ANTIOXIDANTS & REDOX SIGNALING
Volume 19, Number 13, 2013

DOI: 10.1089/ars.2012.4599

Discoveries

COMPREHENSIVE INVITED REVIEW

Thioredoxins, Glutaredoxins, and Peroxiredoxins—Molecular Mechanisms and Health Significance: from Cofactors to Antioxidants to Redox Signaling

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Abstract

Thioredoxins (Trxs), glutaredoxins (Grxs), and peroxiredoxins (Prxs) have been characterized as electron donors, guards of the intracellular redox state, and "antioxidants". Today, these redox catalysts are increasingly recognized for their specific role in redox signaling. The number of publications published on the functions of these proteins continues to increase exponentially. The field is experiencing an exciting transformation, from looking at a general redox homeostasis and the pathological oxidative stress model to realizing redox changes as a part of localized, rapid, specific, and reversible redox-regulated signaling events. This review summarizes the almost 50 years of research on these proteins, focusing primarily on data from vertebrates and mammals. The role of Trx fold proteins in redox signaling is discussed by looking at reaction mechanisms, reversible oxidative post-translational modifications of proteins, and characterized interaction partners. On the basis of this analysis, the specific regulatory functions are exemplified for the cellular processes of apoptosis, proliferation, and iron metabolism. The importance of Trxs, Grxs, and Prxs for human health is addressed in the second part of this review, that is, their potential impact and functions in different cell types, tissues, and various pathological conditions. *Antioxid. Redox Signal.* 19, 1539–1605.

Reviewing Editors: *José Bárcena, Aron B. Fisher, Leopold Flohé, Pietro Ghezzi, Juan-José Lázaro, John J. Mieyal, and Fulvio Ursini*

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I. Introduction

Redox reactions—the transfer of electrons—are an essential requirement for cell metabolism, most notably in the form of biological energy transduction in the inner mitochondrial and plastidal membranes. As a consequence, numerous cellular compounds undergo redox modifications, and some of these redox-modified molecules function in signal transduction. Redox modifications have long been discussed to be the result of increased levels of pro-oxidants, for instance, due to irradiation or decreased levels of antioxidants (14, 714, 715). These conditions, defined as oxidative stress, were often visualized in the form of a scale and an imbalance between pro-oxidants in one pan and antioxidants in the other pan. Up to now, this dis-equilibrium has been correlated with many disorders and pathologies, including cancer, neuro- and cardiovascular diseases (86, 126, 229, 500, 561).

Often, oxidative stress was attributed to the formation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). The biological effects of ROS were first demonstrated by Henry John Horstman Fenton in 1894 (182). He demonstrated that hydrogen peroxide (H_2O_2), previously

isolated by Louis Jacques Thénard in 1818 as "eau oxygenée" (772), in combination with ferrous iron, was able to oxidize biomolecules. This "Fenton reaction" leads to the formation of the hydroxyl radical, which was described by Fritz Haber and Richard Willstätter in 1931 only 2 years after Fenton had passed away (249). It took until 1971 for H_2O_2 production to be measured in respirating mammalian mitochondria from rat liver and pigeon heart (110, 449).

The biological activity of nitric oxide (·NO), the RNS prototype, was recognized early and repeatedly, but its physiological importance remained unnoticed for many decades. In 1867, the British physician Lauder Brunton found that organic nitrates were effective in relieving pain in angina pectoris (79), a disease from which also Alfred Nobel, the inventor of the nitroglycerin-based explosive dynamite and the founder of the Nobel awards, suffered. When in the 1890s Nobel's physicians recommended nitroglycerin as a remedy for his heart disease, he declined it. In a letter to Ragnar Sohlman, his assistant and later executor of his testamentary dispositions, he noted, "Isn't it the irony of fate that I have been prescribed N/G 1 [nitroglycerin], to be taken internally! They call it Trinitrin, so as not to scare the chemist and the public." (727). In 1979, Louis J. Ignarro and his coworkers demonstrated that ·NO and ·NO-releasing drugs induce the relaxation of the coronary artery through the activation of guanylate cyclase (245). However, it was not before 1986 that Robert Francis Furchgott demonstrated that the blood vessel dilating "endothelium-derived relaxing factor" which he had proposed in 1978 was, in fact, endogenously produced ·NO (217). It took another decade before the reaction of NO with thiol groups was recognized as specific redox modification. As early as 1925, John Scott Haldane and coworkers presented a case in which the death of a man who was employed in a colliery was suspected to be caused by carbon monoxide poisoning. However, the victim's blood did not contain CO-modified hemoglobin but "NO-haemoglobin" (39). Eventually, in 1996, Jonathan S. Stamler demonstrated that ·NO may react not only with the heme moiety, but also specifically with thiols in the form of S-nitrosothiols on the cysteine residue at position 93 of hemoglobin's β-chain, implying new regulatory functions through the release of ·NO during arterial-venous transit (341).

