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Comprehensive Invited Review

Thioredoxin and Related Molecules–From Biology to Health and Disease

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ABSTRACT

Thioredoxin and glutaredoxin systems in mammalian cells utilize thiol and selenol groups to maintain a reducing intracellular redox state acting as antioxidants and reducing agents in redox signaling with oxidizing reactive oxygen species. During the last decade, the functional roles of thioredoxin in particular have continued to expand, also including novel functions such as a secreted growth factor or a chemokine for immune cells. The role of thioredoxin and glutaredoxin in antioxidant defense and the role of thioredoxin in controlling recruitment of inflammatory cells offer potential use in clinical therapy. The fundamental differences between bacterial and mammalian thioredoxin reductases offer new principles for treatment of infections. Clinical drugs already in use target the active site selenol in thioredoxin reductases, inducing cell death in tumor cells. Thioredoxin and binding proteins (ASK1 and TBP2) appear to control apoptosis or metabolic states such as carbohydrate and lipid metabolism related to diseases such as diabetes and atherosclerosis. *Antioxid. Redox Signal.* 9, 25–47.

I. INTRODUCTION

RESEARCH ON THIOREDOXIN has a four decade history, naturally reflecting the development of methods and knowledge in biochemistry, genetics, and molecular, cellular, and structural biology. If the main emphasis during the first two decades of thioredoxin research was on the structure and mechanism of bacterial thioredoxins, as reflected in previous reviews (77, 85), the discovery of the regulatory functions of mammalian thioredoxins had only just begun. In the review from 1981 (77), thiol redox control was introduced particularly with respect to chloroplast and plant photosynthetic regulation pioneered by Buchanan and co-workers (77). In the 1985 review, a concluding remark was: *it seems likely that evolution of complex organisms has included potentially useful aspects of the structure and function of thioredoxin, in particular for regulating integrated parts of metabolism and cellular differentiation* (85).

So what has happened in the past two decades? Obviously, DNA sequencing, cloning, knock-out technologies, RNA interference, site-directed mutagenesis, selenium molecular biology, two-dimensional NMR, and the discovery of hydrogen peroxide signaling have had a great impact. Major developments in research on thioredoxin and related molecules have taken place in all fields, but in particular for mammalian systems. It therefore seems adequate to write a review with the somewhat futuristic title of Thioredoxin and Regulated Molecules–From Biology to Health and Disease, a subject also covered by others (59).

Thioredoxin (Trx) was discovered by Peter Reichard and co-workers, when this small dithiol protein was isolated in pure form as the hydrogen donor for ribonucleotide reductase from *Escherichia coli* (114, 154). The characteristic dithiol active site motif of Trx, Cys-Gly-Pro-Cys, was revealed when the protein was sequenced in the late 1960's (76) and is now know to be conserved throughout all kingdoms of life. During the following years, it became obvious that Trxs were more than cofactors for the reduction of ribonucleotides and sulfate, when *E. coli* Trx and human platelet Trx were shown to be general disulfide reductases by using, for instance, fibrinogen (26), choriogonadotropin (86), or insulin (84) as substrates. The first redox-independent function of Trx was discovered in the mid-1970s, when *E. coli* Trx was shown to be a subunit of phage T7 DNA polymerase (87, 133, 171).

Today we look at Trx as a crucial protein for antioxidative defense, the modulation of intra- and extracellular signaling pathways, the regulation of transcription factors, and the modulation of immune response (Fig. 1) (7, 163, 182, 190) Despite the large body of research published until today, the thioredoxin field is still strongly developing, and new functions of Trxs are described almost on a weekly basis. At the time of writing, PubMed (http://www.pubmed.gov) lists 4148 entries for thioredoxin, from which about half (2047) date back to the last 5 years. In this review, we focus on human/mammalian Trxs and related molecules in health and disease, referring back to the fundamental work done on bacterial and fungal Trxs when appropriate. We will try to outline unre-

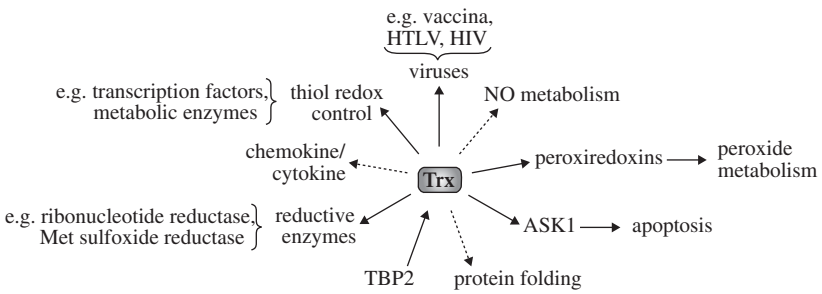

FIG. 1. Functions of human thioredoxin. Details are discussed throughout this review. Direct targets of Trx are indicated using *solid arrows*, less well-defined functions are indicated using *dashed arrows*.

solved questions and predict where we think research will result in clinical applications.

A. The thioredoxin family of proteins

The members of the thioredoxin super family of proteins are characterized by a common structural motif know as the thioredoxin fold. This structural motif is common to a variety of proteins from different classes, both oxidoreductases such as Trxs, glutaredoxins (Grxs), or protein disulfide isomerases, but also functionally different proteins, such as glutathione transferases, glutathione peroxidases, or the recently characterized chloride intracellular channels (CLIC) (10, 134). The Trx fold motif consists of a four-stranded sheet and three surrounding helices (Fig. 2). This basic architecture is adopted by bacterial Grxs (Fig. 2A), while it represents only a substructure or domain in the other members of the family (5, 42, 134). The first high resolution three-dimensional structure of a Trx was obtained in 1975 by X-ray crystallography (88). Trx has, in addition to the basic thioredoxin fold, an extra β-sheet and α-helix at the N terminus (Fig. 2B). Today, approximately 200 different structures of Trxs are available in the protein data bank (http://www.pdb.org), including high resolution structures of both oxidized and reduced species of Trxs, for instance, from *E. coli* Trx1 (94) and human Trx1 (191). In general, the structures of reduced and oxidized Trxs are very similar, but it was recognized as early as 1967 from an increased Trp fluorescence emission that the protein does undergo some conformational changes upon reduction (83, 227). These subtle and local changes involving hydrogen bonds in the active site can have a dramatic effect on the binding activity of Trx to other proteins, which is of physiological importance, as discussed in detail below.

Members of the Trx family catalyze the reversible reduction of disulfides utilizing the cysteinyl residues in the Cys–X–X–Cys active site. The N-terminal Cys residue in the active site of a Trx is a surface exposed and has a low pKa value, being 2 or more pH units below the pKa of free Cys, while the more C-terminal Cys is buried in the molecule and has a much higher pKa value (83, 104). Two modes of catalysis have evolved (82, 104). The dithiol mechanism (Fig. 3), that is catalyzed by both Trxs and Grxs, requires both active site thiol groups. Trxs bind initially noncovalently to a target protein disulfide via a hydrophobic surface area surrounding the active site. Next, the N-terminal cysteine thiolate acts as a nucleophile and attack the target disulfide to form a covalent mixed disulfide intermediate, which in turn is reduced by the C-terminal active site thiolate. This generates a disulfide in the active site of Trx and a dithiol in the target protein. The oxidized active site in Trx is reduced by TrxR (Fig. 4) using electrons from NADPH. The corresponding disulfide in a dithiol Grx is reduced by two molecules of GSH, yielding GSSG, which in turn is reduced by glutathione reductase at the expense of NADPH.

The monothiol mechanism, originally proposed in 1978 for T4 Grx (82), requires only the N-terminal cysteinyl residue of the active site and is unique to Grxs. Grxs can reduce protein–GSH mixed disulfides by formation of an intermediate consisting of a mixed disulfide between Grx and GSH, that is subsequently reduced by a second molecule of GSH (29, 56,

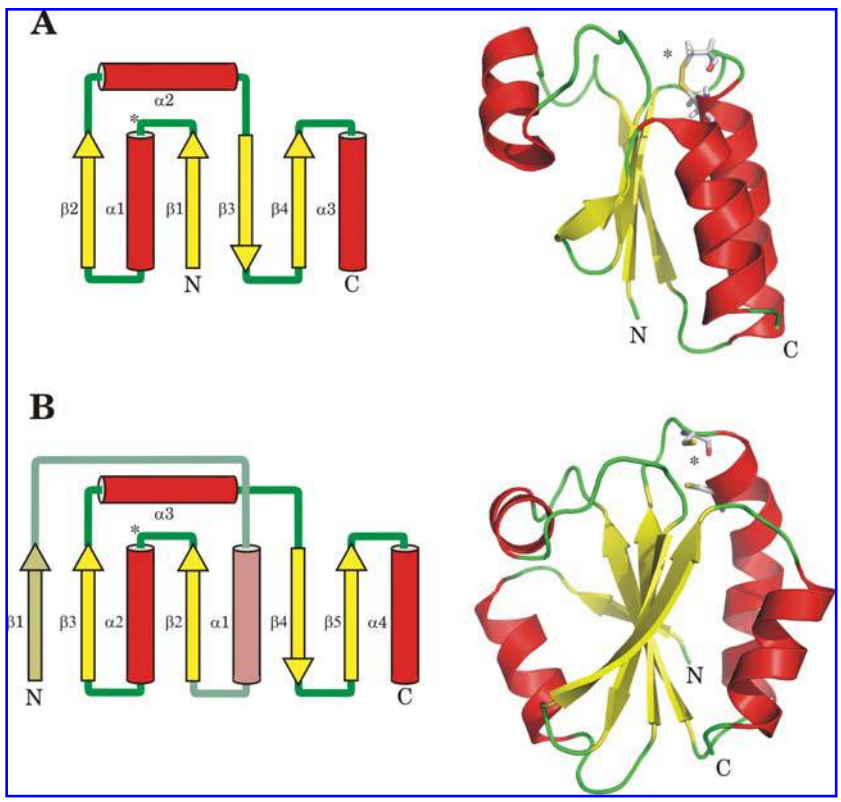

FIG. 2. The thioredoxin fold. (**A**) The basic thioredoxin fold consists of a four stranded β-sheet and three surrounding α-helices (*see* Topology), which is adopted only by bacterial Grxs. The structure of oxidized *E. coli* Grx1 is shown (PDB code: 1EGO). (**B**) Trxs possess an additional α-helix and β-sheet at the N-terminus (*see* Topology). The structure of reduced human Trx1 is shown (PDB code: 1ERT). The positions of the characteristic Cys–X–X–Cys active site motifs are marked by *asterisks*.

