Thioredoxin Reductase as a Pharmacological Target

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Review

Thioredoxin reductase as a pharmacological target

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ABSTRACT

Thioredoxin reductases (TrxRs) belong to the pyridine nucleotide disulfide oxidoreductase family enzymes that reduce thioredoxin (Trx). The couple TrxR and Trx is one of the major antioxidant systems that control the redox homeostasis in cells. The thioredoxin system, comprised of TrxR, Trx and NADPH, exerts its activities via a disulfide-dithiol exchange reaction. Inhibition of TrxR is an important clinical goal in all conditions in which the redox state is perturbed. The present review focuses on the most critical aspects of the cellular functions of TrxRs and their inhibition mechanisms by metal ions or chemicals, through direct targeting of TrxRs or their substrates or protein interactors. To update the involvement of overactivation/dysfunction of TrxRs in various pathological conditions, human diseases associated with TrxRs genes were critically summarized by publicly available genome-wide association study (GWAS) catalogs and literature. The pieces of evidence presented here justify why TrxR is recognized as one of the most critical clinical targets and the growing current interest in developing molecules capable of interfering with the functions of TrxR enzymes.

1. Introduction

The cytosolic and mitochondrial thioredoxin reductase (TrxR) and thioredoxins (Trx1 and Trx2) are critical components of the mammalian thioredoxin system [1]. Trx and TrxR provide a coupled redox system required for redox reactions in biosynthetic pathways involved in controlling redox homeostasis in cells [2,3].

TrxRs are FAD-containing pyridine nucleotide disulfide oxidoreductases that utilize NADPH for reduction of active-site disulfide of Trxs. TrxR is necessary to all biochemical pathways in which Trx is involved as a reducing substrate [4].

Crucial redox-sensitive biological processes, including cell survival, growth, migration, and inhibition of apoptosis is mediated by thioredoxin system. However, the overexpression of TrxR and Trxs, as a defense response against oxidative stress, are also associated to several type of cancers through an unknown mechanism [4]. Moreover, TrxR plays also an important role in diverse physiological and pathological conditions such as parasitoses, chronic inflammatory, autoimmune diseases, and neurodegenerative disorders [5–13].

Rapid proliferation of cancer cells requires high metabolic activity, including increased glycolysis and other metabolic reactions [14]. Due to this increased metabolic rate, cancer cells, particularly those in advanced stages, are subject to high oxidative stress caused by abundant reactive oxygen species (ROS) production, which are considered to originate mainly from the electronic leakage of mitochondrial respiratory complexes [14–16].

Trx, a redox active protein, can be oxidized by ROS, which leads to the formation of a disulfide bridge (vide infra). The reduction by TrxR re-activates Trx providing a circuit for sequential turnover in multiple oxidation/reduction cycles [2,17]. In its reduced form, Trx inhibits apoptosis signal-regulating kinase 1 (ASK1) and the downstream mitogen-activated protein kinase p38 (p38-MAPK). Upon accumulating ROS, Trx is oxidized, and ASK1 is activated, leading to apoptotic cell death [18,19]. In several cancer cells, over-expression of Trx increases the capacity for ROS, which leads to increased drug resistance and promotes tumor progression [20]. Therefore, several small molecules targeting the Trx-TrxR system have been developed to preferentially induce cell death in malignant cells due to the increased dependence of these cells on the anti-oxidative activity of the Trx-TrxR system [21,22].

Recently published reviews are mainly focused on the overactivation/dysfunction of TrxRs linked to the onset and development of can-

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cer. These researchers also indicated that a number of effective natural and synthetic inhibitors of mammalian TrxRs could be used as potential anticancer agents [5,23–29].

This review focuses on the most critical aspects of the cellular functions of TrxRs and their inhibition mechanisms through direct targeting to them or their substrates or protein interactors by metal ions or other chemicals. To update the involvement of overactivation/dysfunction of TrxRs in various pathological conditions, human diseases associated with TrxRs genes were critically summarized by publicly available genome-wide association study (GWAS) catalogs and literature. The evidence presented here justifies why TrxR is increasingly recognized as one of the most critical clinical targets, as well as the growing interest in developing molecules capable of interfering with the functions of TrxR enzymes.

2. Cellular functions of thioredoxin reductase (TrxRs) and thioredoxins (Trxs)

TrxR is a selenoprotein with three isozymes (TrxR1, TrxR2, and TrxR3, Table 1), vulnerable to low dietary selenium (Se) intakes, though less so than glutathione peroxidase-1 (Gpx-1), another crucial antioxidant enzyme in humans [30–34]. TrxR activity in the liver, kidneys, and lungs is decreased by Se deficiency and enhanced by high Se intake, while the activity of the enzyme in animal brains is much less affected by low Se intake because its concentrations in the brain are under much better homeostatic regulation than in most other organs [35,36].

TrxR is also a flavoprotein [27], presumably vulnerable to riboflavin deficiency in a similar way as glutathione reductase (GR) [37,38]. The physiological role of TrxR is the transfer of reducing equivalents from NADPH to Trx recovering its reduced state (Fig. 1) [18,39].

TrxR has a peculiar structure: one part of the molecule is a flavoprotein very similar to GR, while the other is a flexible arm, not found in GR, and which near its end contains an accessible cysteinyl group and a selenocysteine group in vicinal positions [40–42]. This makes it possible for the enzyme to form chelate complexes with heavy metals, where the metal ion is simultaneously coordinated to a selenol group (–SeH) and a thiol group (–SH).

Table 1
Identifiers of three thioredoxin reductase isozymes in freely accessible biological databases. NCBI: National Center for Biotechnology Information, UniProt: protein sequence database, OMIM: Online Mendelian Inheritance in Man, PDB: Protein Data Bank, EC: Enzyme Commission Number.