The major intracellular thiol compound glutathione (GSH), γ-L-glutamyl-cysteinyl-glycine, was likely first isolated around 1888. J. de Rey-Pailhade described a nearly ubiquitous substance that he had isolated from yeast, bovine, sheep, fish, egg, and asparagus. It released hydrogen sulfide (H_2S), bleached several dyes, and reacted with halogenates. Hence, de Rey-Pailhade suggested the name philothion—"sulfur-loving" (637–639). In 1921, Frederick Gowland Hopkins redescribed the compound as an "autooxidizable constituent of the cell." He originally assumed it to be a dipeptide between glutamate and cysteine and, therefore, named it "glutathione" (294); he also characterized it as an "oxidation-reduction system" (296). In 1927, George Hunter and Blythe Alfred Eagles presented evidence for the conjugation of glutamine and cysteine with additional amino acids (313). Hopkins responded that their preparation was likely impure and insisted on the dipeptide nature of GSH. Nevertheless, he ended his response letter with the words: "In any case, although I have myself no doubts as to the [dipetide] nature of GSH, the appearance of Hunter and Eagle's papers make it desirable that I should if possible give greater precision to the account of its isolation. This I hope to do in the near future" (295). It took Hopkins 2 years and 12 additional preparations of GSH, each from ~50 kg of yeast, to confirm: "The tripeptide has been shown to constitute a large portion of the preparation […]. The description of the substance as dipeptide was therefore erroneous" (297). More than 40 years after the discovery of GSH, it was the pioneering work of Alton Meister that unraveled the enzymology and regulation of GSH metabolism, for example, (488, 489). Meister's discoveries opened up several new lines of research into the functions of GSH, for instance, its involvement in detoxification reactions (273), its role as electron donor (184, 778), and its part in redox regulation and homeostasis (495).

Over the past decade, our view of redox biochemistry evolved rapidly, realizing and establishing redox changes as physiological, rapid, specific, and reversible cell signaling events and a form that regulated the activity of key proteins (227, 354). Moreover, redox signaling was shown to be localized to distinct regions within a cell or even a compartment at a given time point, affecting distinct redox couples such as GSH/glutathione disulfide (GSSG) or $NADH/NAD^+$ differently (239, 254). This so-called "compartmentalized redox signaling," therefore, stands in opposition to the view of an overall cellular redox balance, which implies that all cellular redox couples are reduced or oxidized to a similar degree by the same stimuli.

Many key regulators of redox signaling and thus of the intracellular effects of ROS and RNS are members of the thioredoxin (Trx)-fold family of proteins, among them the proteins highlighted in this review: Trxs, glutaredoxins (Grxs), and peroxiredoxins (Prxs) (12, 432, 434, 554, 643). Members of these protein families are ubiquitously expressed in all organisms, tissues, cell types, and organelles. Some of these proteins can even shuttle between cellular compartments and the extracellular space.

Trxs, the first branch and the name-giving proteins of the Trx family of proteins, were discovered by Peter Reichard and coworkers in 1964 in their quest to discover the electron/hydrogen donor for ribonucleotide reductase (RNR) in *Escherichia coli* (418) (Fig. 1). The characteristic dithiol active site motif, Cys-Gly-Pro-Cys, which facilitates the reduction of the disulfide formed in the catalytic cycle of RNR, was determined by protein sequencing in 1968 (284). This motif is, with rare exceptions, conserved throughout all kingdoms of life. In 1976–77, Bob Buchanan and coworkers established the concept of redox regulation by identifying Trx as activator of metabolic enzymes in phototrophic organisms after light exposure (82, 291). The proteins from the second branch of the Trx family were identified as GSH-linked enzymes functioning in thiol-disulfide exchange reactions by Bengt Mannervik and coworkers around 1974 and, despite the oxidation-reduction nature of this reaction, were named "thioltransferases" (170). In parallel, Arne Holmgren faced the challenge to identify alternative electron donors for RNR, because *E. coli* mutants lacking Trx were still viable, despite the essential nature of RNR (285). In his studies, published between 1976 and 1979, he characterized this new group of GSH-dependent oxidoreductases as electron donors for RNR and named them Grxs (287, 288, 455). In contrast to Trxs and Grxs, Prxs reduce peroxides rather than protein disulfides. Prxs were not discovered because of their enzymatic activity. It was because of their high abundance and their distinct