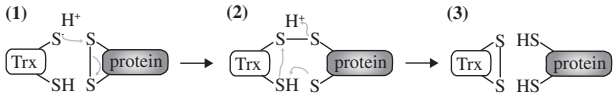

FIG. 3. Reaction mechanism of disulfide reduction by thioredoxin. The N-terminal cysteine thiolate of Trx (or Grx) acts as a nucleophile and attacks the target disulfide (1), resulting in a mixed disulfide intermediate (2), which is in turn reduced by the C-terminal active site residue (3). The resulting disulfide in the active site of Trx can be reduced by TrxR with electrons from NADPH completing the catalytic cycle (not depicted).

131, 224, 271). All this is due to a GSH binding site in Grxs that is not present in Trxs.

B. Mammalian thioredoxin systems

The first mammalian Trx and Trx systems were isolated from rat tumor (71, 153) and calf liver or thymus (43, 81), respectively, using ribonucleotide reductase (RNR). Mammalian cells contain two distinct Trxs (Fig. 5) Trx1 (gene: TXN1) is mainly a cytosolic protein. However, under certain stimuli, Trx1 can be translocated to the nucleus or exported from the cell (137, 202). Trx2 (TXN2) is targeted to mitochondria (223).

Three mammalian TrxR isoenzymes have been described: cytosolic TrxR1 (TXNRD1) (50, 81), mitochondrial TrxR2 (TXNRD2) (117, 144), and the testis-specific thioredoxin glutathione reductase (TGR) (230). Unlike their small bacterial, fungal, and plant counterparts, the mammalian enzymes are large selenoproteins. These homodimeric flavoenzymes contain a penultimate C-terminal selecocysteine in their –Gly–Cys–SeCys–Gly active sites (54, 238, 280). The high reactivity of the active site selenolate and an open accessible active site are the reasons for the wide substrate specificity of mammalian TrxR compared to their bacterial counterparts (279). The list of substrates includes Trxs from other species, Ellmans' reagent (DTNB) (81), and nondisulfide compounds such as selenite (112), lipid peroxide (24), *S*-nitrosoglutathione (167), or the antioxidant drug ebselen (278).

The TXN1 gene is localized on chromosome 3 p11-p12 and organized into five exons separated by four introns. Two overlapping promoters contain many possible regulatory elements, including elements for both a basal constitutive (*e.g.,* by transcription factor SP1), and a regulated inducible transcription (103, 177). Among the elements responsible for inducible transcription, the oxidative stress and antioxidant responsive elements (ARE) are of particular interest, because they are responsible for the induction of Trx1 expression upon oxidative stress (137, 239). Alternative transcript variants have been reported for human and mouse TrxR1 (176, 203, 228), mouse TrxR2 (143), and human Trx1 (19, 66, 96). Alternative splicing of human Trx1 does not lead to the expression of functionally different proteins; however, the alternative mRNA variants could be of some regulatory function (19, 96).

Compared to their bacterial counterparts, mammalian cytosolic Trxs contain additional cysteinyl residues outside their active site, and it was recognized early on that these residues make the proteins susceptible to oxidation, leading to aggregation and inactivation of the proteins (43, 81). Human Trx1 contains three structural Cys residues outside its active site: Cys62, Cys69, and Cys 73 (Fig. 6), that have all been suggested to be important for regulating the activity of Trx1. First, a second intramolecular disulfide, formed between Cys62 and Cys69 under oxidizing conditions, has been identified by mass spectrometry. This disulfide was not a substrate for TrxR and strongly decreased the rate of the reduction of the active site disulfide by TrxR (81). Second, a study by Haendeler *et al.* reported the *S*-nitrosylation of Cys69 under basal conditions, and that this modification was required for scavenging reactive oxygen species (ROS) and for preserving the redox regulatory activity of Trx by means of enzymatic activation (60). Whereas the identification of *S*-nitrosylated Trx1 in this study was technically sound, the enzymatic activation of human Trx1 by nitrosylation has to be taken with caution, because it was determined in an assay containing *E. coli* TrxR, which cannot serve as electron donor for human Trx1 (8, 43, 81). Third, Cys 73, which is close to the active site in the three-dimensional structure of the protein (Fig. 6), was reported to undergo both reversible *S*-nitrosylation, *S*-glutathionylation, or disulfide formation. The *S*-nitrosylation of Cys 73 was demonstrated by mass spectrometry, immunological methods, and site-directed mutagenesis. Trx was able to catalyze the targeted and reversible transnitrosylation of the NO group location at Cys73 to the active site cysteine in caspase 3, thereby regulating the activity of this cysteine protease (148). The *S*-glutathionylation of Cys 73 was identified *in vitro* by mass spectrometry and *in vivo* following treatment of

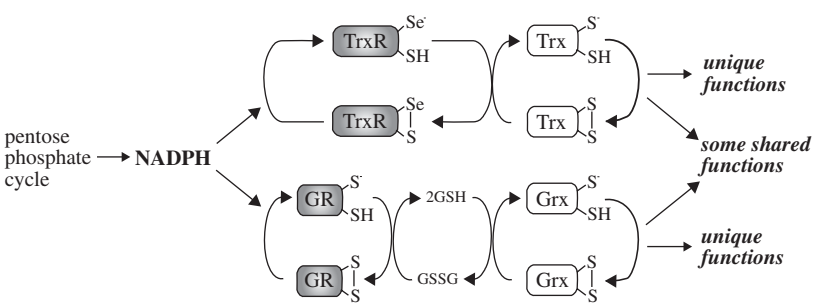

FIG. 4. Electron flow from NADPH via the thioredoxin and glutaredoxin systems to target proteins. Thioredoxin (Trx) reduces mainly protein disulfides using electrons from NADPH via thioredoxin reductase (TrxR). Glutaredoxin (Grx) can reduce both protein disulfides and mixed disulfides between proteins and glutathione (protein–S–SG). Oxidized Grx is reduced by glutathione (GSH) yielding glutathione disulfide (GSSG), which is subsequently reduced by glutathione reductase (GR) using electrons from NADPH. Trxs and Grxs share some common responsibilities, but have unique functions as well.

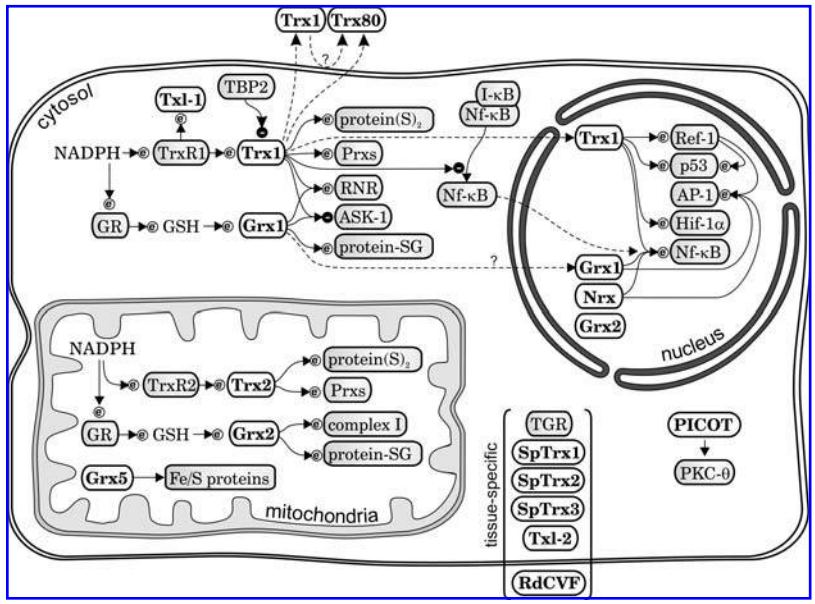

FIG. 5. Overview of the thioredoxin and glutaredoxin systems and some of their targets in and outside the cell. Details are discussed throughout this review. *Solid arrows* indicate direct interactions between the proteins, a *circled* (e^-) indicates the transfer of electrons and a *black circled* (-) indicates an inhibition. *Dashed arrows* indicate the translocation or the conversion of a protein; a *question mark* indicates a speculative pathway.

cells with the strong oxidant diamide. Glutathionylation abolished the enzymatic activity of Trx1, but activity was regained in a process of auto-activation with sigmoidal kinetics (31). An intermolecular disulfide between the Cys73 residues of two trx1 molecules was found in the cystal structure of both pre-reduced and pre-oxidized human Trx1; however, a physiological role of dimerization remains unknown (255).

C. Mammalian glutaredoxins

Grxs and Trxs can compensate for each others functions to a large extent, but at the same time, both systems have their own unique functions (46). Grxs were first discovered as an alternative electron donor for RNR in *E. coli* (79, 80), but have since been shown to catalyze an abundance of reactions *in vitro* and *in vivo* (46, 78). Mammalian cells contain three Grxs (Fig. 5). The classical dithiol Grxs cytosolic Grx1 and mitochondrial Grx2, and a monothiol Grx named Grx5 because of its homology to yeast Grx5, which may also be targeted to mitochondria (151, 260).