	Thioredoxin reductase 1	NThioredoxin reductase 2	Thioredoxin reductase 3
	TrxR1	TrxR2	TrxR3
Gene symbol	*TXNRD1*	*TXNRD2*	*TXNRD3*
NCBI gene	7296	10587	114112
UniProt	Q16881	Q9NNW7	Q86VQ6
OMIM	601112	606448	606235
PDB	3QFB	3DGZ	3H8Q
EC number	1.8.1.9	1.8.1.9	1.8.1.9
Locus	Chr. 12 *q23-q24*	Chr. 22 *q11.21*	Chr. 3 *p13-q13.33*

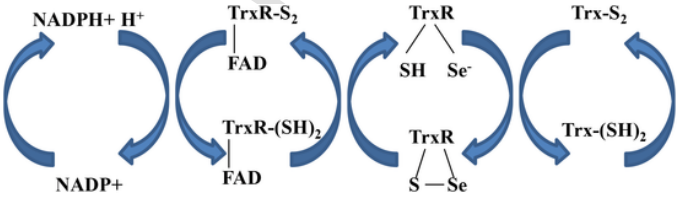

Fig. 1. TrxR's cellular role. The oxidized thioredoxin (Trx-S2) is reduced by NADPH and the selenoenzyme TrxR.

TrxR1 and TrxR2 are generally considered to have comparable properties but functionally separated by their different compartments: cytoplasm, and mitochondria, respectively [43]. They are both similarly Se-dependent but differ in their substrate specificities and their inhibition by metals [43]. Mitochondrial TrxR3, conversely, is completely different and much less Se-dependent than TrxR1 [44]. TrxR3, and also 2-Cys peroxiredoxins (Prxs), are found in several different cell types and organs, including skeletal muscle cells [45,46], cardiomyocytes [47–51], and endothelial cells [52,53], where these enzymes are presumably crucial for scavenging intramitochondrial hydrogen peroxide and peroxynitrite. This may presumably be important in the etiopathogenesis of several different diseases affecting skeletal muscles and cardiomyocytes, including common muscle pains (e.g., "mouse disease" and tension headache), fibromyalgia, and cardiac failure, as well as in the etiopathogenesis of atheromatosis and coronary heart disease [54]. TrxR is an enzyme with broad substrate specificity that can reduce several different oxidizing substrates [55]. In addition to utilizing oxidized Trx as a substrate, other substrates are protein disulfide isomerase, glutaredoxin, glutathione peroxidase, NK-lysin/granulysin, HIV Tat protein, H_2O_2, lipid hydroperoxides, vitamin K, ubiquinone, juglone, ninhydrin, alloxan, dehydroascorbate, lipoic acid/lipoamide, *S*-nitrosoglutathione, selenodiglutathione (GSSeSG), selenite, methylseleninate, selenocysteine, diphenylselenide and ebselen [55–60].

The substrate Trx is similarly found not only in various intracellular compartments but also in blood plasma and other extracellular fluids, with Trx (and not GSH) apparently being the favored reducing substrate for selenoprotein P (Seep1, is the most common selenoprotein found in the plasma), when the latter functions as an antioxidant enzyme [61].

There are two major isoforms of Trx present in cells, Trx1 in the cytoplasm and nucleus and Trx2 in the mitochondria. The catalytic activity and structure of human Trx1 are regulated via oxidation and *S*-nitrosylation of cysteine residues (Fig. 2) [62].

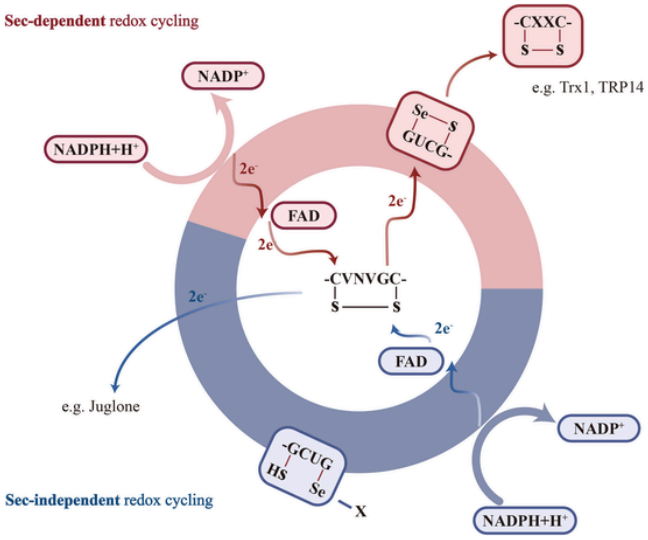

Fig. 2. Catalytic mechanism of TrxR1. Selenocysteine (Sec)-dependent redox cycling (pink part): The electrons flow from NADPH via the FAD moiety to the N-terminal disulfide motif of one subunit and subsequently to the C-terminal selenylsulfide motif of the other subunit. The thereby reduced selenothiol motif allows reduction of substrates such as Trx and TRP14. Sec-independent redox cycling (blue part): The selenolate of the C-terminus can be derivatized with electrophilic agents (indicated with X), which results in an enzyme species that is irreversibly inhibited for the normal substrate reduction via the C-terminal active site. However, NADPH can still donate electrons to FAD and the functional -CVNVGC- motif, which promotes Sec-independent reduction of certain substrates such as juglone and other quinones. Figure created with BioRender (http://biorender.com).

The function of Trx is the reduction of oxidized cysteine (Cys) residues and the cleavage of disulfide bonds. Human Trx1 contains two active Cys sites that cycle between the dithiol and disulfide forms as Trx1 reduces target proteins [63]. The process starts with an attack of Cys-32 in the conserved thioredoxin $C_{32}XXC_{35}$ motif onto the substrate's oxidized group. Following this event, the other conserved Cys-35 forms a disulfide bond with Cys-32, transferring two electrons to the substrate, which is now in its reduced form. TrxR reduces the oxidized Trx1, while NADPH reduces TrxR.