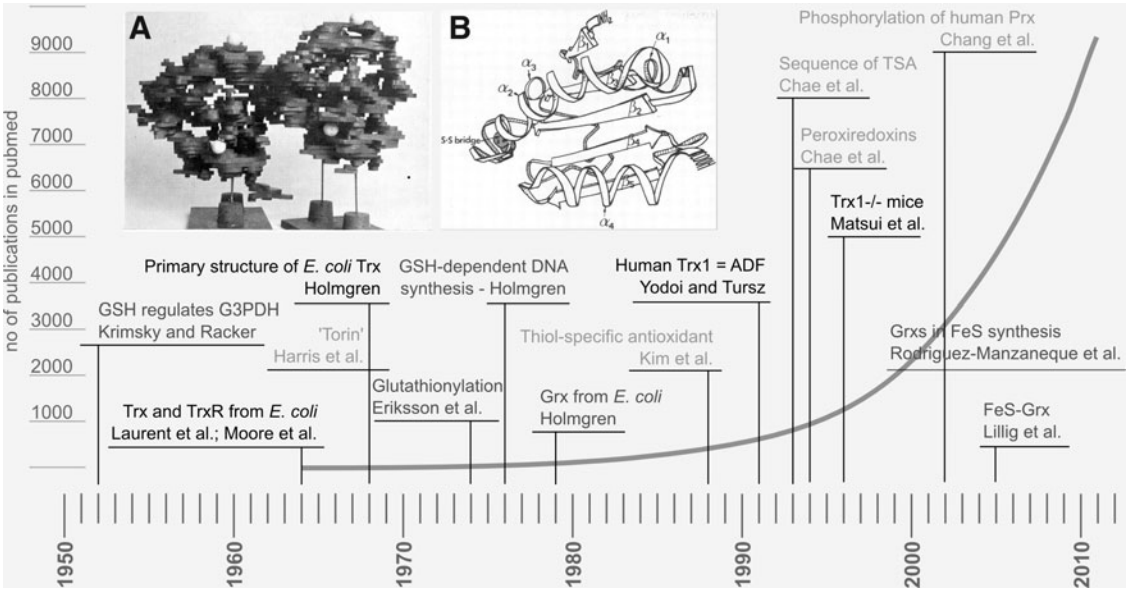


FIG. 1. A brief history of "redoxin" research. The figure highlights some milestones of Trx, Grx, and Prx research and (in the background) the number of publications listed in pubmed with the query "Trx OR Grx OR thioltransferase OR Prx". Black: Trx, dark gray: Grx, and light gray: Prx-related findings. *Insets:* **(A)** The first structure of *Escherichia coli* Trx at 4–5 Å resolution, photography of the balsa model (Söderberg *et al.* 1974) (723). **(B)** Drawing of the first high-resolution structure of *E. coli* Trx at 2.8 Å (Holmgren *et al.* 1975) (293). The work by Krimsky and Racker in 1952 (408) on GSH and glyceralaldehyde-3-phosphate dehydrogenase did not decipher the redox nature of this interaction, but first emphasized the regulatory functions of GSH. GSH, glutathione; Trx, thioredoxin; Grx, glutaredoxin; Prx, peroxiredoxin; ADF, adult T-cell leukemia-derived factor; TSA, thiol-specific antioxidant.

quaternary structure that the first Prx, isolated from human erythrocytes, became known under the name of "torin" in 1968 (265). It was not until 1993 that the previously identified thiol-specific antioxidant activity (380) could be assigned to the torin-homolog from yeast (103). The name Prx was coined by Sue Goo Rhee and coworkers in 1994 in a "note added in proof" (104).

In this review, we summarized the past 50 years of research on Trxs, Grxs, and Prxs, focusing primarily on recent data from vertebrates and mammals (Fig. 1). We discussed redox signaling by looking at reaction mechanisms, oxidative post-translational protein modifications, and interaction partners of the proteins. In the second part of this review, we addressed the importance of Trxs, Grxs, and Prxs for human health, emphasizing the potential impact and functions of redoxins in different cell types, pathways, and pathological conditions.

A. Trx family of proteins

1. Structure and reaction mechanisms. Members of the Trx fold family share a common structural motif, which, in its most basic representation, consists of three α-helices surrounding a central core of a four-stranded β-sheet (Fig. 2A, B) (471). In higher organisms, the motif may contain additional α-helices or β-sheets (Figs. 1A, B and 2C, D). In addition, Grxs display two unique features in their Trx-fold structures: an active site environment that favors the attack of GSH moieties and a hydrophobic surface area for the interaction with protein substrates (85, 831). Trx family proteins are moreover characterized by their active site motifs, containing either one or two cysteinyl residues. These thiol groups are essential for (i) the reduction of protein disulfides, (ii) protein de-/glutathionylation and de-/trans-/nitrosylation, or (iii) the reduction of H_2O_2. Distinct reaction mechanisms have been described for these processes (Figs. 3 and 4). The reduction of protein disulfides depends on the active site motif Cys-X-X-Cys and is catalyzed by Trxs and Grxs *via* the so-called dithiol mechanism (Fig. 3). The N-terminal active site thiol has a low pK_a value, allowing the initiation of a nucleophilic attack on a target disulfide and the formation of a transient covalently bound mixed disulfide intermediate (Fig. 4A, B, reaction 1). In the second step, the C-terminal active site thiol reduces the mixed disulfide, yielding the reduced substrate and an oxidized thio- or Grx (Fig. 4A, B, reaction 2). The protein disulfide in the active site of Trx is reduced by thioredoxin reductase (TrxR), receiving electrons from NADPH (Figs. 3 and 4A, reactions 3–4) (290), whereas the oxidized Grx is reduced by NADPH *via* glutathione reductase (GR) and GSH (Figs. 3 and 4B, reactions 3–4) (289). Reversible (de-)glutathionylation is catalyzed by the monothiol mechanism. This mechanism is unique to Grxs and depends only on the N-terminal active site cysteinyl residue (Fig. 4B, reaction 5), which forms a GSH-mixed disulfide intermediate. Thus, the substrate is reduced. The oxidized, Grx-GSH mixed disulfide is reduced by a second molecule of GSH (Fig. 4B, reaction 4) (240, 286).