Grx1 supports RNR with electrons, is involved in general disulfide–dithiol exchanges (78), dehydroascorbate reduction (2560, cellular differentiation (237), regulation of transcription factors (14, 73, 165), and apoptosis (33, 38). Grx1 is upregulated in pancreatic cancer cells (157) and increased expression is related to doxorubicin/adriamycin resistance in MCF-breast tumor cells (142). Grx2 is a very efficient catalyst of protein deglutathionylation, showing an efficiency (kcal/km) that is about 1.5- to 3-fold higher compared to Grx1. Its oxidized active site, which in all other eukaryotic Grxs is exclusively reduced by GSH, is also a substrate for the seleno-enzyme thioredoxin reductase (TrxR) (98). Thus, Grx2 combines both

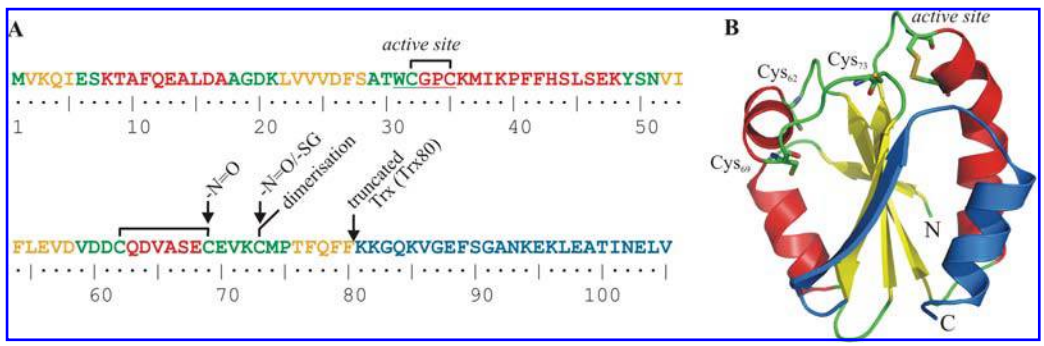

FIG. 6. Regulation and modifications of human thioredoxin 1. The primary structure in (**A**) is colored according to the secondary structure elements shown in (**B**). Intramolecular disulfides have been reported in the active site and between the structural cysteinyl residues Cys62 and Cys69. An intermolecular disulfide between the Cys73 residues of two molecules of thioredoxin that leads to dimerization of the protein has been reported. *S*-nitrosylation has been reported for both Cys69 and Cys73, *S*-glutathionylation for Cys73. In addition, human thioredoxin 1 can be processed *in vivo* yielding truncated thioredoxin (Trx80). The parts missing in Trx80 are shown in *blue* in both the primary and three-dimensional structure.

the characteristics of a Trx and a Grx. Grx2 protects HeLa cells from oxidative stress-induced apoptosis, silenced expressions dramatically sensitized the cells to cell death induced by doxorubicin and phenylarsine oxide (122), overexpression decreases the susceptibility to apoptosis induced by doxorubicin or the antimetabolite 2-deoxy-D-glucose (44). Grx2 has also been characterized as the first member of the Trx family that is also an iron–sulfur protein (121). This unusual Grx can bind a (2Fe–2S) cluster that bridges two molecules of Grx2. Dimeric holo Grx2 is enzymatically inactive, but cluster degradation and monomerization of Grx2 activates the oxidoreductase. The cluster is stabilized by GSH, but destroyed by GSSG and ROS. It has therefore been proposed that the cluster serves as a redox sensor for the activation of Grx2 during conditions of oxidative stress (121). Grx5, which contains only one cysteinyl residue in its active site, was first discovered in yeast (196). Knock-out led to constitutive oxidative damage, iron accumulation in the cell, and inactivation of iron–sulfur-containing enzymes. Thus, a function of yGrx5 in iron–sulfur cluster synthesis was suggested (197). Depletion of Grx5 increased the amount of iron bound to the iron–sulfur cluster scaffold Isu1, indicating that the protein might be required in a step following (Fe–S) cluster synthesis on Isu1 when the (Fe–S) clusters are inserted into apo proteins (155). Recent studies indicate that this function might be conserved in higher eukaryotes as well (151, 260).

D. Mammalian proteins containing thioredoxin homology domains

Apart from the Trx and Grx system proteins mentioned above, mammalian cells contain a series of additional, often tissue- and/or organelle-specific members of the thioredoxin family of proteins (summarized in Table 1, Figs. 5 and 7). These include the spermatocyte/spermatid-specific thioredoxins SpTrx1, SpTrx2, and SpTrx3, as well as the microtubule-specific thioredoxin-like 2 (Txl2) (147). SpTrx1 contains a C-terminal Trx domain as part of a 53 kDa protein. SpTrx1 is composed of an N-terminal Trx domain and three consecutive nucleoside diphosphate kinase domains (NDPk). SpTrx3 is a single Trx-like protein; Txl2 is composed of an N-terminal Trx domain and a single C-terminal NDPk domain.

Despite the fact that all these proteins contain the Trx-specific CGPC active site, none exhibits any oxidoreductase activity (97, 145–147, 206, 207). In contrast, Trx-like 1 (Txl-1), which contains an N-terminal Trx domain with a CGPC active site, is an active disulfide reductase and a substrate for TrxR (115). Nucleoredoxin (Nrx) contains a central thioredoxin domain with the active site CPPC, is active in the reduction of insulin, and may be involved in the redox regulation of transcription factors (73, 113) (Fig. 5). In addition, Nrx was shown to selectively suppress Wnt-catenin signaling through oxidation-sensitive association with disheveled (Dvl) (48).

PICOT (protein kinase C interacting cousin of thioredoxin) was identified in a two-hybrid screening as an interaction partner of protein kinase C-, which is thought to play an important role in T lymphocyte activation. PICOT is composed of an N-terminal Trx domain, which is required for the interaction with protein kinase C, but lacks both active site cysteines. In addition, PICOT contains two C-terminal monothiol Grx domains that both contain a CGFS active site. Overexpression of PICOT in T cells inhibited the activation

TABLE 1. THIOREDOXINS AND RELATED MOLECULES IN HUMAN

	Size (kDa)	*Active site*	*Redox active*	*Tissue*	*Localization*	*Alternative splicing reported*	*References*
					Redoxins		
Trx1	12	CGPC	Yes	Ubiquitous	Cytosol, nucleus upon certain stimuli	Yes	66, 19, 96
Trx-80	9	CGPC	No	Plasma	Extracellular	–	182
Trx2	12*	CGPC	Yes	Ubiquitous	Mitochondria	No	223
Grx1	12	CPYC	Yes	Ubiquitous	Cytosol	Yes	178
Grx2	14*	CSYC	Yes	Ubiquitous	Mitochondria & nucleus	Yes	130, 55
Grx5	17	CGFS	No†	Ubiquitous	Mitochondria, cytosol (?)	No	260
PICOT	37	2 x CGFS	N.D.	Ubiquitous	Cytosol	No	262
SpTrx1	53	CGPC	No	Testis/sperm	Fibrous sheet	No	146
SpTrx2	67	CGPC	No	Testis/sperm	Fibrous sheet	No	206
SpTrx3	15	CGPC	No	Testis/sperm	Golgi-associated	Yes	97
Txl-1	32	CGPC	Yes	Ubiquitous	Cytosol	No	115
Txl-2	37	CGPC	No	Testis/sperm	Microtubuli	Yes	207, 145
RdCVF	13	CPQC	No	Photoreceptors	Extracellular	Yes	119
Nrx	48	CPPC	Yes	N.d.	Nucleus	No	113
					Thioredoxin reductases		
TrxR1	55	CU	Yes	Ubiquitous	Cytosol	Yes	176, 203, 228
TrxR2	53	CU	Yes	Ubiquitous	Mitochondria	Yes	143
TGR	64	CPHS/CU	Yes	Mainly testis	Cytosol	No	230

Proteins of the thioredoxin/protein disulfide isomerase family in the endoplasmatic reticulum have been excluded, for an overview see (17, 47, 111).

*Processed; †no significant activity in the classical Grx assays has been detected for the homologues from *E. coli* and yeast.

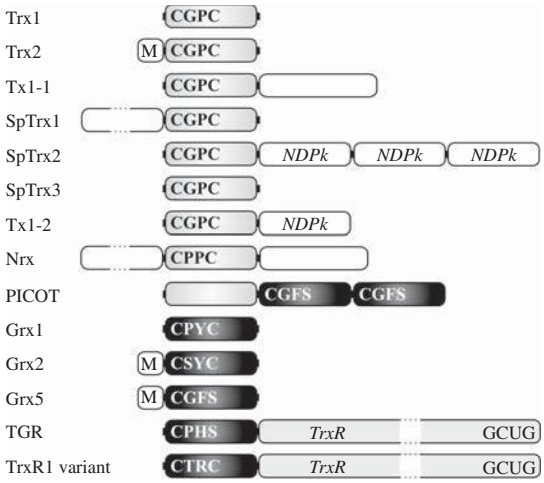

FIG. 7. Domain organization of human thioredoxin and glutaredoxin family members. *Gray shaded boxes* represent Trx domains, *black shaded boxes* Grx domains. The active site Cys–X–X–Cys residues, if present, were included in the boxes. M: mitochondrial translocation signal; NDPk: nucleoside diphosphate kinase homology domain. The *unshaded, unmarked boxes* associated with Txl-1, SpTrx1, and Nrx represent areas with no significant homology to known functional domains.

of *c*-Jun N-terminal kinase and the transcription factors AP-1 and NF-κB (262). Additional Grx homology domains have been identified as N-terminal domain of TGR, containing a redox active CPHS active site (230), andan N-terminal domain of a predominantly testis-specific splice variant of TrxR1, containing a redox-inactive CTRC active site (228).

E. Functions and targets of thioredoxin

a. Trx as an electron donor for metabolic enzymes. As mentioned above, Trx was first identified as electron donor for RNR and sulfate reduction in *E. coli* and yeast, respectively (8, 25, 114, 259). Three classes of RNRs catalyze the conversion of nucleotides to deoxynucleotides, the building blocks for DNA synthesis (reviewed extensively in Refs. 100 and 243). Both the mammalian and the aerobic *E. coli* enzymes belong to the class I and are composed of two subunits, named R1 and R2. Enzymatic turnover requires the reduction of a disulfide in the R1 subunit. In *E. coli,* both Trxs and Grxs can serve as reductants for the reduction of the disulfide (11, 79, 114). However, the kinetic constants, the levels of the proteins, and measurement of thymidine incorporation in newly synthesized DNA in different mutant strains suggest *E. coli* Grx1 to be the main electron donor *in vivo* (79, 189).

In yeast, deletion of the two genes encoding cytosolic Trxs resulted in a viable strain, however, with reduced growth rate due to an elongated S and a shortened G1 phase (156). Recently, it was demonstrated that the dNTP pools in this mutant are reduced to about 60% compared to wild type (109). Together, this indicates a physiological role of both Trxs and Grxs as electron donor for RNR in yeast. The mammalian Trxs are efficient substrates for their endogenous class I RNRs *in vitro* (F. Zahedi Avval and A. Holmgren, unpublished results) (95), but their importance as electron donor *in vivo* is less well understood, because the distribution of Trx and TrxR in tissues is not related to cell proliferation or DNA synthesis (201). For instance, in rat testis, which is undoubtedly a place with high need for deoxynucleotides, RNR by not Trx is localized in the highly proliferative spermatogonia cells (65). More research is required to analyze the situation with respect to tissues.

