.org/10.1016/j.freeradbiomed.2010.10.691
60. Maeda R, Tabata C, Tabata R, Eguchi R, Fujimori Y, Nakano T (2011) Is serum thioredoxin-1 a useful clinical marker for malignant pleural mesothelioma? Antioxid Redox Signal 15(3):685–689. https://doi.org/10.1089/ars.2011.3978
61. Nipp M, Elsner M, Balluff B, Meding S, Sarioglu H, Ueffing M, Rauser S, Unger K, Hofler H, Walch A, Zitzelsberger H (2012) S100-A10, thioredoxin, and S100-A6 as biomarkers of papillary thyroid carcinoma with lymph node metastasis identified by MALDI imaging. J Mol Med (Berl) 90(2):163–174. https://doi.org/10.1007/s00109-011-0815-6
62. Arner ESJ (2017) Targeting the selenoprotein thioredoxin reductase 1 for anticancer therapy. Adv Cancer Res 136:139–151. https://doi.org/10.1016/bs.acr.2017.07.005
63. Yamada M, Tomida A, Yoshikawa H, Taketani Y, Tsuruo T (1996) Increased expression of thioredoxin/adult T-cell leukemia-derived factor in cisplatin-resistant human cancer cell lines. Clin Cancer Res 2(2):427–432
64. Kim SJ, Miyoshi Y, Taguchi T, Tamaki Y, Nakamura H, Yodoi J, Kato K, Noguchi S (2005) High thioredoxin expression is associated with resistance to docetaxel in primary breast cancer. Clin Cancer Res 11(23):8425–8430. https://doi.org/10.1158/1078-0432.ccr-05-0449
65. Penney RB, Roy D (2013) Thioredoxin-mediated redox regulation of resistance to endocrine therapy in breast cancer. Biochim Biophys Acta 1836(1):60–79. https://doi.org/10.1016/j.bbcan.2013.02.005
66. Li C, Thompson MA, Tamayo AT, Zuo Z, Lee J, Vega F, Ford RJ, Pham LV (2012) Over-expression of thioredoxin-1 mediates growth, survival, and chemoresistance and is a druggable target in diffuse large B-cell lymphoma. Oncotarget 3(3):314–326. https://doi.org/10.18632/oncotarget.463
67. Wang J, Yang H, Li W, Xu H, Yang X, Gan L (2015) Thioredoxin 1 upregulates FOXO1 transcriptional activity in drug resistance in ovarian cancer cells. Biochim Biophys Acta 1852(3):395–405. https://doi.org/10.1016/j.bbadis.2014.12.002
68. Sartelet H, Rougemont AL, Fabre M, Castaing M, Duval M, Fetni R, Michiels S, Beaunoyer M, Vassal G (2011) Activation of the phosphatidylinositol 3′-kinase/AKT pathway in neuroblastoma and its regulation by thioredoxin 1. Hum Pathol 42(11):1727–1739. https://doi.org/10.1016/j.humpath.2011.01.019
69. Kaimul AM, Nakamura H, Masutani H, Yodoi J (2007) Thioredoxin and thioredoxin-binding protein-2 in cancer and metabolic syndrome. Free Radic Biol Med 43(6):861–868. https://doi.org/10.1016/j.freeradbiomed.2007.05.032
70. Naranjo-Suarez S, Carlson BA, Tobe R, Yoo MH, Tsuji PA, Gladyshev VN, Hatfield DL (2013) Regulation of HIF-1alpha activity by overexpression of thioredoxin is independent of thioredoxin reductase status. Mol Cells 36(2):151–157. https://doi.org/10.1007/s10059-013-0121-y
71. Tobe R, Yoo MH, Fradejas N, Carlson BA, Calvo S, Gladyshev VN, Hatfield DL (2012) Thioredoxin reductase 1 deficiency enhances selenite toxicity in cancer cells via a thioredoxin-independent mechanism. Biochem J 445(3):423–430. https://doi.org/10.1042/BJ20120618
72. Poerschke RL, Moos PJ (2011) Thioredoxin reductase 1 knockdown enhances selenazolidine cytotoxicity in human lung cancer cells via mitochondrial dysfunction. Biochem Pharmacol 81(2):211–221. https://doi.org/10.1016/j.bcp.2010.09.024

73. Lincoln DT, Ali Emadi EM, Tonissen KF, Clarke FM (2003) The thioredoxin-thioredoxin reductase system: over-expression in human cancer. Anticancer Res 23(3B):2425–2433
74. Lou M, Liu Q, Ren G, Zeng J, Xiang X, Ding Y, Lin Q, Zhong T, Liu X, Zhu L, Qi H, Shen J, Li H, Shao J (2017) Physical interaction between human ribonucleotide reductase large subunit and thioredoxin increases colorectal cancer malignancy. J Biol Chem 292(22):9136–9149. https://doi.org/10.1074/jbc.M117.783365