Similarly, the reduction of H_2O_2 by Prxs is a multi-step reaction, reviewed for instance in (641). In the first step, H_2O_2 is partially reduced to water, leaving a sulfenic acid intermediate at the peroxidatic, N-terminal active site cysteinyl residue (Fig. 4C, reaction 1). In the second step, a resolving cysteinyl residue, outside the classical Trx family active site, forms a disulfide with the N-terminal thiol in a nucleophilic displacement reaction with water as leaving group. In the case of the 2-Cys Prxs (human Prx 1–4), the conserved releasing cysteinyl residue is located in the C-terminus of the proteins. However, these Prxs do not form intramolecular disulfides,

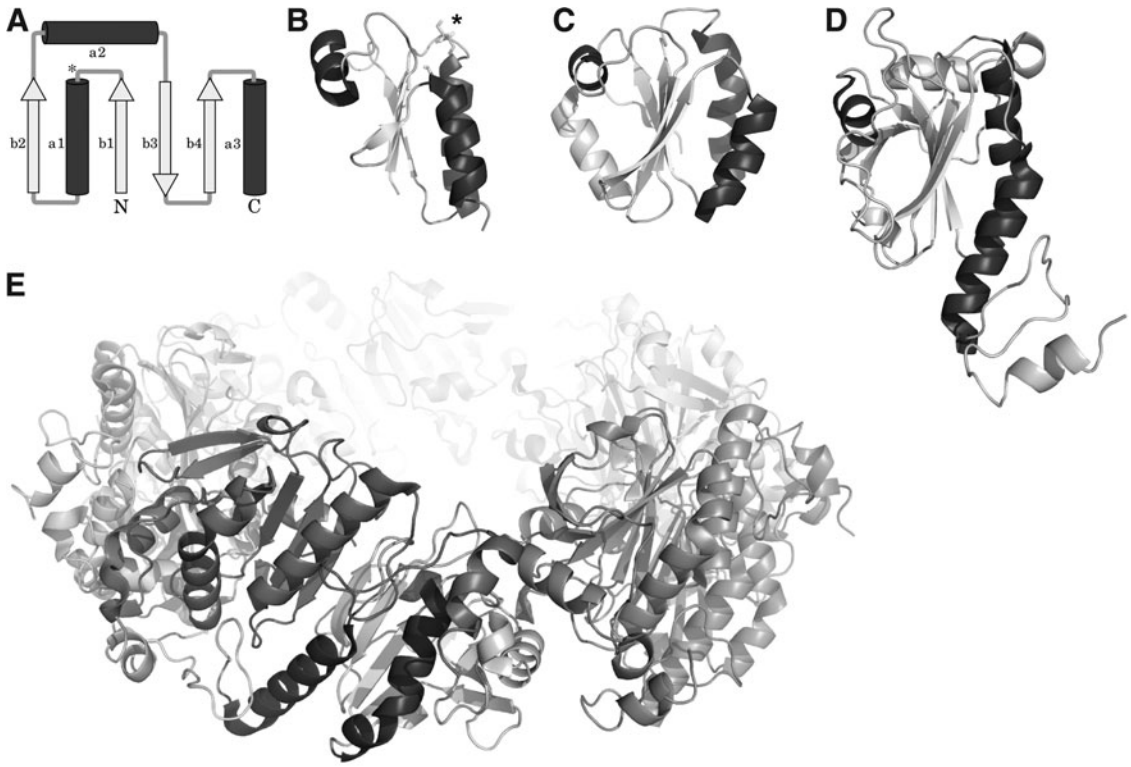


FIG. 2. The Trx fold. (A) Schematic representation of the Trx fold, the *asterisk* marks the position of the proximal active site cysteinyl residue, helices are shown in dark, sheets in light gray. Bacterial Grxs, such as **(B)** *E. coli* Grx1 (PDB accession number: 1EGR), are the most basic representations of the fold. **(C)** Human Trx1 (PDB: 3TRX) contains an additional N-terminal sheet and helix. **(D, E)** The 2-Cys Prx1 is shown as monomer **(D)** and **(E)** decameric torin.

but intermolecular disulfides between two adjacent subunits of the homo-dimeric proteins (Fig. 4C, reaction 2). In contrast, atypical 2-Cys Prxs (*e.g.*, human Prx5) form an intramolecular disulfide, as the releasing cysteinyl residue is located in the C-terminus of the same subunit. The disulfides in both types of 2-Cys Prxs are reduced primarily by Trxs, in the dithiol reactions mechanism outlined earlier, see also Figure 4C, reactions 3–4. Members of the 1-Cys Prx family (human Prx6) lack the additional resolving cysteinyl residue and can be reduced by GSH (121). In yeast, this reduction also involves a dithiol Grx (583).