Peroxiredoxins (Prxs) are a heterogeneous family of thiol-dependent peroxidases present in all kingdoms of life (reviewed in Refs. 75, 194, 195). First described as thiol-specific antioxidants in yeast (105, 106), these proteins can be divided into three subfamilies based on the number and location of their active site Cys residues. The typical (in human Prx1 to Prx4) and atypical 2-Cys Prxs (human Prx5), which can use Trx as electron donor, and the 1-Cys Prxs (human Prx6), the electron donor of which is not yet clear. In bacteria, protists, and plants, Prxs are responsible for antioxidant defense, a function that may be conserved for Prx3 in mammalian mitochondria. In the cytosol of higher animals, the Prxs 1, 2, and 4 appear to be involved in the redox regulation of cellular signaling and differentiation by regulating the levels of the intracellular messenger H_2O_2 (194).

Next to cysteine, methionine is the second sulfur-containing amino acid found in proteins. Methionine can be oxidized to methionine sulfoxide under a broad range of conditions and this conversion can alter the activity of a variety of proteins (120). Methionine sulfoxides can be reduced by methionine sulfoxide reductases (Msr), using Trx as electron donor (28). This reaction might be important in antioxidant defense, regulation of protein function and aging, because mutations that decreased the Msr levels led to a decrease in the maximum life span, whereas over expression of Mse led to a dramatic increase in life span (225).

b. Redox regulation. Trxs, complemented by Grxs, keep a reduced environment inside the cell by reducing protein disulfides, even under severe oxidative stress, and thereby mediate the cellular response to alterations in the redox state. Trx can act as a scavenger of ROS (see above), as well as redox regulator of signaling molecules and transcription factors.

Apoptosis signal-regulating kinase 1 (ASK1) is a mitogen-activated protein (MAP) kinase kinase kinase, which activated the c-Jun N-terminal kinase (JNK) and the p36 MAP kinase pathways and is, for instance, required for tumor necrosis factor-induced apoptosis (90). Human Trx1 binds to ASK1 dependent on its redox status but independent of its redox activity (Fig. 8); reduced Trx forms a complex with the N-terminal portion of ASK1 in which the kinase activity of ASK1 is suppressed. Oxiation of Trx leads to dissociation of the complex and activation of ASK1 (211). Furthermore, binding of Trx1 to ASK1 targets ASK1 for ubiquitination and degradation (126). Thus, Trx1 can serve as a negative inhibitor and redox sensor of apoptosis induction via the JNK and p38 MAPK pathways. A similar regulation of ASK1 has also been described for Grx1 (222); however, Grx1 was shown to bind to the C-terminal domain of ASK1 and may regulate its kinase activity in response to the glutathione

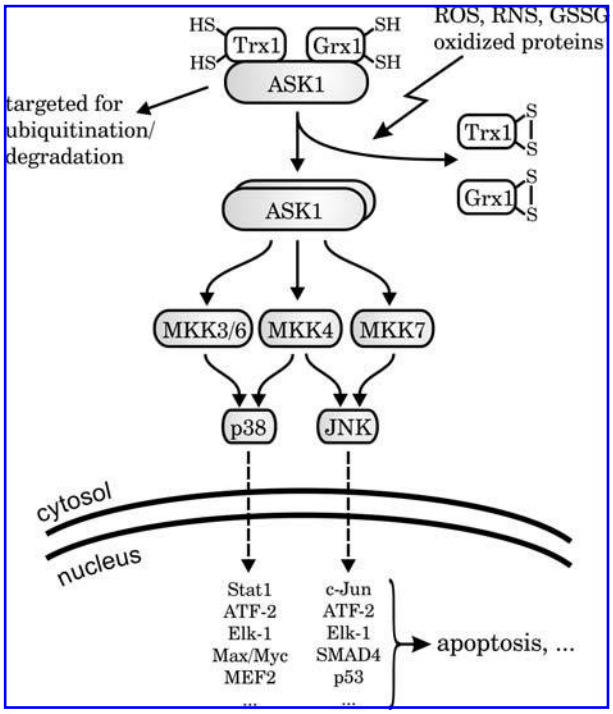

FIG. 8. Thioredoxin and glutaredoxin as negative regulators of apoptosis signal-regulating kinase 1 (ASK1). ASK1 is a mitogen-activated protein (MAP) kinase kinase kinase, which signals downstream to the *c*-Jun N-terminal kinase (JNK) and the p38 MAP kinase pathways via MAP kinase kinases 3, 4, 6, and 7. Reduced human thioredoxin 1 and glutaredoxin 1 can bind to ASK1, leading to an inactive complex. Oxidation of thioredoxin or glutaredoxin leads to dissociation of the complex and activation of ASK1. Moreover, the Trx1/ASK1 complex is targeted for ubiquitination and degradation.

redox state (221). Trx binding protein-2 (TBP-2), also named vitamin D3 upregulated protein 1 (VDUP1), or thioredoxin interacting protein (Txnip), was identified as a thioredoxin binding protein in yeast two-hybrid experiments (101, 169, 269). TBP-2 binds specifically to reduced Trx and can thereby serve as a negative regulator of Trx function. Overexpression of TBP-2 leads to a decline in proliferation and inhibits the interaction of Trx1 with ASK1, which in turn inhibits JNK suppression (101). Knock out mice show a decreased number in natural killer cells (116). Treatment of cells with a tumor-specific histone deacetylase inhibitor induced the expression of TBP-2 in transformed cells (30). As a consequence, the reduced levels of active Trx1 may contribute to the sensitivity of transformed, but not normal, cells, to cell death caused by histone deacetylase inhibitors (252).

Numerous redox-regulated transcription factors have been identified and many of these contain redox-sensitive critical cysteines in their DNA binding domains. Trxs, and perhaps also Grxs, may provide the mechanisms for redox regulation of these factors in response to the cellular redox state. NF-κB, for example, contains a cysteine (Cys62) in the DNA binding domain of its p50 subunit that is susceptible to oxidation. After dissociation of IκB and translocation of NF-κB to the nucleus, reduction of Cys62 is necessary for the binding of NF-κB to its target site in the DNA (Fig. 9). Trx1 reduces Cys62 disulfides in the nucleus, thus promoting the binding of NF-κB to the B site (69, 141). Paradoxically, in the cytoplasm, Trx1 inhibits NF-κB activation by blocking the dissociation and degradation of 1κB (74). Moreover, Grx1 may be part of this redox regulon as well, because Cts62 of p50 can also undergo glutathionylation (73, 187). More detailed information on the complex redox regulation of NF-κB can be found in a recent review by Kabe *et al.* (102).

Further transcription factors directly activated by Trx1 include hypoxia-inducible factor 1 (Hif-1) (257), the tumor suppressor p53 (250), the glucocorticoid receptor (132), the estrogen receptor (68), and polyoma virus enhancer-binding protein 2 (P EBP2/CBF) (2). Other transcription factors such as the family of AP-1 protein complexes, comprised mainly of homo- and heterodimers of c-Fos and c-Jun, as well as p53, appear to be redox regulated involving the direct association between Trx and redox factor-1 (Ref-1) (72, 250), a redox ac-

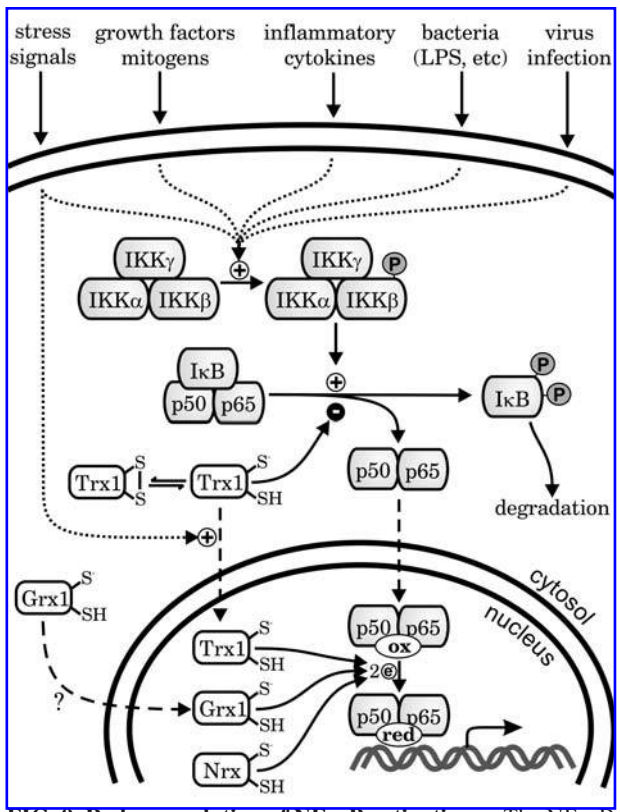

FIG. 9. Redox regulation of NF-κB activation. The NF-κB subunit p50 contains a cysteine (Cys 62) in its DNA binding site that is susceptible to oxidation. After dissociation of the I-κB/NF-κB complex, which is promoted by phosphorylation of I-κB in response to a variety of signals but also inhibited by reduced thioredoxin 1 (74), NF-κB is translocated to the nucleus. In the nucleus, reduction of Cys62 in the p50 subunit of NF-κB is necessary for binding of the transcription factor to its target site in the DNA. In the nucleus, thioredoxin 1 (Trx1), glutaredoxin 1 (Grx1), as well as nucleoredoxin (Nrx) have been reported to promote NF-κB binding to the κB site in the DNA (69, 73, 141).

tive protein that also possesses DNA endonuclease activity involved in base excision repair (265, 266), see below.