In addition to the active site thiol groups, human Trx1 contains three non-active Cys residues at positions 62, 69, and 73 [63,64]. A two-disulfide form of Trx1, containing the cited active disulfide site between Cys-32 and Cys-35, and a non-active disulfide site between Cys-62 and Cys-69, is inactive either as a disulfide reductase or as a substrate for TrxR [64]. This could provide a structural switch affecting Trx1 function during oxidative stress and redox signaling [64].

Within actively growing human leukemia monocytic cell lines (THP1), most of the active site of Trx1 was found to be in the dithiol form, whereas the non-active site was totally in the dithiol form [63]. It was also found that the addition of increasing concentrations of diamide to these cells resulted in oxidation of the active site at fairly low levels and oxidation of the non-active site at higher concentrations [63].

Trx itself is an important protein repair enzyme, which helps to remove abnormal disulfide groups that have formed as a result of aberrant oxidation of protein molecules while using GSH as a reducing cofactor [65,66]. There is a cooperation between Trx and glutaredoxin (or thioltransferase), both of which help remove abnormal disulfide groups from proteins, but with different roles, since glutaredoxin has a high specificity for GSH-protein mixed disulfides, while Trx reduces abnormal intra-protein disulfide bonds [65].

Trx2 performs many of the same functions in the mitochondria as Trx1, but it would seem that it plays an even more critical role than the Trx1 isoform. The Trx2 mitochondrial interactome was recently reported extending its biological role [67]. The Trx2 network consists of 53 interactors, and though it is well known that thioredoxins are thiol-employing disulfide oxidoreductases, approximately half of the reported interactions were not due to covalent disulfide bonds. Analysis of the protein-protein interactions revealed that human Trx2 is involved potentially in mitochondrial integrity, the formation of iron-sulfur clusters, detoxification of aldehydes, mitoribosome assembly and protein synthesis, protein folding, ADP ribosylation, amino acid and lipid metabolism, glycolysis, the TCA cycle, and the electron transport chain [67].

3. Functions of reduced thioredoxin

Reduced Trx (which is regenerated by TrxR) has several different important roles [68]. It functions as one of the two alternatives reducing substrates for ribonucleotide reductase and is therefore important for DNA synthesis and repair [69]. Reduced glutaredoxin, which depends on GSH as a reducing cofactor for regeneration, is used by ribonucleotide reductase as a secondary alternative reducing substrate [70]. Therefore, it is especially unfavorable if both of the two parallel electron transport chains from NADPH to ribonucleotide reductase are partially blocked simultaneously because the GSH concentration in the cell is low at the same time as ribonucleotide reductase is inhibited by toxic metals or by Se or riboflavin depletion. This will lead to depletion of monodeoxyribonucleotide building blocks that are equally much needed both for DNA repair as for *de novo* synthesis of DNA molecules. Simultaneous GSH depletion and TrxR inhibition must therefore be expected to lead to inhibition of DNA synthesis, which will be especially unfavorable for fast-replicating cells, such as leukocytes (or leukocyte progenitors) and enterocytes – which may not only lead to immunosuppression (which might be potentially significant in the etiopathogenesis of chronic fatigue syndrome), but also to various pathological disturbances of intestinal function - with potential consequences also for other parts of the body, including the brain [71–73]. However, it must also be expected to cause inhibition of DNA repair, leading to abnormal enhancement of the rate of mitochondrial DNA aging as well as enhancing the risk of cancer.

Reduced Trx is also important for antioxidant defense for several reasons. It functions as a reducing cofactor for all 2-Cys peroxiredoxins [74,75]; however, at least one of the 2-Cys peroxiredoxins can alternatively use glutaredoxin as a reducing cofactor [75]. These enzymes scavenge H_2O_2, peroxynitrite, and organic hydroperoxides [76]. However, again, there is a cooperation between enzyme systems dependent on Se and GSH-dependent ones, since 1-Cys peroxiredoxin (peroxiredoxin-6) cannot use Trx as a reducing cofactor, but uses instead either GSH assisted by one of the glutathione-*S*-transferases [77], ascorbate [78] or dihydrolipoate [79] as alternative reducing cofactors (with perhaps only GSH and ascorbate being physiologically important since the intracellular abundance of dihydrolipoate might normally be much smaller than the GSH and ascorbate concentrations).

Reduced Trx functions, moreover, also as reducing substrate for various methionyl sulfoxide reductases, which are important for repair of oxidized protein molecules [80], being in turn very important for protection against degenerative processes associated with aging [81,82] – which appears to be similar even in insects [83,84]. However, it has been reported that methionine sulfoxide reductases (at least one of them) can also use glutaredoxin as an alternative reducing cofactor [85], thus providing a backup when reduced Trx is depleted.

4. Thioredoxin reductase inhibition by metals

TrxR is very sensitive to inhibition by several metals including gold, palladium, and platinum, as well as by silver, zinc, mercury, cadmium and gadolinium (Fig. 3) [86–91].