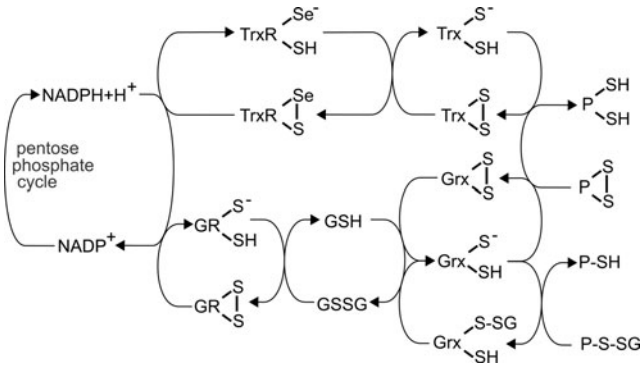


FIG. 3. Electron flow from NADPH to substrates *via* the Trx and GSH/Grx systems. NADPH as the main electron source reduces the selenoprotein thioredoxin reductase (TrxR), which delivers electrons to Trx, which then reduces protein (P) disulfides. NADPH also donates electrons to glutathione reductase (GR), which reduces glutathione disulfide (GSSG), thereby generating two molecules of reduced GSH. Electrons can then be delivered to oxidized Grx, which either possesses an active site disulfide bridge due to reduction of protein disulfides or a glutathionylated N-terminal active site Cys from reducing a GSH-mixed disulfide.

In the access of substrate, Prxs may be over-oxidized by formation of sulfinic and sulfonic acids on the peroxidatic N-terminal active site thiol (Fig. 4C, reactions 5 and 9). In most cases, the formation of sulfonic acids is an irreversible modification under physiological conditions, see section I.C.1. Prxs are, so far, the only class of proteins for which a specific reductase of the sulfinic acid has been described—sulfiredoxin (Srx); for an elaborate discussion on this topic, see Ref. (640). In brief, Srx is an ATP-dependent enzyme that activates the sulfinic acid to a sulfinic phosphoryl ester (355) (Fig. 4C, reaction 6), which subsequently reacts to a thiosulfinate with Srx (Fig. 4C, reaction 7) (356). This intermediate is reduced to a sulfenic acid on the peroxidatic cysteinyl residue of Prx, a reaction that depends on the disulfide formation between Srx and other thiols (Fig. 4C, reaction 8) (64). In addition, Srx has also been reported to specifically catalyze the de-glutathionylation of 2-Cys Prxs (576).

2. Trx, Grx, and Prx family proteins in mammals. The Trx fold family of proteins comprises numerous proteins. Besides the name-giving Trxs, glutathione peroxidases (GPxs), Grxs, protein disulfide isomerases (PDIs), and Prxs share both the Trx fold and oxidoreductase activity.