75. Choksi S, Lin Y, Pobezinskaya Y, Chen L, Park C, Morgan M, Li T, Jitkaew S, Cao X, Kim YS, Kim HS, Levitt P, Shih G, Birre M, Deng CX, Liu ZG (2011) A HIF-1 target, ATIA, protects cells from apoptosis by modulating the mitochondrial thioredoxin, TRX2. Mol Cell 42(5):597–609. https://doi.org/10.1016/j.molcel.2011.03.030
76. Zhang X, Zheng Y, Fried LE, Du Y, Montano SJ, Sohn A, Lefkove B, Holmgren L, Arbiser JL, Holmgren A, Lu J (2011) Disruption of the mitochondrial thioredoxin system as a cell death mechanism of cationic triphenylmethanes. Free Radic Biol Med 50(7):811–820. https://doi.org/10.1016/j.freeradbiomed.2010.12.036
77. Xu Y, Fang F, Zhang J, Josson S, St Clair WH, St Clair DK (2010) miR-17* suppresses tumorigenicity of prostate cancer by inhibiting mitochondrial antioxidant enzymes. PLoS One 5(12):e14356. https://doi.org/10.1371/journal.pone.0014356
78. Zhang H, Du Y, Zhang X, Lu J, Holmgren A (2014) Glutaredoxin 2 reduces both thioredoxin 2 and thioredoxin 1 and protects cells from apoptosis induced by auranofin and 4-hydroxynonenal. Antioxid Redox Signal 21(5):669–681. https://doi.org/10.1089/ars.2013.5499
79. You BR, Shin HR, Park WH (2014) PX-12 inhibits the growth of A549 lung cancer cells via G2/M phase arrest and ROS-dependent apoptosis. Int J Oncol 44(1):301–308. https://doi.org/10.3892/ijo.2013.2152
80. You BR, Shin HR, Han BR, Park WH (2015) PX-12 induces apoptosis in Calu-6 cells in an oxidative stress-dependent manner. Tumour Biol 36(3):2087–2095. https://doi.org/10.1007/s13277-014-2816-x
81. Shin HR, You BR, Park WH (2013) PX-12-induced HeLa cell death is associated with oxidative stress and GSH depletion. Oncol Lett 6(6):1804–1810. https://doi.org/10.3892/ol.2013.1637
82. Tan Y, Bi L, Zhang P, Wang F, Lin F, Ni W, Wu J, Jiang L (2014) Thioredoxin-1 inhibitor PX-12 induces human acute myeloid leukemia cell apoptosis and enhances the sensitivity of cells to arsenic trioxide. Int J Clin Exp Pathol 7(8):4765–4773
83. Wang F, Lin F, Zhang P, Ni W, Bi L, Wu J, Jiang L (2015) Thioredoxin-1 inhibitor, 1-methylpropyl 2-imidazolyl disulfide, inhibits the growth, migration and invasion of colorectal cancer cell lines. Oncol Rep 33(2):967–973. https://doi.org/10.3892/or.2014.3652
84. Konig J, Wyllie S, Wells G, Stevens MF, Wyatt PG, Fairlamb AH (2011) Antitumor quinol PMX464 is a cytocidal anti-trypanosomal inhibitor targeting trypanothione metabolism. J Biol Chem 286(10):8523–8533. https://doi.org/10.1074/jbc.M110.214833
85. Hall G, Bradshaw TD, Laughton CA, Stevens MF, Emsley J (2011) Structure of Mycobacterium tuberculosis thioredoxin in complex with quinol inhibitor PMX464. Protein Sci 20(1):210–215. https://doi.org/10.1002/pro.533
86. Wondrak GT (2009) Redox-directed cancer therapeutics: molecular mechanisms and opportunities. Antioxid Redox Signal 11(12):3013–3069. https://doi.org/10.1089/ARS.2009.2541
87. Mukherjee A, Martin SG (2008) The thioredoxin system: a key target in tumour and endothelial cells. Br J Radiol 81(Spec No 1):S57–S68. https://doi.org/10.1259/bjr/34180435
88. Mukherjee A, Huber K, Evans H, Lakhani N, Martin S (2007) A cellular and molecular investigation of the action of PMX464, a putative thioredoxin inhibitor, in normal and colorectal cancer cell lines. Br J Pharmacol 151(8):1167–1175. https://doi.org/10.1038/sj.bjp.0707342
89. Lu H, Yang XF, Tian XQ, Tang SL, Li LQ, Zhao S, Zheng HC (2016) The in vitro and vivo anti-tumor effects and molecular mechanisms of suberoylanilide hydroxamic acid (SAHA) and MG132 on the aggressive phenotypes of gastric cancer cells. Oncotarget 7(35):56508–56525. https://doi.org/10.18632/oncotarget.10643
90. You BR, Park WH (2016) The levels of HDAC1 and thioredoxin1 are related to the death of mesothelioma cells by suberoylanilide hydroxamic acid. Int J Oncol 48(5):2197–2204. https://doi.org/10.3892/ijo.2016.3402