II. THIOREDOXIN AND RELATED MOLECULES IN TISSUES AND DISEASES

A. Reproduction and development

a. Testis. Cell division and DNA synthesis in the seminiferous tubules of the testis require a constant supple of deoxyribonucleotides by ribonucleotide reductase. Surprisingly, none of the established electron donors for RNR, Trx1 or Grx1, co-localizes with the enzyme in rat and calf testes, where RNR is primary localized in spermatogonia (65, 200). Trx1 was found highly expressed in the interstitial Leydig cells and in a small fraction of spermatogonia, while spermatocytes, spermatids, and the nondividing somatic Sertoli cells lack Trx1 but do contain TrxR1 (65, 201). In calf testes, prominent staining of Grx1 was detected in Sertoli cells and weak staining in Leydig cells. The complexity of this puzzling picture increased even further since the detection of additional testis-specific members of the thioredoxin family (147). SpTrx 1 and 2, that both contain a Trx domain as part of a larger protein (Fig. 7), are found in the fibrous sheet of the sperm (146, 206). SpTrx3 is associated with the Golgi apparatus of spermatocytes and spermatids (97) and Txl-2 is associated with microtubule in cilia and flagella (207). TGR staining was primarily found in elongating spermatids and associated with the vicinities of the assembling mitochondrial sheath. It was proposed that this protein is part of the disulfide formation and isomerization system (229).

b. Pregnancy. trx1 expression is increased in several different areas of the female reproductive system during the estrous stage of the menstrual cycle, for example, in uterus, cervix, and ovary (91, 135, 175). Both the expression of Trx1 and Grx1 are induced during pregnancy, and Grx1 may be involved in the regulation of cervical ripening, particularly following prostaglandin E1 treatment, which is the most commonly used substance for cervical priming and induction of labor (209, 210).

Pre-eclampsia is one of the major contributors to perinatal morbidity. Both Trx1 and Grx1 expression is affected in placenta from pregnancies with pre-eclampsia and/or growth restriction of fetuses, and the decrease in expression correlates to the severity of the condition (208). This was confirmed on the protein level, where both Trx1 and TrxR1 were found to be significantly reduced when comparing pre-eclamptic placental tissue homogenates to gestational age-matched control placentae from nonpre-eclamptic pregnancies (253). The reduced enzymatic antioxidant capacity may therefore contribute to the pathogenesis of pre-eclampsia.

Within hours after fertilization, the early pregnancy factor (EPF) activity is detected in maternal sera. EPF is defined as lymphocyte-modifying activity causing increased rosette inhibition titers (*i.e.*, decreased binding of red blood cells to a subpopulation of lymphocytes). EPF activity is present for at least the first two-thirds of pregnancy, dependent upon the presence of a viable embryo or fetus (34). Trx is an essential component of the EPF activity. Trx isolated from placental extracts possesses EPF activity; the activity of the serum is lost when endogenous Trx is removed by immunoaffinity columns and regained upon addition of recombinant Trx to the Trx–EPF activity itself (35).

c. Embryonic development. Both mammalian Trx systems are essential for differentiation and morphogenesis of the stripped medium. However, recombinant Trx does not possess embryo. Mice carrying a homozygous disruption of the Trx1 gene die shortly after implantation, and the concepti are resorbed prior to gastrulation, while heterozygotes are viable, fertile, and appear normal (140). Homozygous $Trx2^{-/-}$ mutant mice embryos display an open anterior neural tube, show massively increased apoptosis at embryonic day 10.5, and have disappeared at day 12.5. The timing of the embryonic lethality coincides with the start of oxidative phosphorylation in the mitochondria. In addition, embryonic fibroblasts from $Trx2^{-/-}$ mice cannot be cultured *in vitro,* demonstrating that functional Trx2 is essential for actively respiring cells (170).

Conditionally targeted deletions of both the mouse TrxR1 gene (TXNRD1) and the TrxR2 gene (TXNRD2) have been prepared recently (36, 92). Systemic inactivation of cytosolic TrxR1 leads to early embryonic lethality between gestational days 9.5 and 10.5, inactivation of mitochondrial TrxR2 is associated with death at embryonic day 13. $TrxR1^{-/-}$ mutant embryos display severe growth retardation and fail to turn, and deficient embryonic fibroblasts do not proliferate *in vitro.* $Trx2^{-/-}$ embryos are smaller compared to their litter mates, severely anemic, and show increased apoptosis in the liver. TrxR2-deficient embryonic fibroblasts proliferate, but are highly sensitive to oxidative stress, especially when glutathione synthesis is inhibited. The ventricular heart wall of $Trx2^{-/-}$ embryos is thinned, proliferation of cardiomyocytes is decreased, and cardiac tissue-restricted deletion of TrxR2 results in fatal dilated cardiomyopathy, a condition reminiscent of that in Keshan disease and Friedreich's ataxia. Both TrxR1 and TrxR2 play essential roles during different stages of embryogenesis. TrxR1 is required for most developing tissues except the heart, whereas TrxR2 plays a pivotal role in hematopoiesis and heart function (36, 92). An interesting aspect confirmed by the knock-out studies was that both Trxs and TrxRs must possess at least some functions that are independent of each other, because neither the phenotypes of $Trx1^{-/-}$ and $TrxR1^{-/-}$ nor $Trx2^{-/-}$ and $TrxR2^{-/-}$ mutants match each other perfectly.

B. Nervous system

Neurons are highly metabolically active and therefore exposed to large quantities of ROS, which makes them especially vulnerable to oxidative stress-induced cell death (4). Here, we have focused on the role of Trx in the protection of the Trx system in the nervous system from oxidative stress. Extensive reviews of the roles of the Trx system in the central nervous system and as neurotrophic factor have been published elsewhere (136, 180).

a. Expression and localization of Trx in the nervous system. Trx1 and TrxR immunostaining in the ner-

vous system was first demonstrated for the rat sciatic nerve (226). Immunoreactivity was detected in the cytoplasm of Schwann cells and at the nodes of Ranvier. Moreover, both Trx1 and TrxR were rapidly microtubule-dependent and bidirectionally transported in axons, as demonstrated by accumulation of immunostaining both proximally and distally to crushes of the nerve. Most nerve cells show immunoreactivity for both Trx1 and TrxR, while the proteins are almost absent from glial cells (64). Trx1 mRNA expression was detected in nerve cells of a variety of rat brain regions, especially in regions with high energy demands, for example, the cerebral cortex, piriform cortex, medial preoptic area, CA3/CA4 region of the hippocampus, dentate gyrus, paraventricular nucleus of the hypothalamus, arcuate nucleus, substantia nigra pars compacta, locus coeruleus, ependyma of the fourth ventricle, and the epithelial cells of the choroids plexus. It was also demonstrated that mechanical injury induced expression of Trx1, suggesting a function of the protein in the regeneration of the brain following injury (123) (Fig. 10). In human non-neurological brains, Trx1 immunoreactivity and mRNA expression was detected in white matter astrocytes and in Schwann cells in the posterior root (9). Similar to Trx1, mitochondrial Trx2 is highly expressed in neurons in several regions of the rat brain, including the olfactory bulb, frontal cortex, hippocampus, some hypothalamic and thalamic nuclei, cerebellum, and numerous brainstem nuclei (205).

b. Cerebral ischemia. Induction of global or focal cerebral ischemia in rodents is a common model for the analysis of the morphological, cellular, and molecular changes in the brain upon hypoxia-reperfusion injury. Immunohistochemistry of Trx1 in gerbil brain during reperfusion after transient cerebral ischemia demonstrated Trx induction in glial cell in the hippocampus, not seen in control animals. The Trx-specific staining in these astroglia peaked at 72 h and diminished after 7 days of reperfusion (245). During ischemia in rat brain, induced by middle cerebral artery occlusion, Trx staining decreased in the ischemic regions (*i.e.*, in the lateral striatum and frontoparietal cortex). In the perifocal ischemic region, however, Trx immuno- and mRNA staining increased from 4 to 24 h after occlusion (236). Trx induction during transient occlusion was stronger in the hippocampus and more widespread in the contralateral cortex than in permanent occlusion. Moreover, the induced Trx1 translocated from the cytosol into the nucleus, indicating a role of the protein in both oxidative stress defense and signal transduction during and in recovery from ischemia (233) (*see also* Redox regulation of this review). This was confirmed when transgenic mice overexpressing human Trx1 were subjected to focal brain ischemia. At 24 h after artery occlusion, infarct areas and volume were significantly smaller in transgenic compared to wild-type mice. Consequently, the transgenic mice exhibited decreased neurological deficits (234). Similar to Trx1, Grx1 expression was shown to be reduced after middle cerebral artery occlusion, parallel with the neuronal damage (235). These results clearly demonstrate the importance of the cellular thiol redox regulating systems for neuronal survival during focal ischemia.

c. Degenerative diseases. Oxidative stress is strongly associated with the loss of neurons in several neurodegenerative diseases, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis, or Parkinson disease (PD). Although it is impossible to assess whether oxidative stress is a major cause or merely a consequence of neuronal cell death, modulating the protective effects of key enzymes of the oxidative stress response represents a primary aim of developing new therapies based on biological understanding (4).

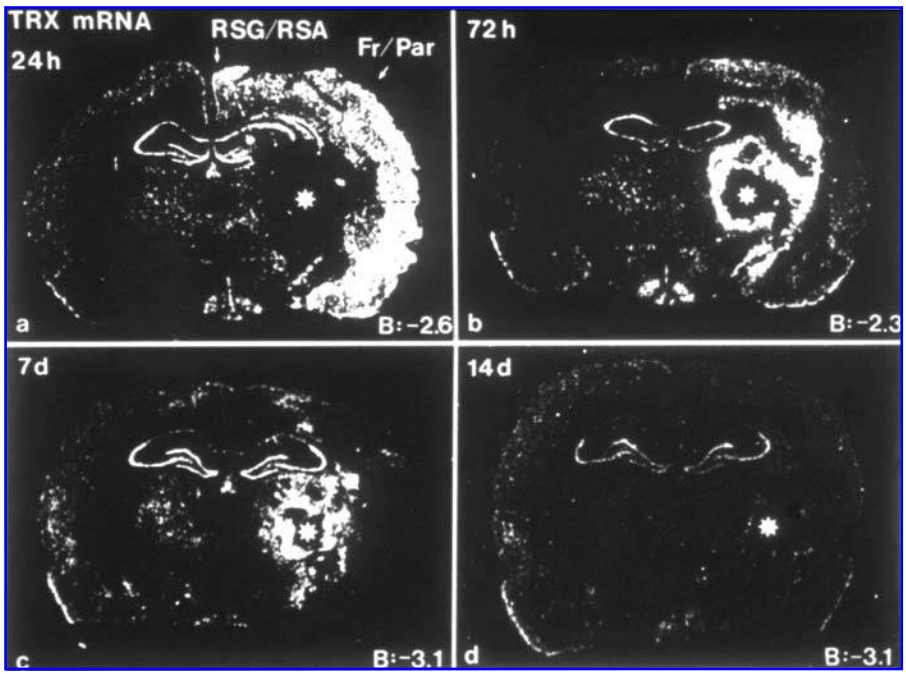

FIG. 10. Upregulation of thioredoxin 1 mRNA after unilateral partial hemitranssection as revealed by *in situ* hybridization. (**a**) Trx1 mRNA 24 h after injury, RSG/RSA: retrospinal granular and agranular cortices, Fr/Par: fronto-parietal cortex. (**b**) Trx1 expression 72 h after injury, and (**c**) 7 days after injury. (**d**) Fourteen days after the lesion the Trx1 mRNA levels have returned to normal (73). *, lesion site.