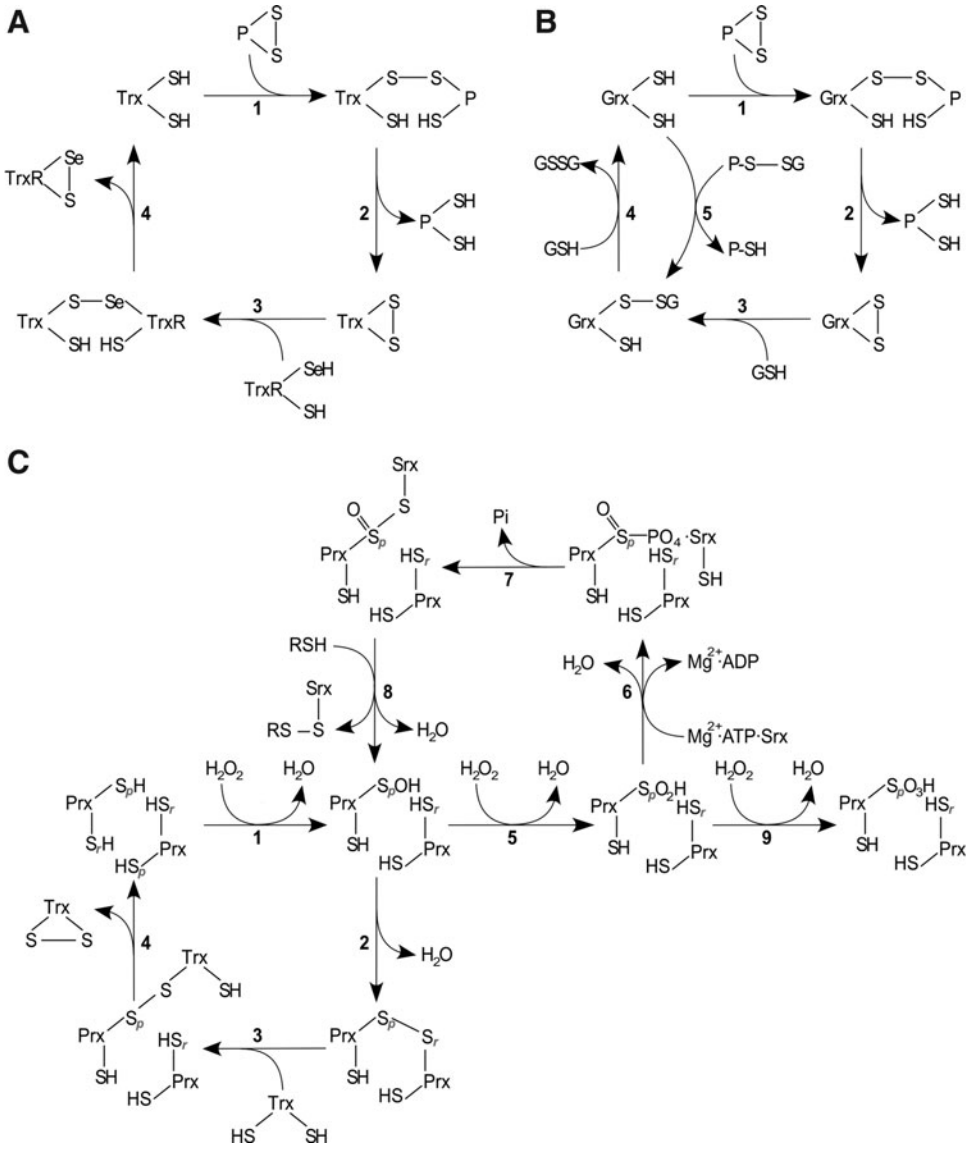


FIG. 4. Reaction mechanisms of Trx family proteins. (A) Trxs reduce protein disulfides *via* the dithiol mechanism, depending on both active site cysteines. The N-terminal active site Cys forms a covalently bound mixed disulfide intermediate **(A** 1**)**, which is reduced by the C-terminal active site Cys, releasing the reduced protein **(A** 2**)**. Oxidized Trx is reduced by TrxR in a similar reaction sequence **(A** 3–4**)**. **(B)** Grxs also reduce protein disulfides *via* the dithiol mechanism, being reduced by two GSH molecules **(B** 1–4**)**. In addition, they reduce glutathionylated proteins *via* the monothiol mechanism **(B** 5–4**)**, only depending on the N-terminal active site Cys, that attacks the GSH moiety and forms a GSH-mixed disulfide intermediate **(B** 5**)**, which is reduced by another GSH molecule **(B** 4**)**. **(C)** During the reduction of H_2O_2 by Prxs, the redox-active, peroxidatic Cys (labeled *p*) is oxidized to sulfenic acid **(C** 1**)**, which either forms an inter-(2-Cys Prxs) **(C** 2**)** or an intramolecular disulfide (atypical 2-Cys Prxs) (not shown) with the resolving Cys residue (labeled *r*), with both being reduced by Trx as outlined in **(A) (C** 3–4**)**. 1-Cys Prxs lack an additional resolving cysteine and are reduced by GSH (not shown). In the presence of H_2O_2, the sulfenic acid can be further oxidized ("over-oxidized") to sulfinic acid [5] and sulfonic acid [9]. Sulfinic acid-modified Prxs can be recovered by the ATP-dependent action of sulfiredoxin (Srx) [6–8]. For a detailed discussion, see section I.A.1. H_2O_2, hydrogen peroxide.

Moreover, various eukaryotic proteins containing one or more domains are evolutionary related to Trx, Grx, or PDI. All these proteins share similar structural motifs, but most of them have unique functions, which do not necessarily depend on the catalysis of redox reactions. Table 1 lists the more than 50 human proteins that contain Trx, Grx, or Prx domains with putative or confirmed redox activity, including their localization, structural domains, and active site motifs. Figure 5 depicts the compartmentalization of a cell into nucleus, cytosol, mitochondrium, and peroxisome as well as the localization, structural motifs, and the electron transfer between members of the Trx, Grx, and Prx systems.

a. Trx systems. In the Trx system, electrons (in conjunction with protons) are transferred from NADPH to the flavo- and selenoprotein TrxR to the oxidoreductase Trx and are ultimately used to reduce disulfides in target proteins (Fig. 3). The 12 kDa Trx contains the active site motif Cys-Gly-Pro-Cys,

which is highly conserved throughout different species from bacteria to humans (165). Due to the variety of substrates, the Trx system is required for DNA synthesis *via* the reduction of RNR (418), proliferation (see section II.B.2), and protection against apoptosis *via* for example, the reduction of the mitogen-activated protein (MAP) kinase kinase kinase apoptosis signal-regulating kinase 1 (ASK1) and initiated downstream cascades (479, 670) (see also section II.A.1), regulation of transcription by controlling the activity of nuclear factor kappa B (NF-κB) or activating protein 1 (AP-1) (1, 480), modulation of the immune response *via* for example, cytokine expression (685) (see also section II.B.8.b), and the H_2O_2 and lipid hydroperoxide levels *via* Prxs (55, 196, 642).