91. You BR, Park WH (2014) Suberoylanilide hydroxamic acid-induced HeLa cell death is closely correlated with oxidative stress and thioredoxin 1 levels. Int J Oncol 44(5):1745–1755. https://doi.org/10.3892/ijo.2014.2337
92. Ungerstedt J, Du Y, Zhang H, Nair D, Holmgren A (2012) In vivo redox state of human thioredoxin and redox shift by the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA). Free Radic Biol Med 53(11):2002–2007. https://doi.org/10.1016/j.freeradbiomed.2012.09.019
93. Butler LM, Zhou X, Xu WS, Scher HI, Rifkind RA, Marks PA, Richon VM (2002) The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredoxin-binding protein-2, and down-regulates thioredoxin. Proc Natl Acad Sci USA 99(18):11700–11705. https://doi.org/10.1073/pnas.182372299
94. You BR, Park WH (2017) Suberoylanilide hydroxamic acid induces thioredoxin1-mediated apoptosis in lung cancer cells via up-regulation of miR-129-5p. Mol Carcinog 56(12):2566–2577. https://doi.org/10.1002/mc.22701
95. Zhang B, Liu Y, Li X, Xu J, Fang J (2018) Small molecules to target the selenoprotein thioredoxin reductase. Chem Asian J 13(23):3593–3600. https://doi.org/10.1002/asia.201801136
96. Zhang J, Zhang B, Li X, Han X, Liu R, Fang J (2019) Small molecule inhibitors of mammalian thioredoxin reductase as potential anticancer agents: an update. Med Res Rev 39(1):5–39. https://doi.org/10.1002/med.21507
97. Ouyang Y, Peng Y, Li J, Holmgren A, Lu J (2018) Modulation of thiol-dependent redox system by metal ions via thioredoxin and glutaredoxin systems. Metallomics 10(2):218–228. https://doi.org/10.1039/c7mt00327g
98. Gandin V, Fernandes AP, Rigobello MP, Dani B, Sorrentino F, Tisato F, Bjornstedt M, Bindoli A, Sturaro A, Rella R, Marzano C (2010) Cancer cell death induced by phosphine gold(I) compounds targeting thioredoxin reductase. Biochem Pharmacol 79(2):90–101. https://doi.org/10.1016/j.bcp.2009.07.023
99. Wang H, Bouzakoura S, de Mey S, Jiang H, Law K, Dufait I, Corbet C, Verovski V, Gevaert T, Feron O, Van den Berge D, Storme G, De Ridder M (2017) Auranofin radiosensitizes tumor cells through targeting thioredoxin reductase and resulting overproduction of reactive oxygen species. Oncotarget 8(22):35728–35742. https://doi.org/10.18632/oncotarget.16113
100. Fiskus W, Saba N, Shen M, Ghias M, Liu J, Gupta SD, Chauhan L, Rao R, Gunewardena S, Schorno K, Austin CP, Maddocks K, Byrd J, Melnick A, Huang P, Wiestner A, Bhalla KN (2014) Auranofin induces lethal oxidative and endoplasmic reticulum stress and exerts potent preclinical activity against chronic lymphocytic leukemia. Cancer Res 74(9):2520–2532. https://doi.org/10.1158/0008-5472.CAN-13-2033
101. Cohen-Kutner M, Khomsky L, Trus M, Aisner Y, Niv MY, Benhar M, Atlas D (2013) Thioredoxin-mimetic peptides (TXM) reverse auranofin induced apoptosis and restore insulin secretion in insulinoma cells. Biochem Pharmacol 85(7):977–990. https://doi.org/10.1016/j.bcp.2013.01.003

102. Roder C, Thomson MJ (2015) Auranofin: repurposing an old drug for a golden new age. Drugs R D 15(1):13–20. https://doi.org/10.1007/s40268-015-0083-y
103. Karaca O, Scalcon V, Meier-Menches SM, Bonsignore R, Brouwer J, Tonolo F, Folda A, Rigobello MP, Kuhn FE, Casini A (2017) Characterization of hydrophilic gold(I) N-heterocyclic carbene (NHC) complexes as potent TrxR inhibitors using biochemical and mass spectrometric approaches. Inorg Chem 56(22):14237–14250. https://doi.org/10.1021/acs.inorgchem.7b02345
104. Schuh E, Pfluger C, Citta A, Folda A, Rigobello MP, Bindoli A, Casini A, Mohr F (2012) Gold(I) carbene complexes causing thioredoxin 1 and thioredoxin 2 oxidation as potential anticancer agents. J Med Chem 55(11):5518–5528. https://doi.org/10.1021/jm300428v
105. Cheng X, Holenya P, Can S, Alborzinia H, Rubbiani R, Ott I, Wolfl S (2014) A TrxR inhibiting gold(I) NHC complex induces apoptosis through ASK1-p38-MAPK signaling in pancreatic cancer cells. Mol Cancer 13:221. https://doi.org/10.1186/1476-4598-13-221