While TrxR strongly binds particularly toxic metals, its substrate Trx is also a heavy metal-binding protein. This probably means that the substrate can help protect the enzyme itself from inhibition by the metal ion, when the total concentration of the latter is substantially lower than the concentration of Trx. This makes it more difficult to study the kinetics of inhibition than most other enzymatic reactions, where the substrate does not function as a potent anti-inhibitor. Perhaps it will commonly be a two-phase process, first with the rapid binding of the toxic metal to the substrate rather than to the enzyme, and

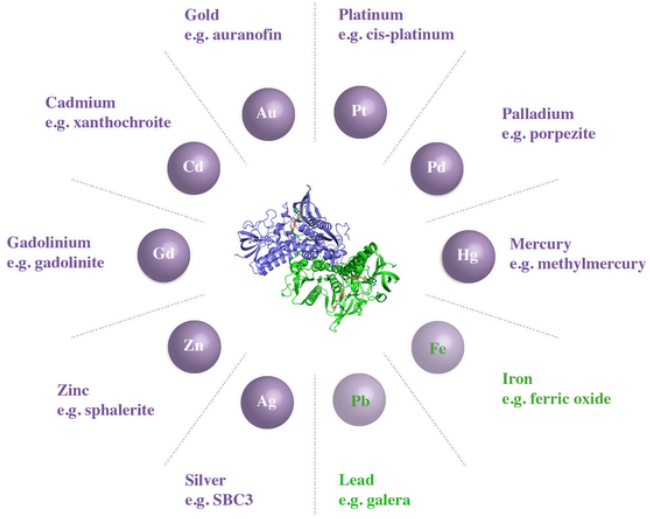

Fig. 3. Metal inhibitors of TrxR. The selenol groups of TrxR have more affinity for chalcophilic heavy metal atoms than thiol groups; the metal ions could strongly bound to Se. Figure created with BioRender (http://biorender.com).

next with a much slower process of transfer of the toxic metal from the substrate to the enzyme itself.

It seems that the end result of the second stage determines the level of inhibition in vivo, but it is more difficult to study by in vitro experiments, and perhaps this is not even possible unless an inert atmosphere is used in order to protect the system from reactions of spontaneous oxidation (not enzyme-catalyzed).

Selenol groups have more affinity for chalcophilic heavy metal ions than thiol groups [92], consequently the latter will be more strongly bound to Se, which is most likely the case for all toxic metals. Gold compounds, either Au(I) or Au(III), are strong TrxR inhibitors [93]. The inhibitory constant K_i of TrxR, by the Au(I) complex auranofin, is only about 4 nM (IC_{50} = 20 nM), while 1000-fold higher concentrations, (μM levels) are needed for inhibition of human glutathione reductase (that is also a dithiol enzyme capable of forming chelates with toxic metals), and the selenoenzyme glutathione peroxidase (that contains not closely spaced selenol groups and cannot form chelates with the toxic metals) [94]. The ability of auranofin, a drug used to treat rheumatoid arthritis, to suppress TrxR activity at nanomolar concentrations is considered critical to its therapeutic effects [95,96].

Gold complexes inhibitors toward TrxR patented in 2017–2020 have been reviewed recently [5]. Among these a series of triazole Au(I) compounds have been reported, with inhibitory activity in a nM level (the most potent showed IC_{50} 6.3 nM).

For inhibition of recombinant rat TrxR by $HgCl_2$ and MeHg, IC_{50} values of 7.2 and 19.7 nM, respectively, have been determined [87]. TrxR is similarly sensitive to inhibition by Hg^{2+} as it is to inhibition by auranofin. In addition to gold also platinum and other metals (including gadolinium) used for cancer therapy have also been well studied regarding their inhibition property of TrxR (see for instance [6,86, 97–99]. Thioredoxin peroxidase-1 (TrxP-1) is inhibited by Hg^{2+} ions in the concentration range of 5–50 nM [88]. This inhibition may be crucial for understanding the pathogenetic mechanisms of Hg poisoning since there may be no other enzyme except Seep1 that is similarly vulnerable to inhibition by Hg. Further amplification of the toxic effects of Hg on TrxR is likely because the enzyme itself is inhibited by the secondary lipid peroxidation products 4-hydroxynonenal [100,101] and acrolein [102,103], while its substrate Trx can also be inactivated by the latter [103], by nitration caused by peroxynitrite [104–106], and by methylglyoxal [107].

When Hg inhibits antioxidant defense enzymes, it must be expected that the rates of 4-hydroxynonenal and acrolein production will increase, which is the reason why there will be an auto-amplification of the toxic effects of Hg. When the oxidative stress is severe enough to cause porphyria, it must be expected that lipid peroxidation rates will be elevated too, so the TrxR/Trx system may be inhibited both by porphyrins and aldehydes formed as products of lipid peroxidation, as well as by Hg itself. Inhibition of TrxR by Hg has also been demonstrated in vivo, using an experimental fish model [90]. Selenium can be used as an antidote to protect the fishes against Hg-caused TrxR inhibition, as well as for partial protection against Hg-induced tissue damage [89, 90].

TrxR has also been found to be inhibited by cadmium (Cd) and by tributyltin (organotin compounds) [108]. However, it has been reported that Cd^{2+} enhances the expression of TrxR1 [109,110], which might represent a compensatory mechanism shared by more than one toxic metal. It is nevertheless a reasonable working hypothesis that the in vivo sensitivity to inhibition by these toxic metals may be far greater for TrxR than for the glutathione peroxidases. Cadmium has been reported to activate the transcription factor Nrf2 [111], and Nrf2 upregulates the expression of TrxR [109,112–114].

TrxR is also irreversibly inhibited by arsenic trioxide or arsenite with an IC_{50} of 0.25 μM [115].

Two organic arsenicals PIM-PAO-PDT and PAM-PAO-PDT bearing the S-As-S chemical scaffold (2-(((4-(1,3,2-dithiarsinan-2-yl) phenyl) imino) methyl) phenol and N-(4-(1,3,2-dithiarsinan-2-yl) phenyl)-2-hydroxybenzamide) showed the best TrxR inhibition in vitro in HL-60 cells with IC_{50} of 0.94 and 0.84 μM respectively [116]. The amino group link has been suggested to helps improve the selectivity of PAM-PAO-PDT compared with Schiff base group link in PIM-PAO-PDT. Though arsenicals are a kind of promising anticancer drugs [117], TrxR is far less sensitive to them than it is to auranofin (IC_{50} = 20 nM) and Hg^{2+} (IC_{50} = 7.2 nM). Upregulation of selenoproteins TrxR and GPx through Se supplementation has been demonstrated as a detoxification pathway against oxidative damage due to arsenic [118]. However, another enzyme that is far more vulnerable to arsenite is poly-(ADP-ribose) polymerase (PARP) [119]. PARP is an enzyme needed for normal DNA repair [120,121], and inhibition of the latter enzyme must probably be much more important for explaining the genotoxic effects of arsenic than inhibition of TrxR.