Trx1 itself is regulated both by hypoxia (54) and by oxidative conditions *via* binding of nuclear factor E2-related factor 2 (Nrf2) to an antioxidant responsive element in the Trx promotor (384, 761). Knockout of p53 and DJ-1 in mice resulted in either up- or down-regulation of Trx1, and also *via* increased or decreased levels of Nrf2, respectively (41, 320).

TrxR exists as a 55–60 kDa homo-dimer in a head-to-tail conformation, with every subunit containing a flavin adenine dinucleotide (FAD) domain, an NADPH binding domain, and an interface domain. It possesses two active site motifs; Gly-Cys-Sec-Gly at the C-terminus and Cys-Val-Asn-Val-Gly-Cys at the N-terminus, adjacent to the FAD domain (28). TrxR is known for its broad substrate specificity, which can be explained by the high accessibility and reactivity of selenocysteine. Moreover, different isoforms of TrxR have been described, giving rise to different proteins with distinct functions (657, 785). Besides its main substrate Trx, it was shown to reduce other targets, including PDI (454), Grx2 (349), and dehydroascorbate (482).

Mammalian genomes encode two Trx systems. Trx1 and TrxR1 constitute the cytosolic system (Fig. 5). Trx1 was also shown to translocate into the nucleus on various stimuli (280) or to be secreted (655) (see also section II.B.8.b). Mitochondria contain Trx2 and TrxR2 (Fig. 5). In addition, there is a third testis-specific TrxR3, also named thioredoxin glutathione reductase (TGR), which is mainly expressed in germ cells (see section II.B.10.c). Trx1 and Trx2 share 35% sequence homology and similar catalytic properties *in vitro* (736) with mitochondrial Trx2 possessing the active site motif of Trx1, but lacking additional structural cysteines. Another protein worth mentioning is the 43–44 kDa Trx interacting protein (Txnip) (Fig. 5), also named thioredoxin-binding protein 2 (TBP2) or Vitamin D up-regulated protein 1 (VDUP1), which does not possess a Trx fold, but belongs to the arrestin superfamily of regulatory proteins. It was found as an interaction partner for Trx in a yeast two-hybrid system (548, 689, 839). Txnip binds to the active site of Trx, inhibiting its disulfide reductase activity, and it was, thus, suggested to be an endogenous Trx inhibitor. Txnip is involved in various cellular processes, such as the regulation of the Trx1/ASK1-dependent apoptosis pathway (115). Knock-down of single components of the Trx systems, that is, Trx1, Trx2, TrxR1, or TrxR2, results in embryonic lethality (135, 270, 474, 759); however, Txnip is not essential (see also section II.B.1).

b. Grx systems. Grxs are, depending on the number of active site Cys residues, divided into dithiol (Cys-X-X-Cys) and monothiol (Cys-X-X-Ser) Grxs, the latter being moreover classified as single- and multi-domain monothiol Grxs (277, 432). Dithiol Grxs act in a system in which electrons are transferred from NADPH, *via* GR and GSH to Grx (Fig. 3) and subsequently to the oxidized target, conducting similar functions as the Trx system. They act in the regulation of proliferation (see section II.A.2) and differentiation *via* the MAP kinase ASK1 and downstream targets (82, 529), apoptosis (see section II.A.1) by inhibiting caspase activation (571) and cytochrome c release from mitochondria (167), transcription *via* modulating the activity of NF-κB (140), and levels of H_2O_2 *via* some Prxs (258).