106. Reddy TS, Priver SH, Mirzadeh N, Bhargava SK (2018) Synthesis of gold(I) phosphine complexes containing the 2-Br C6F4PPh2 ligand: evaluation of anticancer activity in 2D and 3D spheroidal models of HeLa cancer cells. Eur J Med Chem 145:291–301. https://doi.org/10.1016/j.ejmech.2017.12.048
107. Engman L, McNaughton M, Gajewska M, Kumar S, Birmingham A, Powis G (2006) Thioredoxin reductase and cancer cell growth inhibition by organogold(III) compounds. Anticancer Drugs 17(5):539–544
108. Saggioro D, Rigobello MP, Paloschi L, Folda A, Moggach SA, Parsons S, Ronconi L, Fregona D, Bindoli A (2007) Gold(III)-dithiocarbamato complexes induce cancer cell death triggered by thioredoxin redox system inhibition and activation of ERK pathway. Chem Biol 14(10):1128–1139. https://doi.org/10.1016/j.chembiol.2007.08.016
109. Cattaruzza L, Fregona D, Mongiat M, Ronconi L, Fassina A, Colombatti A, Aldinucci D (2011) Antitumor activity of gold(III)-dithiocarbamato derivatives on prostate cancer cells and xenografts. Int J Cancer 128(1):206–215. https://doi.org/10.1002/ijc.25311
110. He L, Chen T, You Y, Hu H, Zheng W, Kwong WL, Zou T, Che CM (2014) A cancer-targeted nanosystem for delivery of gold(III) complexes: enhanced selectivity and apoptosis-inducing efficacy of a gold(III) porphyrin complex. Angew Chem Int Ed Engl 53(46):12532–12536. https://doi.org/10.1002/anie.201407143
111. Cai W, Zhang L, Song Y, Wang B, Zhang B, Cui X, Hu G, Liu Y, Wu J, Fang J (2012) Small molecule inhibitors of mammalian thioredoxin reductase. Free Radic Biol Med 52(2):257–265. https://doi.org/10.1016/j.freeradbiomed.2011.10.447
112. Kelland L (2007) The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer 7(8):573–584. https://doi.org/10.1038/nrc2167
113. Zhang J, Wang X, Lu H (2008) Amifostine increases cure rate of cisplatin on ascites hepatoma 22 via selectively protecting renal thioredoxin reductase. Cancer Lett 260(1–2):127–136. https://doi.org/10.1016/j.canlet.2007.10.023
114. Zatloukal P, Petruzelka L (2002) Gemcitabine/carboplatin in advanced non-small cell lung cancer. Lung Cancer 38(Suppl 2):S33–S36
115. Xie Q, Lan G, Zhou Y, Huang J, Liang Y, Zheng W, Fu X, Fan C, Chen T (2014) Strategy to enhance the anticancer efficacy of X-ray radiotherapy in melanoma cells by platinum complexes, the role of ROS-mediated signaling pathways. Cancer Lett 354(1):58–67. https://doi.org/10.1016/j.canlet.2014.07.046
116. Wang FY, Tang XM, Wang X, Huang KB, Feng HW, Chen ZF, Liu YN, Liang H (2018) Mitochondria-targeted platinum(II) complexes induce apoptosis-dependent autophagic cell death mediated by ER-stress in A549 cancer cells. Eur J Med Chem 155:639–650. https://doi.org/10.1016/j.ejmech.2018.06.018
117. Qin QP, Wang SL, Tan MX, Wang ZF, Luo DM, Zou BQ, Liu YC, Yao PF, Liang H (2018) Novel tacrine platinum(II) complexes display high anticancer activity via inhibition of telomerase activity, dysfunction of mitochondria, and activation of the p53 signaling pathway. Eur J Med Chem 158:106–122. https://doi.org/10.1016/j.ejmech.2018.09.008
118. Fang J, Lu J, Holmgren A (2005) Thioredoxin reductase is irreversibly modified by curcumin: a novel molecular mechanism for its anticancer activity. J Biol Chem 280(26):25284–25290. https://doi.org/10.1074/jbc.M414645200
119. Shao FY, Du ZY, Ma DL, Chen WB, Fu WY, Ruan BB, Rui W, Zhang JX, Wang S, Wong NS, Xiao H, Li MM, Liu X, Liu QY, Zhou XD, Yan HZ, Wang YF, Chen CY, Liu Z, Chen HY (2015) B5, a thioredoxin reductase inhibitor, induces apoptosis in human cervical cancer cells by suppressing the thioredoxin system, disrupting mitochondrion-dependent pathways and triggering autophagy. Oncotarget 6(31):30939–30956. https://doi.org/10.18632/oncotarget.5132