Ag^+ was reported to directly inhibit the activities of TrxR and Trx1 [122] by leading the oligomerization and functional disruption [123]. The IC_{50} values calculated for several of phosphino Ag^+ complexes are in the nanomolar range suggesting that TrxR could be an important target for silver derivatives [124]. As an Ag-based compound, SBC3 (1,3-dibenzyl-4,5-diphenyl-imidazol-2-ylidene silver(I) acetate) targeting bacterial TrxR is a promising antibiotic drug candidate [125]. Silver nanoparticles (Ag-NPs) could inhibit the antioxidant defense of the astrocytes by prevents the TrxR to induce neurotoxicity [126] and to kill multi-drug resistant bacteria targeting bacterial thiol redox system [127]. Iron-complexes are considered alternative to conventional platinum-based anticancer drugs due to their broad range of reactivity and to the targeting of different biological systems [128]. For example a series of ferrocenyl diphenol complexes showed an efficient inhibitor effect on TrxR with IC_{50} in the nM level [129]. Some newly Fe(II)-phenanthroline complexes has been showed to exhibit anticancer activity against esophageal squamous cell carcinoma cells (ESCC). Combined treatment with cisplatin showed promising synergistic anticancer effects [130].

TrxR activity in rat kidneys has, paradoxically, been reported to be enhanced by lead (Pb) exposure [131]. One might speculate that this could be because Pb^{2+} enhances the expression of TrxR more strongly than it directly inhibits this enzyme. Since Pb^{2+} would be expected to bind strongly both to thiol and selenol groups, it is very strange that it is not a strong inhibitor of TrxR, similar to many other chalcophilic or siderophilic metals. One possible explanation might be a stronger binding of Pb^{2+} to substrate Trx than to the enzyme TrxR itself, which might be possible if Trx has 3 or 4 thiol groups available for simultaneous binding to Pb^{2+} rather than only two thiol groups at the active site [63]. Observations presented above would appear compatible with a hypothesis that the primary function of the second dithiol group configuration outside the active site might be to help to bind toxic metals together with the two thiol groups at the active site so that the active site of TrxR might be protected against the toxic metals.

It is also conceivable that there might be some other Pb-binding protectant chelator inside the cells, rather than Trx. A study of intramolecular disulfide bond formation in glutaredoxin-1 (Grx1) has shown that Cys-8 in glutaredoxin-1 can form disulfide bonds either with Cys-79 or Cys-83 [132]. On this background, it is not inconceivable that this protein might form a trithiolate complex with Pb^{2+}, where the Pb atom is simultaneously coordinated to Cys-8, Cys-79, and Cys-83. In that case, it might be Grx rather than Trx that protects TrxR against inactivation by Pb^{2+} in vivo. Pb^{2+} might prefer binding to Trx1 or Grx1 rather than to TrxR, not only because as much as 4 or 3 thiol groups, respectively, might be available for Pb^{2+} binding on the Trx1 or Grx1 molecules, but also because of the different geometry of the complexes formed when Pb^{2+} binds, respectively, to TrxR or to either Trx1 or Grx1.

The fact that gold, platinum and mercury bind to Se atoms more strongly than lead seems to be the most important reason why TrxR is much more sensitive to their inhibition.

Then, because of weaker binding to selenol groups, compared to the more noble metals, Pb^{2+} probably prefers coordination to 4 S atoms simultaneously in Trx1 rather than simultaneous coordination to 1 Se atom and 1 S atom in TrxR. The metals Au and Hg might prefer coordination to 1 Se atom and 1 S atom in TrxR over coordination to 4 thiol group S atoms in Trx1.

Grx2 has been reported to be an iron-sulfur protein, which perhaps might play a role as a redox sensor [133]. Perhaps that protein might bind Pb^{2+} fairly tightly as well.

There is no doubt that Pb^{2+} is an important oxidant stressor in vivo, but inhibition of TrxR does not appear to be the mechanism explaining this. An alternative hypothesis might be Pb catalysis of non-enzymatic, spontaneous catalysis of GSH oxidation to GSSG by molecular O_2, similarly as Fe can catalyze non-enzymatic oxidation of other small thiol molecules, such as cysteinylglycine [134,135], cysteine [135,136], and homocysteine [137,138]. It has been reported that Pb exposure causes depletion of intracellular GSH [139].

GSH has an important protective effect because it helps decrease peroxynitrite formation rate [140] and due to its role as a catalytic cofactor when methylglyoxal is scavenged by the glyoxalases [141,142]. This example shows how GSH and Se-dependent enzymes collaborate closely in the cellular mechanism for antioxidant defense and protect the integrity of the cellular genome.

It is far more dangerous when both the GSH-dependent and Se-dependent elements of antioxidative and antimutagenic defense systems are inhibited simultaneously, e.g., because of a combination of toxic metal exposure and protein malnutrition compared to what happens to only one of these elements [143,144].

5. Thioredoxin reductase inhibition by other chemicals

A series of other chemicals can form covalent adducts to selenocysteine and cysteine residues of TrxR and Trx causing irreversible effects on their activity [145].