Oxidative imbalance is a prominent feather of AD, and likely both cause and consequence of the characteristic pathological changes such as the formation of intracellular tangles and extracellular plaques (281). Initially Asahina *et al.* have reported the augmentation of Trx1 localization and expression; however, only two out of five AD brains showed a clear increase in Trx1 (9). Lovell *et al.* measured the levels of Trx1 and the activity of TrxR in 10 brains from AD patients, compared to 10 control subjects, and demonstrated a statistically significant decrease in Trx levels in amygdala, hippocampus/parahippocampal gyrus, and the superior and middle temporal gyri in AD brains, while TrxR activity levels were increased. Further on, when primary hippocampal cultures were treated with Trx or TrxR, concentration-dependent enhancements in cell survival against toxic doses of amyloid-β were demonstrated (129). Thus, it was suggested that the increase of TrxR activity observed in AD brain offers no sufficient protection due to the significant decrease in Trx1 levels and that the loss of Trx1 may contribute to the increased neuronal oxidative stress and cell death observed in AD.

Nerve growth factor (NGF) is a major survival factor of sympathetic neurons. NGF activates the expression of Trx1 via a cAMP-responsive element and induces the nuclear translocation of Trx1, indicating that Trx1 may contribute to the positive effects of NGF in AD (13). Expression profiling for the analysis of approximately 18,000 expressed sequence tagged complementary cDNAs in single tangle-bearing versus normal CA1 neurons aspirated from sections of AD and control brains, revealed the reduction of Grx1 mRNA levels in the tangle-bearing neurons (53). In a recent study, increased Grx1 and decreased neuronal Trx1 levels were demonstrated in AD brains. Using neuroblastoma SH-SY5Y cells, the authors demonstrated oxidation of both intracellular Grx1 and Trx1 by amyloid-β treatment and the attenuation of amyloid-β toxicity by overexpression of both Grx1 and Trx1. Thus, amyloid-β toxicity might be mediated by oxidation of Grx1 and Trx1 and subsequent activation of ASK1 (3) (Figs. 5 and 8). Deregulation of both Trx1 and Grx1 could be important events in the pathogenesis of AD.

PD is characterized by the loss of dopaminergic neurons in the substantia nigra caused by a dysregulation of redox and iron homeostasis due to the propensity for dopamine to autooxidize and thereby produce elevated levels of hydrogen peroxide. Although the importance of the cellular thiol redox status in PD is well documented (*e.g.*, in form of the loss and oxidation of the GSH pool) (22), there is surprisingly little experimental evidence for a protective role of the Trx or Grx systems in PD. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), that is, its active metabolite MPP^+ (1-methyl-4-phenylpyridinium ion), causes loss of dopaminergic neurons and Parkinsonism in humans and mice (reviewed in Ref. 220). MPTP/MPP^+ induces cell death in the rat pheochromocytoma PC12 cell line, and suppresses Trx1 expression in these cells. Overexpression as well as administration of Trx1 attenuates MPTP/MPP^+-induced neurotoxicity in PC12 cells (12). Human Grx1 and *E. coli* Grx2, administered to the medium, have been shown to protect cerebellular granulae neurons from dopamine-induced apoptosis by activating NF-κB via Ref1 (38) involving the Ras-phosphoinositide 3-kinase and JNK pathways (37), supporting a protective role of Grxs in PD. It remains to be investigated whether alterations in the Trx or Grx systems are directly involved in the etiology of PD.

d. The eye. The roles of Trxs, Grxs, and GSH in protecting the lens against exogenous and endogenous oxidative stress have been reviewed elsewhere (127, 128). In the developing and mature retina, Trx1 and TrxR immunoreactivities were demonstrated in neurons and photoreceptor cells (63). Temporary ischemia and photodynamic retinal vascular thrombosis strongly induced Trx1 in the retinal pigment epithelial cells, suggesting a role of Trx1 in the defense mechanism against cellular damage caused by oxidative stress to the retina (172), which was nicely confirmed by attenuation of retinal photooxidative damage in Trx1 transgenic mice (240). Trx1, TrxR, as well as Grx1 activity and expression, are induced in lens cells under oxidative stress, indicating that both the Trx and the Grx system contribute to the protection of the lens (152).

Retinitis pigmentosa is an untreatable, inherited retinal disease that leads to blindness due to rod photoreceptor degeneration, followed by irreversible progressive loss of cone photoreceptors. Secretion of viability factors from rods is essential for cone viability. Interestingly, one of these factors, the rod-derived cone viability factor (RdCVF), was shown to be a truncated Trx-like protein specifically expressed by photoreceptors (119). RdCVF may represent the first therapeutic strategy to prevent loss of the cone receptors and therefore blindness in retinitis pigmentosa patients.

C. The immune system

a. Thioredoxin as chemokine and cytokine. Trx is actively secreted by a variety of normal and transformed cells, including fibroblasts, airway epithelial cells, and activated monocytes and lymphocytes. Similar to secretion of interleukin (IL) 1β, secretion of Trx is independent of the exocytotic pathway and does not involve a leader (202). Activation of B cells from healthy donors and B-type chronic lymphocytic leukemia (B-CLL) strongly induced expression of Trx mRNA, from which about two thirds were released into the medium (45). Secreted Trx can act as cytokine in transformed T cells (231, 242). Treatment of monocytes with Trx strongly enhances the expression of various cytokines such as TNF, IL-1α, IL-2, and IL-8, and in fibrosarcoma and endothelial cells, Trx dose-dependently increased the synthesis of IL-6 (214). Extracellular Trx, in the nanomolar range, can act as a chemotactic factor for monocytes, polymorphonuclear leukocytes, and T lymphocytes, both *in vitro* and *in vivo*. This activity is not dependent on intracellular Ca^{2+} levels and is not inhibited by pertussis toxin. Thus, it is G-protein-independent. However, chemotactic activity is dependent of the presence of the two active site cysteines of Trx (21). The redox state of both the active site and the structural cysteines of Trx in plasma is an open question, however; under the given conditions in plasma, one would expect the active site to present mainly in the oxidized form. Although the mechanism of Trx secretion remains to be unraveled, extracellular Trx might be an important link between oxidative stress and inflammation.

b. Truncated thioredoxin (Trx80). The truncated form of Trx (Trx80) was first described as eosinophil cytotoxicity enhancing factor in plasma of patients suffering from schistosomiasis (41) that was secreted from adherent monocytes (118). Two proteins of 10 and 14 kDa were isolated from peripheral blood mononuclear cell cultures, and N-terminal sequencing revealed that both were identical to Trx. The 10 kDa protein exhibited the strongest activity in enhancing eosinophilic cytotoxicity (217, 218). Using recombinant Trx1 variants, it was possible to attribute the enhancing activity to C-terminally truncated forms of Trx, which comprise the first 80 (Trx80) or 84 (Trx84) amino acids of the protein (219). In solution, Trx80 is present as a homodimer, most likely mediated by a hydrophobic surface that becomes exposed upon loss of the C-terminal part (including β-sheet 5 and α-helix 4, see Figs. 2 and 6). Trx80 is not active as oxidoreductase and is neither an inhibitor nor a substrate for TrxR; however, it can be reduced by full-length Trx. Trx80 is present in the plasma of healthy blood donors and recombinant Trx80 induces proliferation in cultured peripheral blood mononuclear cells and monocytes (182, 185). When the latter cells were exposed to Trx80, they showed elevated expression of the surface antigens CD14, CD40, CD54, and CD86, as well as induced release of interleukin 12 (IL-12) in the presence of T cells (Fig. 11) (183). Trx80 induces differentiation of $CD14^+$ monocytes into a previously unknown cell type, named Trx80-activated monocytes (TAMs), as a consequence of activation of the MAPK pathways p38, JNK, and extracellular signal-regulated kinase (ERK). TAMs express high levels of the pattern recognition receptors CD1a, CD14, and mannose receptor (MR). TAMs exhibit a high pinocytotic capacity, release high amounts of pro-inflammatory cytokines (Fig. 11), and have the capacity to induce production of the anti-inflammatory cytokine IL-10 (184). A recent study demonstrated that the released IL-12 activates specific helper T cells to inhibit the proliferation of Epstein–Barr virus-infected cord blood B-cells (124). In addition, Trx80 retains the chemotactic activity of full-length Trx towards both monocytes and polymorphonuclear neutrophils (23).

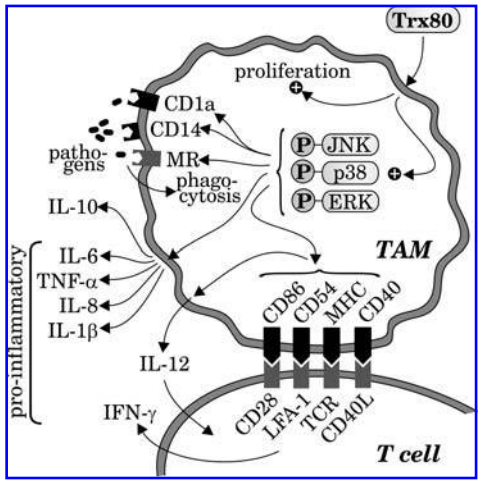

FIG. 11. Functions of truncated thioredoxin (Trx80). Trx80 induces differentiation of $CD14^+$ monocytes into Trx80 activated monocytes (TAMs), as a consequence of activation of the MAPK pathways p38, JNK, and extracellular signal-regulated kinase (ERK). Trx80 induces proliferation in cultured peripheral blood mononuclear cells and monocytes (182, 185), leading to elevated expression of the surface antigens CD14, CD40, CD54, and CD86, as well as to the release of interleukin 12 (IL-12) in the presence of T cells (183), thereby inducing the expression of IFN-γ in the T cells. TAMs express high levels of the pattern recognition receptors CD1a, CD14, and mannose receptor (MR). TAMs exhibit a high pinocytotic capacity, release high amounts of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα. In addition, TAMs have the capacity to induce production of the anti-inflammatory cytokine IL-10 (184).

c. Virus infections. Trxs and Grxs play an essential role in the life cycles of many viruses and phages as well as in host–virus interactions (78). *Escherichia coli* Trx is essential for the assembly of the filamentous phages f1 and M13 (204) and an essential subunit of phage T7 DNA polymerase (133). Phage T4 and orthopoxviruses such as vaccinia, ectromelia, and smallpox encode their own Grxs (20, 99), which are essential for DNA synthesis, disulfide bond formation, and virus assembly (193, 243, 258).