120. Li Y, Zhang LP, Dai F, Yan WJ, Wang HB, Tu ZS, Zhou B (2015) hexamethoxylated monocarbonyl analogues of curcumin cause G2/M cell cycle arrest in NCI-H460 cells via michael acceptor-dependent redox intervention. J Agric Food Chem 63(35):7731–7742. https://doi.org/10.1021/acs.jafc.5b02011
121. Jayakumar S, Patwardhan RS, Pal D, Singh B, Sharma D, Kutala VK, Sandur SK (2017) Mitochondrial targeted curcumin exhibits anticancer effects through disruption of mitochondrial redox and modulation of TrxR2 activity. Free Radic Biol Med 113:530–538. https://doi.org/10.1016/j.freeradbiomed.2017.10.378
122. Zhao R, Holmgren A (2002) A novel antioxidant mechanism of ebselen involving ebselen diselenide, a substrate of mammalian thioredoxin and thioredoxin reductase. J Biol Chem 277(42):39456–39462. https://doi.org/10.1074/jbc.M206452200
123. Liu C, Liu Z, Li M, Li X, Wong YS, Ngai SM, Zheng W, Zhang Y, Chen T (2013) Enhancement of auranofin-induced apoptosis in MCF-7 human breast cells by selenocystine, a synergistic inhibitor of thioredoxin reductase. PLoS One 8(1):e53945. https://doi.org/10.1371/journal.pone.0053945
124. Fan C, Zheng W, Fu X, Li X, Wong YS, Chen T (2014) Enhancement of auranofin-induced lung cancer cell apoptosis by selenocystine, a natural inhibitor of TrxR1 in vitro and in vivo. Cell Death Dis 5:e1191. https://doi.org/10.1038/cddis.2014.132
125. Zou Q, Chen YF, Zheng XQ, Ye SF, Xu BY, Liu YX, Zeng HH (2018) Novel thioredoxin reductase inhibitor butaselen inhibits tumorigenesis by down-regulating programmed death-ligand 1 expression. J Zhejiang Univ Sci B 19(9):689–698. https://doi.org/10.1631/jzus.B1700219
126. Zheng X, Ma W, Sun R, Yin H, Lin F, Liu Y, Xu W, Zeng H (2018) Butaselen prevents hepatocarcinogenesis and progression through inhibiting thioredoxin reductase activity. Redox Biol 14:237–249. https://doi.org/10.1016/j.redox.2017.09.014
127. Zheng X, Xu W, Sun R, Yin H, Dong C, Zeng H (2017) Synergism between thioredoxin reductase inhibitor ethaselen and sodium selenite in inhibiting proliferation and inducing death of human non-small cell lung cancer cells. Chem Biol Interact 275:74–85. https://doi.org/10.1016/j.cbi.2017.07.020
128. Liang YW, Zheng J, Li X, Zheng W, Chen T (2014) Selenadiazole derivatives as potent thioredoxin reductase inhibitors that enhance the radiosensitivity of cancer cells. Eur J Med Chem 84:335–342. https://doi.org/10.1016/j.ejmech.2014.07.032
129. Xie Q, Zhou Y, Lan G, Yang L, Zheng W, Liang Y, Chen T (2014) Sensitization of cancer cells to radiation by selenadiazole

derivatives by regulation of ROS-mediated DNA damage and ERK and AKT pathways. Biochem Biophys Res Commun 449(1):88–93. https://doi.org/10.1016/j.bbrc.2014.04.151
130. Purohit MP, Verma NK, Kar AK, Singh A, Ghosh D, Patnaik S (2017) Inhibition of thioredoxin reductase by targeted selenopolymeric nanocarriers synergizes the therapeutic efficacy of doxorubicin in MCF7 human breast cancer cells. ACS Appl Mater Interfaces 9(42):36493–36512. https://doi.org/10.1021/acsami.7b07056
131. von Nida J, Quirk C (2003) Successful treatment of in-transit melanoma metastases using topical 2–4 dinitrochlorobenzene. Australas J Dermatol 44(4):277–280
132. Nordberg J, Zhong L, Holmgren A, Arner ES (1998) Mammalian thioredoxin reductase is irreversibly inhibited by dinitrohalobenzenes by alkylation of both the redox active selenocysteine and its neighboring cysteine residue. J Biol Chem 273(18):10835–10842
133. Cenas N, Prast S, Nivinskas H, Sarlauskas J, Arner ES (2006) Interactions of nitroaromatic compounds with the mammalian selenoprotein thioredoxin reductase and the relation to induction of apoptosis in human cancer cells. J Biol Chem 281(9):5593–5603. https://doi.org/10.1074/jbc.M511972200
134. Tian C, Gao P, Zheng Y, Yue W, Wang X, Jin H, Chen Q (2008) Redox status of thioredoxin-1 (TRX1) determines the sensitivity of human liver carcinoma cells (HepG2) to arsenic trioxide-induced cell death. Cell Res 18(4):458–471. https://doi.org/10.1038/cr.2007.112
135. Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, Zhu J, Tang W, Sun GL, Yang KQ, Chen Y, Zhou L, Fang ZW, Wang YT, Ma J, Zhang P, Zhang TD, Chen SJ, Chen Z, Wang ZY (1997) Use of arsenic trioxide ($As_2O_3$) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 89(9):3354–3360
136. Lu J, Chew EH, Holmgren A (2007) Targeting thioredoxin reductase is a basis for cancer therapy by arsenic trioxide. Proc Natl Acad Sci USA 104(30):12288–12293. https://doi.org/10.1073/pnas.0701549104
137. Liu Y, Duan D, Yao J, Zhang B, Peng S, Ma H, Song Y, Fang J (2014) Dithiaarsanes induce oxidative stress-mediated apoptosis in HL-60 cells by selectively targeting thioredoxin reductase. J Med Chem 57(12):5203–5211. https://doi.org/10.1021/jm500221p
138. Yao XF, Zheng BL, Bai J, Jiang LP, Zheng Y, Qi BX, Geng CY, Zhong LF, Yang G, Chen M, Liu XF, Sun XC (2015) Low-level sodium arsenite induces apoptosis through inhibiting TrxR activity in pancreatic beta-cells. Environ Toxicol Pharmacol 40(2):486–491. https://doi.org/10.1016/j.etap.2015.08.003
139. Lillig CH, Holmgren A (2007) Thioredoxin and related molecules—from biology to health and disease. Antioxid Redox Signal 9(1):25–47. https://doi.org/10.1089/ars.2007.9.25
140. Ghezzi P (2013) Protein glutathionylation in health and disease. Biochim Biophys Acta 1830(5):3165–3172. https://doi.org/10.1016/j.bbagen.2013.02.009
141. Benhar M, Forrester MT, Stamler JS (2009) Protein denitrosylation: enzymatic mechanisms and cellular functions. Nat Rev Mol Cell Biol 10(10):721–732. https://doi.org/10.1038/nrm2764
142. Mandal PK, Schneider M, Kolle P, Kuhlencordt P, Forster H, Beck H, Bornkamm GW, Conrad M (2010) Loss of thioredoxin reductase 1 renders tumors highly susceptible to pharmacologic glutathione deprivation. Cancer Res 70(22):9505–9514. https://doi.org/10.1158/0008-5472.CAN-10-1509
143. Habermann KJ, Grunewald L, van Wijk S, Fulda S (2017) Targeting redox homeostasis in rhabdomyosarcoma cells: GSH-depleting agents enhance auranofin-induced cell death. Cell Death Dis 8(10):e3067. https://doi.org/10.1038/cddis.2017.412
144. Rodman SN, Spence JM, Ronnfeldt TJ, Zhu Y, Solst SR, O'Neill RA, Allen BG, Guan X, Spitz DR, Fath MA (2016) Enhancement of radiation response in breast cancer stem cells by inhibition of thioredoxin- and glutathione-dependent metabolism. Radiat Res 186(4):385–395. https://doi.org/10.1667/RR14463.1
145. Du Y, Zhang H, Lu J, Holmgren A (2012) Glutathione and glutaredoxin act as a backup of human thioredoxin reductase 1 to reduce thioredoxin 1 preventing cell death by aurothioglucose. J Biol Chem 287(45):38210–38219. https://doi.org/10.1074/jbc.M112.392225
146. Fath MA, Ahmad IM, Smith CJ, Spence J, Spitz DR (2011) Enhancement of carboplatin-mediated lung cancer cell killing by simultaneous disruption of glutathione and thioredoxin metabolism. Clin Cancer Res 17(19):6206–6217. https://doi.org/10.1158/1078-0432.CCR-11-0736
147. Sobhakumari A, Love-Homan L, Fletcher EV, Martin SM, Parsons AD, Spitz DR, Knudson CM, Simons AL (2012) Susceptibility of human head and neck cancer cells to combined inhibition of glutathione and thioredoxin metabolism. PLoS One 7(10):e48175. https://doi.org/10.1371/journal.pone.0048175
148. Scarbrough PM, Mapuskar KA, Mattson DM, Gius D, Watson WH, Spitz DR (2012) Simultaneous inhibition of glutathione- and thioredoxin-dependent metabolism is necessary to potentiate 17AAG-induced cancer cell killing via oxidative stress. Free Radic Biol Med 52(2):436–443. https://doi.org/10.1016/j.freeradbiomed.2011.10.493
149. Roh JL, Jang H, Kim EH, Shin D (2017) Targeting of the glutathione, thioredoxin, and Nrf2 antioxidant systems in head and neck cancer. Antioxid Redox Signal 27(2):106–114. https://doi.org/10.1089/ars.2016.6841