4-Hydroxynonenal and acrolein are formed as secondary products of peroxidation of polyunsaturated fatty acids. The peroxidation rate in vivo depends on the ratio of polyunsaturated to monounsaturated fatty acids in the diet [146], with dietary stearic acid having a similar but not equally strong effect as dietary linoleic acid because of partial conversion to oleic acid following intestinal absorption [147]. For given dietary intake levels of the different fatty acids, the rate of formation of aldehydes that are formed as secondary products of lipid peroxidation depends strongly on the capacity of cellular enzymes that scavenge H_2O_2, peroxynitrite, and organic hydroperoxides, such as Se-dependent glutathione peroxidases, 2-Cys peroxiredoxins and 1-Cys peroxiredoxin [79,148,149].

Selenoenzymes can resist permanent inactivation by oxidation since the Se oxides can be rapidly reduced back to the selenol due to the lability of the Se–O bond. A recent work of Ste Marie et al. reported that selenoenzymes can resist also permanent inactivation by alkylation. Acrolein-inactivated Sec-TrxR and the (αMe)Sec-TrxR mutant could regain 25% and 30% activity, respectively, when incubated with 2 mM H_2O_2 and 5 mM imidazole. The Sec residue undergoes rapid elimination of β-syn selenoxide, that discharges the electrophile, leaving the enzyme in the oxidized selenosulfide state restoring its enzymatic activity [150].

It should be noted that the rate of scavenging of oxidizing substrates by glutathione peroxidases for a given oxidizing substrate (e.g., H_2O_2) concentration is linearly proportional to the concentration of active enzyme, which depends on the intake of Se, but proportional to the square of the GSH concentration. The latter depends on the dietary intake of GSH precursor amino acids, especially cysteine and methionine, but can also be reduced because of protein catabolic diseases, including infectious diseases, many cancers, and alcoholism. The aldehydes concerned can all react with DNA and are therefore mutagenic, which is an important reason to avoid overconsumption of polyunsaturated fatty acids [151]. Official recommendations in the United States and Western Europe for the dietary intake of polyunsaturated fatty acids for many years may have been set far too high because only the effects of fatty acids on concentrations of blood plasma lipoproteins were taken into consideration and not the mutagenic effect of products of in vivo lipid peroxidation.

Methylglyoxal is formed as a byproduct of glycolysis and is scavenged by the consecutive action of two enzymes, glyoxalase-1 and glyoxalase-2, using GSH as a catalytic cofactor so that GSH is consumed in the glyoxalase-1 reaction and regenerated in the glyoxalase-2 reaction [142].

Methylglyoxal can affect the GR and Trx/TrxR reducing system impairing peroxide removal by glutathione peroxidase and peroxiredoxin, as both peroxidases depend on reduced GSH and Trx, respectively [152]. Methylglyoxal can accumulate during physiological aging and at an accelerated rate in diabetes and other chronic degenerative diseases [153]. The scavenging efficacy of the glyoxalase system depends on the cellular concentration of GSH and is impaired when the intracellular GSH concentration is low [154]. It has recently been reported that an aging-dependent reduction in glyoxalase-1 delays wound healing [153]. The expression of glyoxalase-1 is, similarly to the expression of TrxR, enhanced by Nrf2, which a stress-responsive defense against dicarbonyl glycation [155].

4-Hydroxynonenal can, however, also induce TrxR [156]. It has been reported that the expression of both TrxR and Trx is upregulated by the Nrf2-antioxidant responsive element pathway [157], and this signal pathway is activated by 4-hydroxynonenal [158]. For inhibition of TrxR by 4-hydroxynonenal, an inhibitory constant $IC_{50} = 1 \pm 0.2$ μM has been reported [100].

TrxR is also inhibited by another product of 15-lipoxygenase-catalyzed lipid peroxidation, viz. the metastable hydroperoxide 15(S)-hydroperoxy-5,8,11-*cis*-13-*trans*-eicosatetraenoic acid, albeit more weakly than by 4-hydroxynonenal with $IC_{50} = 13 \pm 1.5$ μM [100]. Furthermore, it is inhibited by electrophilic, cyclopentenone prostaglandins of the A and J series, which cause repression of redox-sensitive transcription factors p53 and hypoxia-inducible factors [159]. However, it has also been reported that TrxR is required for the inactivation of the tumor suppressor protein p53 and for apoptosis induced by endogenous electrophiles [160]; so it has apparently double-sided and opposite effects in relation to p53, being necessary both for normal activity and for inactivation.

Electrophilic prostaglandins covalently modify and inhibit TrxR [159]. The total rate of prostaglandin biosynthesis in tissue depends strongly (other factors being equal) on the ratio of *omega*-6 to *omega*-3 fatty acids, because the cyclooxygenases COX-1 and COX-2 oxidize the *omega*-6 polyunsaturated fatty acid arachidonic acid (AA) to prostaglandin H_2 (PGH_2) (which is converted to other prostaglandins by other enzymes in subsequent reactions), much faster than the *omega*-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) is converted to prostaglandin H_3 (PGH_3) [161]. The long-chain *omega*-3 fatty acid docosahexaenoic acid (DHA) is a competitive inhibitor both of AA conversion to PGH_2 and of EPA conversion to PGH_3. However, the rate of prostaglandin biosynthesis is also redox-regulated in a complicated way, with the consequence that poor Se status or intracellular GSH depletion also will enhance the total rate of prostaglandin biosynthesis, especially under disease conditions where the expression of COX-2 is enhanced. At the same time as a high dietary *omega*-6/*omega*-3 PUFA ratio, poor Se status, and poor GSH status also will change the balance between antithrombotic prostacyclin (PGI_2 and PGI_3) and prothrombotic thromboxanes (TxA_2 and TxA_3) in prothrombotic direction, causing an enhancement of the risk of thrombosis [162,163].