The role of Trx retroviral infections was recently subject to a review (139). Adult T cell leukemia (ATL) induced by the retro virus human T-cell lymphotrophic virus type I (HTLV-I) was identified in the 1970s (188, 248, 272). The ATL-derived factor (ADF) was originally described as IL-2 receptor α-chain inducer in T cells transformed by the virus (242). Cloning and sequencing of this factor revealed that it was identical to human thioredoxin (231), which had been cloned independently 1 year before from a cDNA library from a lymphoblastoid B cell line of Epstein–Barr virus-immortalized human lymphocytes (263). Interestingly, recombinant human Trx1 does not induce the IL-2 receptor α-chain in a lymphocyte cell line, suggesting that ADF might differ from recombinant Trx in some way or that further factors are involved in this activation (163). Two recent studies indicate that loss of TBP-2 expression might be an important step in transformation of the T cells towards IL-2-independent growth and therefore in the progression of ATL leukemogenesis (1, 168).

Imbalance between oxidative stress and antioxidant defense, such as loss of intracellular antioxidants like GSH and increased production of ROS, contribute to both the manifestation and the progression of human immunodeficiency virus (HIV) infection. HIV infection induces a dysregulation of Trx expression and distribution that leads to a loss of cells that highly express Trx in lymphoid tissue (138) and to an elevation of the Trx levels in plasma (158). The levels of Trx in the plasma of patients appear to be inversely correlated to the number of CD4 cells and to the life expectancy of the patients. Nakamura *et al.* proposed that the elevated Trx levels impair innate immunity by blocking pathogen-induced chemotaxis by acting directly on neutrophils, thus eliminating the last barrier against infections in the immunodeficient patients (159, 160). Remarkably, exogenous Trx was shown to inhibit expression of HIV in macrophages by 71%, whereas Trx80, which can be generated from full length Trx by macro-

phages, had the opposite effect and induced HIV production by 67% (166). It remains to be established which effects of plasma Trx in HIV infections can be reduced to full length Trx and which ones to Trx80. Moreover, Grx1 was detected both within and on the surface of HIV particles. Grx1 can regulate the activity of HIV-1 protease *in vitro*, and could therefore be important for the regulation of protease activity in infected cells (40).

d. Bacterial and protozoan infections. In brief, bacterial and protozoan infections represent an oxidative challenge for both the host and the parasite. The parasite has to cope with the continuous production of ROS by the host immune system and, to maintain redox homeostasis, must be equipped with a range of low molecular weight and enzymatic antioxidants. Because of the central role of the Trx system in oxidative stress defense in most species and the diversity in structure and mechanism of TrxRs from different organisms, the development of specific TrxR inhibitors against infections such as leprosy, trypanosomiasis, or malaria has been suggested (15, 16, 110) and some potential compounds have been identified [*e.g.*, anti-malaria agents (5)].

D. Cardiovascular diseases

The possible roles of Trx as a regulator of cardiovascular homeostasis and in defense against oxidative stress in cardiovascular diseases have been discussed before (216, 270). Briefly, Trx1 levels are elevated in endothelial cells treated with H_2O_2 (162), in plasma of patients suffering from heart failure, in patients with acute coronary syndromes and cardiomyopathy (108), and after angioplasty in peripheral arterial disease (254). Trx1 is expressed in both endothelial cells and macrophages in atherosclerotic plaques but not in atherosclerotic lesions (232). In nonatherosclerotic coronary arteries, Grx1 and Trx1 are expressed in endothelial cells, fibroblasts of the adventitia, and in medial smooth muscle cells. In addition, infiltrating macrophages in atherosclerotic lesions highly express Grx1 and Trx1 (174). Mice transgenically overexpressing human Trx1 show an attenuated adriamycin-induced cardiotoxicity (215) and, following ischemia, hearts from these mice display significantly improved ventricular recovery and reduced myocardial infarct size as compared to hearts from wild-type mice (246). Moreover, even exogenously applied human Trx1 reduces myocardial injury in an *in vivo* ischemia/reperfusion mouse model and this effect was potentiated by *S*-nitrosation of Trx1 before application (241). Transgenic mice with cardiac-specific overexpression of a dominant negative mutant lacking both active site cysteinyl residues, but not mice overexpressing wild-type Trx1, exhibit cardiac hypertrophy with maintained cardiac function at baseline. Thoracic aortic banding caused greater increases in myocardial oxidative stress and enhanced hypertrophy in the dominant negative transgenic compared to wild-type animals (268). In an experimental autoimmune myocarditis mouse model, Trx1 attenuates myocarditis by suppressing the expression of chemokines and leukocyte chemotaxis (125). Together, these results suggest that the cellular thiol–disulfide oxidoreductases may play a pivotal role in antioxidant protection in human cardiovascular tissue.

E. The airway system

The lungs are directly exposed to high concentrations of oxygen and therefore require a sophisticated antioxidative defense system. Moreover, many airway-related disorders involve the immune system and inflammatory processes, implying a role of the cellular thiol–disulfide redox systems in both physiology and pathology of the airway system (192). Trx1 as well as TrxR1 expression are rapidly upregulated with the onset of breathing in the lungs of primates, supporting an important role of the Trx system in the lung during the transition from relatively anaerobic conditions to oxygen breathing (39). In healthy lung, Trx1 and TrxR1 are expressed in bronchial epithelium and alveolar macrophages. Trx and TrxR are highly concentrated in areas of metaplastic epithelium in usual interstitial pneumonia and in alveolar macrophages in desquamative interstitial pneumonia. Fibrotic areas in usual interstitial pneumonia are mainly negative. The expression of both Trx1 and TrxR1 is weaker in usual interstitial pneumonia associated with collagen vascular diseases, whereas granulomas of sarcoidosis show moderate to intense Trx immunoreactivity (244). Together these results highlight the importance of Trx1 and TrxR1 in primary defense and inflammation in bronchial epithelium, alveolar epithelium, and macrophages in human lungs. Patients with asthma show significantly increased serum Trx1 levels. The Trx1 serum levels are also inversely correlated with the forced expiratory volume in 1 second during asthma attack, suggesting that extracellular Trx (or Trx80, see above) in serum may be related to the state of asthma exacerbation and allergic inflammation (267). Monitoring of Trx1 levels and redox state in the plasma, airway, and lung tissue may be useful for the diagnosis of pulmonary inflammation. Administration of recombinant Trx1 or induction of endogenous Trx may be useful for the therapy of oxidative stress-associated lung disorders (164). As examples, exogenously applied human Trx1 attenuates ischemia-reperfusion injury in rabbit lungs (173) and suppresses IL-18/IL-2-induced interstitial infiltration of cells and lung tissue damage in a mouse model for interstitial lung diseases (89).

Grx1 immunostaining is highly concentrated in alveolar macrophages and weakly positive in the bronchial epithelium. The expression of Grx1 is decreased significantly in alveolar macrophages of sarcoidosis and allergic alveolitis compared to controls. Bronchial epithelium of these diseases revealed no Grx1 immunoreactivity. The localization of Grx1 and the impairment of the Grx1 system both in inflammatory and fibrotic lung diseases suggest a prominent role of Grx1 in the primary defense of the human lung (186).

F. Cancer

Malignant transformation is a multistep process involving dynamic changes in the genome, the regulation of transcription, the cellular architecture, and cellular interactions. Two classes of cancer genes have been identified, oncogenes with dominant gain of function, and tumor suppressor genes with recessive loss of function (62). Trx is essential for cell growth and development in most tissues (140). Trx is a strong antioxidant and regulator of transcription factor activity (see above) and actively secreted Trx is a powerful (co-)cytokine (202,

231, 242) (see below). Trx is mildly upregulated in about half of the cancers investigated, for instance, from liver (161), lung (51), and colon (18); Trx promotes the growth of tumors and its levels are negatively correlated with apoptosis in cancer cells (57). Can we therefore deduce that Trx qualifies as an oncogene? The strongest counter-argument comes from mice transgenically overexpressing human Trx1 under control of the β-actin promotor. These mice are functionally normal and do not show an increase in malignancies, instead their life expectancy is increased (149, 234, 276). The lack of tumorigenic potential of Trx overexpression supports the idea that the high expression of Trx in some tumors is the consequence of their special metabolic needs and their high proliferation rate, rather than the malignant transformation being caused by Trx overexpression. However, the importance of the Trx system for the survival of Trx-positive cancer cells is undoubted and makes the Trx system a prime target in anticancer therapy. For example, reduced levels of Trx sensitized human bladder cancer T24 cells to doxorubicin, mitomycin C, etoposide, and UV irradiation (273); L929 fibrosarcoma cells overexpressing Trx1 displayed increased resistance to cis-diamminedichloroplatinum-induced cytotoxicity (213); and high Trx1 expression was associated with resistance to docetaxel in primary breast cancer (107).

The tumor suppressor p53 is frequently inactivated in human cancers and plays a central role in the cellular response to conditions that cause DNA damage by activating the transcription of genes essential for DNA repair, cell cycle arrest, and apoptosis (52, 199). The DNA binding activity of p53 to its target sites is controlled by the thiol redox status of some critical cysteinyl side chains in its DNA binding domain (61, 179) (Fig. 12). The redox state of these residues appears to be regulated by both Ref-1 and Trx. Ref-1 is a dual function protein that can both regulate the redox state of a number of proteins and function as a DNA repair endonuclease. The redox and repair activities are encoded by distinct regions of Ref-1; the N-terminal domain is required for the redox activity, the C-terminal region encodes the DNA repair activity (265, 266). Ref-1 stimulates p53 activity by both redox-dependent and -independent means (93), Trx can stimulate the DNA binding activity of p53 and potentiate Ref-1-stimulated p53 activity both *in vitro* and *in vivo* (250). In yeast and fission yeast, the Trx system is essential for activation of p53, since thioredoxin reductase mutants fail to induce p53-dependent gene activation (32, 181). Furthermore, the expression of Trx1 and p53 appears to be correlated in breast carcinomas, with about 90% of the mutant p53 cases being Trx positive (251) and cases with high p53 expression exhibiting significantly higher Trx staining in the nucleus (247). Together, Trx- and Ref-1-dependent redox regulation of p53 DNA binding activity functionally couples the oxidative stress response and the p53-dependent DNA repair and apoptosis activation (Fig. 12).