150. Mahmood DF, Abderrazak A, El Hadri K, Simmet T, Rouis M (2013) The thioredoxin system as a therapeutic target in human health and disease. Antioxid Redox Signal 19(11):1266–1303. https://doi.org/10.1089/ars.2012.4757
151. Nishiyama A, Matsui M, Iwata S, Hirota K, Masutani H, Nakamura H, Takagi Y, Sono H, Gon Y, Yodoi J (1999) Identification of thioredoxin-binding protein-2/vitamin D(3) up-regulated protein 1 as a negative regulator of thioredoxin function and expression. J Biol Chem 274(31):21645–21650
152. Chen KS, DeLuca HF (1995) Cloning of the human 1 alpha,25-dihydroxyvitamin D-3 24-hydroxylase gene promoter and identification of two vitamin D-responsive elements. Biochim Biophys Acta 1263(1):1–9
153. Yamawaki H, Pan S, Lee RT, Berk BC (2005) Fluid shear stress inhibits vascular inflammation by decreasing thioredoxin-interacting protein in endothelial cells. J Clin Invest 115(3):733–738. https://doi.org/10.1172/JCI23001
154. Yu FX, Goh SR, Dai RP, Luo Y (2009) Adenosine-containing molecules amplify glucose signaling and enhance txnip expression. Mol Endocrinol 23(6):932–942. https://doi.org/10.1210/me.2008-0383
155. Spindel ON, World C, Berk BC (2012) Thioredoxin interacting protein: redox dependent and independent regulatory mechanisms. Antioxid Redox Signal 16(6):587–596. https://doi.org/10.1089/ars.2011.4137
156. Zhou J, Yu Q, Chng WJ (2011) TXNIP (VDUP-1, TBP-2): a major redox regulator commonly suppressed in cancer by epigenetic mechanisms. Int J Biochem Cell Biol 43(12):1668–1673. https://doi.org/10.1016/j.biocel.2011.09.005
157. Cadenas C, Franckenstein D, Schmidt M, Gehrmann M, Hermes M, Geppert B, Schormann W, Maccoux LJ, Schug M, Schumann A, Wilhelm C, Freis E, Ickstadt K, Rahnenfuhrer J, Baumbach JI, Sickmann A, Hengstler JG (2010) Role of thioredoxin reductase 1 and thioredoxin interacting protein in prognosis of breast cancer. Breast Cancer Res 12(3):R44. https://doi.org/10.1186/bcr2599
158. Kwon HJ, Won YS, Suh HW, Jeon JH, Shao Y, Yoon SR, Chung JW, Kim TD, Kim HM, Nam KH, Yoon WK, Kim DG, Kim JH,

Kim YS, Kim DY, Kim HC, Choi I (2010) Vitamin D3 upregulated protein 1 suppresses TNF-alpha-induced NF-kappaB activation in hepatocarcinogenesis. J Immunol 185(7):3980–3989. https://doi.org/10.4049/jimmunol.1000990

159. Feingold PL, Surman DR, Brown K, Xu Y, McDuffie LA, Shukla V, Reardon ES, Crooks DR, Trepel JB, Lee S, Lee MJ, Gao S, Xi S, McLoughlin KC, Diggs LP, Beer DG, Nancarrow DJ, Neckers LM, Davis JL, Hoang CD, Hernandez JM, Schrump DS, Ripley RT (2018) Induction of thioredoxin-interacting protein by a histone deacetylase inhibitor, entinostat, is associated with DNA damage and apoptosis in esophageal adenocarcinoma. Mol Cancer Ther 17(9):2013–2023. https://doi.org/10.1158/1535-7163.MCT-17-1240
160. Zhu G, Zhou L, Liu H, Shan Y, Zhang X (2018) MicroRNA-224 promotes pancreatic cancer cell proliferation and migration by targeting the TXNIP-mediated HIF1alpha pathway. Cell Physiol Biochem 48(4):1735–1746. https://doi.org/10.1159/000492309
161. Jung H, Kim MJ, Kim DO, Kim WS, Yoon SJ, Park YJ, Yoon SR, Kim TD, Suh HW, Yun S, Min JK, Lee HG, Lee YH, Na HJ, Lee DC, Kim HC, Choi I (2013) TXNIP maintains the hematopoietic cell pool by switching the function of p53 under oxidative stress. Cell Metab 18(1):75–85. https://doi.org/10.1016/j.cmet.2013.06.002
162. Sheth SS, Bodnar JS, Ghazalpour A, Thipphavong CK, Tsutsumi S, Tward AD, Demant P, Kodama T, Aburatani H, Lusis AJ (2006) Hepatocellular carcinoma in Txnip-deficient mice. Oncogene 25(25):3528–3536. https://doi.org/10.1038/sj.onc.1209394
163. Li J, Yue Z, Xiong W, Sun P, You K, Wang J (2017) TXNIP overexpression suppresses proliferation and induces apoptosis in SMMC7221 cells through ROS generation and MAPK pathway activation. Oncol Rep 37(6):3369–3376. https://doi.org/10.3892/or.2017.5577