Moreover, TrxR has been reported to be inhibited by the porphyrins protoporphyrin IX, which is a heme precursor molecule, with a $K_i = 2.7$ μM with regard to Trx1, hemin, rottlerin, and the ferrochelatase

inhibitor NMPP [8]. Protoporphyrin IX in the absence of Trx1 displayed time-dependent irreversible inhibition with an apparent second-order rate constant (k_{inact}) of (0.73 ± 0.07) × 10^{-3} μM^{-1} min^{-1} [8]. This negative regulation of TrxR expression by porphyrins may be important in patients suffering from porphyria, especially in the form of porphyria cutanea tarda, a skin disease with very characteristic symptoms in the form of a combination of skin areas with hyperpigmentation and other skin areas with hypopigmentation [164].

TrxR has also been found to be inhibited by 2,4-dinitrochlorobenzene (DNCB) [165]. Furthermore, it has been reported that TrxR is a caveolar membrane resident protein and that caveolin-1, the structural protein component of caveolae, is a TrxR-1-binding protein [166]. Overexpression of caveolin-1 inhibits TrxR activity, whereas the lack activates TrxR, both in vitro and in vivo [166]. This might be relevant in connection with the pathogenesis of atheromatosis since transcytosis, where LDL is transported with caveolin through the endothelial cells, is an important mechanism of LDL transport during the endothelium from the blood plasma into the arterial wall [167,168].

TrxR is induced by Se (selenium-methylselenocysteine and sodium selenite) [31] and isothiocyanates, such as sulforaphane, erucin, and iberin [31,169]. This effect of isothiocyanates on TrxR expression may probably be explained as a consequence of their effect as activators of the transcription factor Nrf2 [170], which is a positive regulator of TrxR [109,112–114,157] and Trx [157,171,172] expression. Nrf2 is also activated by curcumin [173] and resveratrol [174]. However, the organoselenium compound ethaselen (currently in a phase I clinical trial) has been proved to inhibit cancer metastasis with a mechanisms based to the markedly elevated ROS level followed by TrxR inhibition [175]. Several Michael acceptors compounds have been designed to be able to inhibit TrxR by covalent interaction with the catalytic selenocysteine residue in the enzyme's active site (see for instance [5]). Trx can also be inactivated by nitration caused by peroxynitrite [104,105,176], which is formed in a reaction between superoxide anion radical and NO [177].

With peroxynitrite inhibition of Trx, there may be a vicious circle since 2-Cys peroxiredoxins, which use Trx as one of their reducing substrates [74,75], are important scavengers of peroxynitrite [76]. However, this scavenging will be impaired when Trx is inactivated by direct reaction with peroxynitrite instead of peroxynitrite being scavenged by the enzymes.

6. TrxR protein interactors

TrxR may regulate signaling and metabolic pathways though its interaction with proteins, receptors and enzymes respectively. From this perspective, all the interactors of TrxR1, TrxR2 and TrxR3 deposited in the publicly available bioGRID protein-protein interaction (PPI) database (https://thebiogrid.org) [178] and reported in the literature were mined and presented in the Table 2. Interestingly, according to the recent reported human heavy metal proteome [179], 25% of the interactors of TrxR1 are putative toxic heavy metal-binding proteins. In general, the substitution of essential metals such as (Zn^{+2}) by non-essential heavy metals (such as Cd^{+2}, Pb^{+2} and Hg^{+2}) in the binding motifs of proteins cause destabilization of their fold and deregulations of their biological processes [180–182]. Thus, toxic heavy metals could potentially inhibit TrxR1 involvement in various biological processes such as Estrogen Signaling, p53 and Apurinic/apyrimidinic endonuclease stability and activity [183,184]. Specifically, TrxR1 interacts with the estrogen alpha and beta and the thyroid alpha receptors and p53 tumor suppressor which both contain zinc-finger motif [183,184]. This cysteine-rich motif interacts with zinc ions as part of the native protein function and is a potential target for perturbation by heavy metals. In the same way, heavy metal binding to DNA-(apurinic or apyrimidinic site) lyase (APEX1), is likely to inhibit it's interaction with TrxR1 [185,186]. This protein-protein interaction interfere with the cellular response to oxidative stress and it's inhibition is likely to produce undesirable outcomes to the native activities of APEX1 which are DNA repair and redox regulation of transcriptional factors [185,186].

Table 2
Interactors of TrxR1, 2, and 3 mined from the literature and BioGRID database (https://thebiogrid.org/).

	Thioredoxin reductase 1		Thioredoxin reductase 2		Thioredoxin reductase 3	
Interactors	IDs	Protein name	IDs	Protein name	IDs	Protein name
	Q8IXT2	Doublesex- and mab-3-related transcription factor C2	O75528	Transcriptional adapter 3	Q9H3K6	BolA-like protein 2
	Q9UII4	E3 ISG15--protein ligase HERC5, EC 2.3.2	O75934	Pre-mRNA-splicing factor SPF27	Q9UI47	Catenin alpha-3
	P09086	POU domain, class 2, transcription factor 2	Q14686	Nuclear receptor coactivator 6	Q9Y3E2	BolA-like protein 1
	P14859	POU domain, class 2, transcription factor 1	O75376	Nuclear receptor corepressor 1	O95721	Synaptosomal-associated protein 29, SNAP-29
	P10827	Thyroid hormone receptor alpha	P17980	26S proteasome regulatory subunit 6A	Q8N2N9	Ankyrin repeat domain-containing protein 36B
	P60896	26S proteasome complex subunit SEM1	Q15596	Nuclear receptor coactivator 2	Q14192	Four and a half LIM domains protein 2, FHL-2
	Q9H3M7	Vitamin D3 up-regulated protein 1	P32780	General transcription factor IIH subunit 1	Q8N7B6	PACRG-like protein
	Q6ZVN7	SEM1 26S proteasome complex subunit			Q96KK5	Histone H2A type 1-H
	P05161	Ubiquitin-like protein ISG15			Q9BW66	Cyclin-dependent kinase 2-interacting protein, CDK2-interacting protein
	Q9BRA2	Thioredoxin domain containing 17				
	Q9NS18	Glutaredoxin 2				
	Q03135	Caveolin-1				
	Q96I34	Protein phosphatase 1 regulatory subunit 16A				
With heavy metal-binding motifs	P03372	Estrogen receptor, ER (ER-alpha)				
	Q92731	Estrogen receptor beta, ER-beta				
	P04637	Cellular tumor antigen p53				
	P27695	DNA-(apurinic or apyrimidinic site) endonuclease				