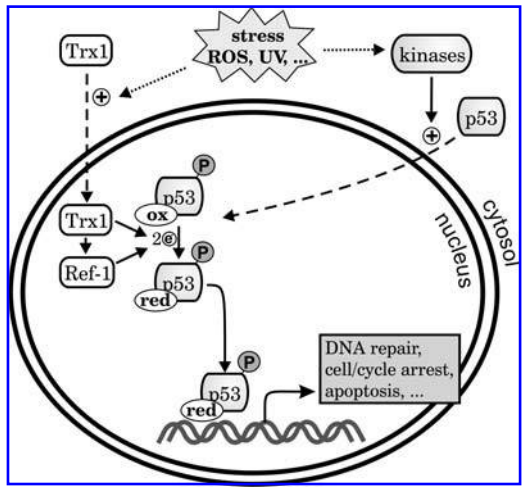

FIG. 12. Thiol redox control of the tumor suppressor p53. The DNA binding activity of p53 to its target sites is controlled by the thiol redox status of some critical cysteinyl sidechains in its DNA binding domain. Oxidized p53 can be reduced by both Ref-1 and Trx (72, 250). Oxidative stress or UV light, for instance, promote the nuclear translocation of Trx1 (137) and activate various kinases, which phosphorylate p53, resulting in stabilization and activation of p53 in the nucleus (27). Reduced activated p53 interacts with specific DNA binding sites in the DNA. The following transcriptional activation of various genes may lead to cellular responses such as apoptosis or cell-cycle arrest.

G. Aging

The free radical (or mitochondrial) theory of aging was first proposed by Herman in 1956 (70). According to this theory, free radicals are continuously produced in the cell as a byproduct of aerobic life. Over time, these radicals cause an accumulation of irreversible DNA mutations and waste products, which, in a vicious cycle, cause an increase in free radicals. This theory is supported by a large body of experimental data, however, it is still being critically discussed (212). Trx is undoubtedly an important part of the cellular antioxidant defense system and can both directly and indirectly contribute to the scavenging of free radicals (*i.e.*, reactive oxygen and nitrogen species). The strongest support for a role of Trx1 in the aging process came from the transgenic mice overexpressing human Trx1 developed by Yodoi and co-workers (149). When 53 transgenic and wild-type C57Bl/6 mice were compared, the transgenic mice showed a statistical significant increase in medium (35%) and maximum (22%) life span (149, 276). What functions of Trx1 could contribute to its life span-increasing activity? As already mentioned above, targeted deletion of the gene encoding Msr led to a decrease in the maximum life span, whereas overexpression increased the maximum life span (225). Because Msr and Trx1 are functionally connected, at least some of the effects seen in Trx1 overexpressing mice could be based on the interactions between these two proteins. Other important interacting proteins with respect to scavenging of free radicals and aging could be the peroxiredoxins (150), TBP2 (275), and, of course, the mitochondrial thioredoxin system (198). In addition, Trx may be involved in a number of processes that affect age-related diseases, for example, atherosclerosis, neurodegeneration, and cancer (see above).

III. THERAPEUTIC APPROACHES, FUTURE DEVELOPMENTS

Thioredoxin reductase is a key enzyme with functions of its own and the only way to reduce Trx by NADPH. The fundamental differences between the mammalian and bacterial thioredoxin reductase offer a unique possibility to target specifically Trx-dependent reactions such as RNR and DNA synthesis or Trx peroxidase-dependent defense against reactive oxygen species. Recently, it was found that ebselen is a substrate for mammalian TrxR and a fast oxidant of Trx, making the thioredoxin system a prime mechanism of action for this promising antioxidant (277), which has been tried in clinical trials against stroke and was recently found to be active in motor neuron disease (264). However, ebselen is an efficient inhibitor of *E. coli* and other bacterial TrxRs and will inhibit growth of certain pathogenic bacteria like *Mycobacterium tuberculosis, Helicobacter pylori*, and *Staphylococcus aureus,* for which the Trx system is essential (J. Lu, A. Vlamis–Gardikas, R. Zhao, T.N. Gustafsson, L. Engstrand, S. Hoffner, and A. Holmgren, unpublished results). These results suggest that ebselen and related drugs are promising new antibiotics with a mechanism directed against the fundamental differences between the TrxR enzymes in the host and the pathogen.

Thioredoxin reductase is also a key enzyme in the tumor phenotype and the tumorigenicity by lung carcinoma cells as recently revealed (274). Dietary selenium has potent cancer prevention activity and both low molecular weight selenocompounds and selenoproteins are implicated in this effect with TrxR as a prime candidate (49, 58). Of particular interest is that selenium-modified TrxR is proapoptotic (6), because several clinically used drugs target the selenol of TrxR and induce apoptosis (261) (Fig. 13).

Many anticancer agents increase ROS production in tumor cells and thereby induce apoptosis. A novel redox active drug targeting TrxR is motexafin gadolineum, which is used in clinical trials against cancer and is known to be a substrate for thioredoxin reductase generating ROS (67). In addition, the drug is an inhibitor of RNR (67).

The increased level of Trx seen in many human cancers may detract from therapy by scavenging the ROS involved in the mechanism of chemotherapeutic drugs or radiation. Furthermore, many human cancers have low levels of TBP2 (see above). TBP2 binds to reduced Trx and blocks its reducing activity. Histone deacetylase inhibitors like suberoylanilide hydroxamic acid (SAHA) upregulate TBP2 in cancer cells and downregulate the Trx levels (30, 168). Normal cells can cope with the oxidative stress induced by SAHA by upregulating Trx expression, but cancer cells cannot (252). Many hematologic and solid tumors show sensitivity to SAHA and the upregulation of TBP2 and downregulation of Trx appears to be a mechanistic explanation.

Extracellular Trx1 is a cytoprotective agent against oxidative stress and, at high concentrations, also acts as an antichemotactic factor to block recruitment of neutrophils, monocytes, and T cells. This anti-inflammatory action of thioredoxin may be useful for treatment of diseases like acute respiratory distress syndrome (ARDS) (249).

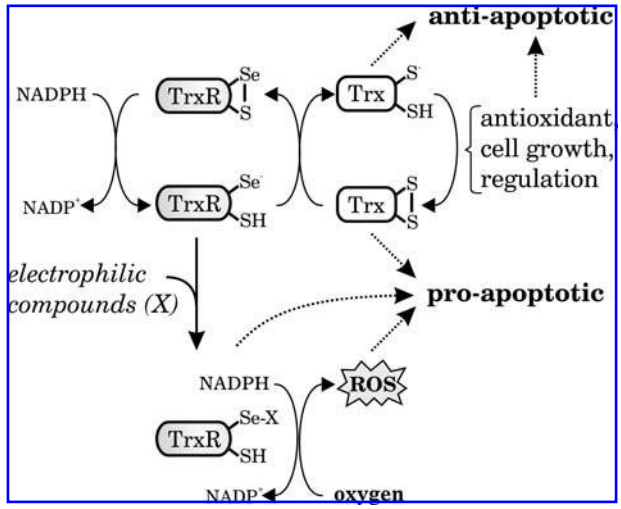

FIG. 13. The thioredoxin system as drug target in cancer therapy. Reduced Trx exhibits anti-apoptotic activity, for example, through its interaction with ASK-1, as direct antioxidant, and as stimulator of cell growth. Covalent modification of TrxR with a series of electrophilic compounds blocks the reduction of oxidized Trx, stimulates the NADPH oxidase activity of TrxR, causing an increased generation of ROS, and converts TrxR itself into an inducer of apoptosis.

IV. CONCLUDING REMARKS

The development of the redox regulation and signaling field during the last two decades has been quite fast. Obviously the thioredoxin and glutaredoxin systems are important players involved in the reductive side to counteract the influence of ROS generated by metabolism, but also in signal transduction. A concept of redox regulation involving a balance between the level of ROS via control of generation and removal through enzymes will probably have to be defined for each cell type in a specific metabolic state. The targets, involving protein substrates, will have to be defined. The fluxes through the redoxins need to be defined again for each cell type and the functional context may play a major role. Contrasting expression patterns of cells will have to be defined. How Trx and Grx can be secreted through the plasma membrane or taken up in cells is still poorly understood. How are Trx, TrxR, and Grx transported into and out of the nucleus? Even the concept of cell surface-localized Trx and TrxR needs to be investigated further. How are the molecules bound? However, as outlined in this review, we are already close to clinical applications of thioredoxins and related molecules and they are likely to continue to be explored as novel functions of thioredoxin and related molecules are coming to light.

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ABBREVIATIONS

AD, Alzheimer's disease; ADF, ATL-derived factor; ATL, adult T cell leukemia; ASK1, apoptosis signal-regulating kinase 1; DTNB, Ellmann's reagent (5,5′-dithio-bis (2-nitrobenzoic acid)); EPF, early pregnancy factor; ERK, extracellular signal-regulated kinase; Grx, glutaredoxin; HIV, human immunodeficiency virus; IL, interleukin; JNK, *c*-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MR, mannose receptor; Msr, methionine sulfoxide reductase; NDPk, nucleoside diphosphate kinase domain; Nrx, nucleoredoxin; PD, Parkinson disease; PICOT, protein kinase C interacting cousin of thioredoxin; Prx, peroxiredoxin; RdCVF, rod-derived cone viability factor; Ref-1, redox factor-1; RNR, ribonucleotide reductase; SpTrx, spermatocyte/spermatid-specific thioredoxin; TAM, thioredoxin 80-activated macrophages; TBP-2; thioredoxin binding protein 2; TGR, thioredoxin glutathione reductase; Trx, thioredoxin; Trx80, truncated thioredoxin (*i.e.*, the N-terminal 80 amino acids of full length thioredoxin); TrxR, thioredoxin reductase; Txl, thioredoxin-like.

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