164. Woolston CM, Madhusudan S, Soomro IN, Lobo DN, Reece-Smith AM, Parsons SL, Martin SG (2013) Thioredoxin interacting protein and its association with clinical outcome in gastro-oesophageal adenocarcinoma. Redox Biol 1:285–291. https://doi.org/10.1016/j.redox.2013.04.006
165. Nishizawa K, Nishiyama H, Matsui Y, Kobayashi T, Saito R, Kotani H, Masutani H, Oishi S, Toda Y, Fujii N, Yodoi J, Ogawa O (2011) Thioredoxin-interacting protein suppresses bladder carcinogenesis. Carcinogenesis 32(10):1459–1466. https://doi.org/10.1093/carcin/bgr137
166. Zhou Y, Zhou J, Lu X, Tan TZ, Chng WJ (2018) BET Bromodomain inhibition promotes De-repression of TXNIP and activation of ASK1-MAPK pathway in acute myeloid leukemia. BMC Cancer 18(1):731. https://doi.org/10.1186/s12885-018-4661-6
167. Morrison JA, Pike LA, Sams SB, Sharma V, Zhou Q, Severson JJ, Tan AC, Wood WM, Haugen BR (2014) Thioredoxin interacting protein (TXNIP) is a novel tumor suppressor in thyroid cancer. Mol Cancer 13:62. https://doi.org/10.1186/1476-4598-13-62
168. Park JW, Lee SH, Woo GH, Kwon HJ, Kim DY (2018) Down-regulation of TXNIP leads to high proliferative activity and estrogen-dependent cell growth in breast cancer. Biochem Biophys Res Commun 498(3):566–572. https://doi.org/10.1016/j.bbrc.2018.03.020
169. Kwon HJ, Won YS, Nam KT, Yoon YD, Jee H, Yoon WK, Nam KH, Kang JS, Han SU, Choi IP, Kim DY, Kim HC (2012) Vitamin D(3) upregulated protein 1 deficiency promotes *N*-methyl-*N*-nitrosourea and *Helicobacter pylori*-induced gastric carcinogenesis in mice. Gut 61(1):53–63. https://doi.org/10.1136/gutjnl-2011-300361
170. Masaki S, Masutani H, Yoshihara E, Yodoi J (2012) Deficiency of thioredoxin binding protein-2 (TBP-2) enhances TGF-beta signaling and promotes epithelial to mesenchymal transition. PLoS One 7(6):e39900. https://doi.org/10.1371/journal.pone.0039900
171. Hirata Y, Saito M, Tsukamoto I, Yamaguchi F, Sui L, Kamitori K, Dong Y, Uehara E, Konishi R, Janjua N, Tokuda M (2009) Analysis of the inhibitory mechanism of D-allose on MOLT-4F leukemia cell proliferation. J Biosci Bioeng 107(5):562–568. https://doi.org/10.1016/j.jbiosc.2008.12.021
172. Hoshikawa H, Mori T, Mori N (2010) In vitro and in vivo effects of D-allose: up-regulation of thioredoxin-interacting protein in head and neck cancer cells. Ann Otol Rhinol Laryngol 119(8):567–571. https://doi.org/10.1177/000348941011900810
173. Noguchi C, Kamitori K, Hossain A, Hoshikawa H, Katagi A, Dong Y, Sui L, Tokuda M, Yamaguchi F (2016) D-Allose inhibits cancer cell growth by reducing GLUT1 expression. Tohoku J Exp Med 238(2):131–141. https://doi.org/10.1620/tjem.238.131
174. Yamaguchi F, Takata M, Kamitori K, Nonaka M, Dong Y, Sui L, Tokuda M (2008) Rare sugar D-allose induces specific up-regulation of TXNIP and subsequent G1 cell cycle arrest in hepatocellular carcinoma cells by stabilization of p27kip1. Int J Oncol 32(2):377–385
175. Kanaji N, Kamitori K, Hossain A, Noguchi C, Katagi A, Kadowaki N, Tokuda M (2018) Additive antitumour effect of dallose in combination with cisplatin in non-small cell lung cancer cells. Oncol Rep 39(3):1292–1298. https://doi.org/10.3892/or.2018.6192
176. Hoshikawa H, Indo K, Mori T, Mori N (2011) Enhancement of the radiation effects by D-allose in head and neck cancer cells. Cancer Lett 306(1):60–66. https://doi.org/10.1016/j.canlet.2011.02.032
177. Yamaguchi F, Kamitori K, Sanada K, Horii M, Dong Y, Sui L, Tokuda M (2008) Rare sugar D-allose enhances anti-tumor effect of 5-fluorouracil on the human hepatocellular carcinoma cell line HuH-7. J Biosci Bioeng 106(3):248–252. https://doi.org/10.1263/jbb.106.248
178. Hoshikawa H, Kamitori K, Indo K, Mori T, Kamata M, Takahashi T, Tokuda M (2018) Combined treatment with D-allose, docetaxel and radiation inhibits the tumor growth in an in vivo model of head and neck cancer. Oncol Lett 15(3):3422–3428. https://doi.org/10.3892/ol.2018.7787