7. Association of thioredoxin reductase 1, 2, and 3 genes with human diseases

There are many reported associations between the TrxR genes and their variants with human diseases in GWAS (Genome-Wide Association Studies) catalogs and literature. TrxR1 (TXNRD1) gene is associated with nervous system diseases, including epilepsy [187], aura [188], cryptogenic and awakening epilepsy [187]), neoplasms (adenoma [189], mesothelioma [190], pancreatic cancer [191], trabecular, papillary, monomorphic, microcystic, basal cell and follicular thyroid adenomas [189]), skin and connective tissue diseases (contact dermatitis and contact hypersensitivity [192]) and musculoskeletal diseases (osteoarthritis deformans and degenerative polyarthritis [193]). TrxR2 (TXNRD2) gene is associated with cardiovascular diseases (dilated cardiomyopathy, cardiac conduction disorder [194]), eye diseases (primary open-angle [195] and angle-closure glaucoma [196]), male urogenital diseases (malignant neoplasm of the prostate [197]), depressive symptoms [198], and x-linked adrenal hypoplasia [199]. TrxR3 (TXNRD3) gene is associated with cardiovascular diseases (hypertensive disease [200], myocardial infarction, and diabetic cardiomyopathies [201]) and Parkinson's disease [202]. Although there are only clinical trials related to thioredoxin can be found (NCT01985113, NCT01980212, NCT02166242 and NCT00736372) up-to-date, lots of research works have shown that TrxR is a promising drug target, e.g. leukemia, rheumatoid arthritis and melanoma [203,204]. Chemoresistance and high incidence of relapse in acute myeloid leukemia patients are associated with Trx system overexpression [117]. Nrf2 is involved in tumor drug resistance, and it has been found that the knockdown of Nrf2 in K562/G01 cells, positively correlated with TrxR expression, which enhanced the intracellular ROS level, suppressed cell proliferation, and increased apoptosis in response to imatinib treatments [205]. Further, the MAPK/ERK and PI3K/AKT signaling pathways have been implicated in the pathogenesis of leukemia, which affect Nrf2-TrxR axis [206]. In addition, as the CML specific oncoprotein, bcr-abl could be down-regulated by TrxR inhibition [207]. All the above results highlighted the therapeutic potential of targeting the TrxR to improve treatment outcomes.

The oxidative aggression generates modifications in the redox status of the rheumatoid arthritis [208]. Decreased TrxR expression contributes to the disease activity [209], which could explain the causes of oxidative stress related to rheumatoid arthritis disease. Thus, TrxR levels may therefore serve as a new biomarker in addition of the traditional biomarkers of assessing the risk and severity of rheumatoid arthritis [210].

It has been found that TrxR is highly expressed in cultured normal skin melanocytes and malignant melanoma cell lines, which is correlated to resistance against cytotoxic attack, indicating that TrxR is as component of its protective mechanisms [211]. Thus, ROS-boosted therapy could be designed to weaken the hypoxic tumor environment based on the targeted inhibition of the activity of antioxidant defense enzymes, including TrxR [212].

8. Conclusion

The present review aims to carry out a critical reappraisal of the literature on the rationale of targeting TrxR for pharmaceutical purposes. TrxR is necessary to all biochemical pathways in which Trx is involved as a reducing substrate; those have been suggested to play roles in such diverse physiological and pathological conditions. There are two redox sites of TrxR: the first is constituted by the FAD and a couple of Cys residues that receives electrons from NADPH, and the second in the C-terminal of the enzyme, which is constituted by a Sec-Cys couple that transfers the electrons from the FAD/Cys redox site to bound Trx. Since the reduction of the physiological substrate Trx requires the full functionality of both the redox sites, there are multiple sites where inhibitors of TrxR may bind. This structural and catalytic feature of TrxR, combined with its dysregulation in various pathological processes, makes its inhibition of great relevant to pharmacology. Designing and testing of double action pharmacophore inhibitors combination targeting these active sites is a big challenge to pursue.

Currently, several drugs deposited in the DrugBank [213] target TrxR: e.g., motexafin gadolinium (chemotherapeutic agent in the treatment of brain metastases), fotemustine (treatment of metastatic melanoma), trisenox (treatment of acute promyelocytic leukemia), sodium aurothiomalate and auranofin (used in rheumatoid arthritis), and antimony potassium tartrate (treatment of schistosomiasis and leishmaniasis). However, finding the specific inhibitors of TrxR over other related enzymes remains a high challenge and appears a bottleneck for further development of them as clinical agents.

Author contributions

All authors confirmed they have contributed to the intellectual content of this paper and have met the following three requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

CRediT authorship contribution statement

Geir Bjørklund: Conceptualization, Writing – original draft, Data curation, Visualization, Investigation, Writing – review & editing, Supervision, Project administration. **Lili Zou:** Data curation, Visualization, Investigation, Writing – review & editing. **Jun Wang:** Data curation, Visualization, Investigation, Writing – review & editing. **Christos T. Chasapis:** Data curation, Visualization, Investigation, Writing – review & editing. **Massimiliano Peana:** Conceptualization, Writing – original draft, Data curation, Visualization, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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