Monothiol Grxs, on the other hand, have so far not been shown to be catalytically active in the Grx-specific HED assay (277). However, recent studies clearly demonstrate that they function primarily in both iron homeostasis and the biosynthesis of FeS proteins (647) (Section II.A.3.a). So far, four Grxs have been discovered in mammals: Grx1, Grx2, Grx3 (also known as protein interacting cousin of Trx—PICOT), and Grx5 (Fig. 5). The dithiol 12 kDa Grx1 is mainly localized in the cytosol, but can be translocated into the nucleus, exported from the cell, and was found in the intermembrane space of mitochondria (187, 453, 456, 565). The dithiol Grx2 is located in mitochondria, but different cancer/testis-specific isoforms, restricted to the cytosol, have been described in mouse and human (310, 447). The 14 kDa Grx2 shares 34% sequence homology with Grx1. It does not possess the active site motif Cys-Pro-Tyr-Cys, but instead Cys-Ser-Tyr-Cys. This single amino acid change is essential for the coordination of a [2Fe2S] cluster (56) (see also section II.A.3.a) and enables the protein to receive electrons from TrxR (349). TrxR is, compared with GSH, a poor electron donor for Grx2 (218); however, when GSSG levels increase, the reaction may become significant (349). The 38 kDa monothiol Grx3 is a multidomain protein that contains two N-terminal monothiol Grx domains with the active site Cys-Gly-Phe-Ser and an additional C-terminal Trx domain with the active site motif Ala-Pro-Gln-Cys. It is localized in the cytosol and the nucleus. Grx3 was identified as a potential binding partner of protein kinase C-θ in a yeast-two hybrid screening (819) and was furthermore described as an FeS protein, with two monomers coordinating two [2Fe2S] clusters (271). The monothiol Grx5 has a molecular weight of around 17 kDa, has a mitochondrial translocation signal, shares the active site motif of Grx3, and has the ability to bind a [2Fe2S] cluster (350, 647). So far, no disulfide reductase activity was observed for the mitochondrial Grx5. Knock-down of Grxs shows severe phenotypes; however, only knockout of Grx3 in mice is embryonically lethal (105) (see also section II.B.1).

c. Peroxiredoxins. Prxs are 20–30 kDa proteins, which are expressed as different isoforms, that are located in different cellular compartments (283, 822). They are high abundance proteins that can account for up to 1% of soluble cellular proteins (102, 822). In addition to their peroxidase activity, alternative functions have been proposed, for instance, as molecular chaperones and phospholipase A2 (121, 333, 413).

Mammalian cells contain six Prxs (Fig. 5), which are divided into three groups, based on their structure and the catalytic mechanisms described earlier: 2-Cys Prxs (Prx1–4), atypical 2-Cys Prxs (Prx5), and 1-Cys Prx (Prx6) (641, 698). Most Prxs function as homo-dimers, the 2-Cys Prxs also form decamers, and the different conformations are linked to switches in function (42).

Table 1. Members of the Trx Family of Proteins with Putative or Confirmed Redox Activity Encoded in the Human Genome Are Enlisted

	Uniprot	Gene	Name	aa	Compartment	Trx-domain(s)	Active site
			Thioredoxin related				
1	DJC16	DNAJC16	DnaJ homlog subfamily C member 16	782	Membrane	119–247	CFSC
2	NHLC2	NHLRC2	NHL repeat-containing protein 2	726		43–200	CINC?
3	NXN	NXN	Nucleoredoxin	435	Cytosol, nucleus	(–), 167–321	SAPC, CPPC
4	NXNL1	NXNL1	Nucleoredoxin-like protein 1	212	Nucleus, membrane	1–164	CPQC
5	NXNL2	NXNL2	Nucleoredoxin-like protein 2	156		9–147	CAPS?
6	QSOX1	QSOX1	Sulfhydryloxidase 1	747	Golgi, membrane, secreted	36–156	CGHC
7	QSOX2	QSOX2	Sulfhydryloxidase 2	698	Nucleus, membrane, secreted	34–178	CGHC
8	TMX1	TMX1	Thioredoxin-related transmembrane protein 1	280	ER, membrane	27–132	CPAC
9	TMX2	TMX2	Thioredoxin-related transmembrane protein 2	296	Membrane	114–269	SNDC?
10	TMX3	TMX3	Protein disulfide-isomerase TMX3	454	ER, membrane	25–128	CGHC
11	TMX4	TMX4	Thioredoxin-related transmembrane protein 4	349	Membrane	30–137	CPSC
12	THIO	TXN	Thioredoxin 1	105	Cytosol, nucleus, secreted	1–105	CGPC
13	THIOM	TXN2	Thioredoxin 2, mitochondrial	166	Mitochondria	61–166	CGPC
14	TXND2	TXNDC2	Thioredoxin domain-containing protein 2 (Sp-Trx1)	553	Cytosol	429–553	CGPC
15	TXND3	TXNDC3	Thioredoxin domain-containing protein 3 (Sp-Trx2)	588	Cytosol	2–119	CGPC
16	TXND5	TXNDC5	Thioredoxin domain-containing protein 5	432	ER lumen	36–169, 170–295, 304–429	CGHC, CGHC, CGHC
17	Q3KNW3	TXNDC6	TXNDC6 protein	174			CGPC
18	B7ZME0	TXNDC8	TXNDC8 protein	95			CGPC
19	A9Z1W9	TXNDC8	Thioredoxin domain-containing 8 (Spermatozoa) (Sp-Trx3)	108			CGPC
20	TXND9	TXNDC9	Thioredoxin domain-containing protein 9	226		74–180	TFRC?
21	TXD11	TXNDC11	Thioredoxin domain-containing protein 11	985	ER, membrane	92–214, 649–749	CELC, CGFC
22	TXD12	TXNDC12	Thioredoxin domain-containing protein 12	172	ER lumen	27–172	CGAC
23	TXD15	TXNDC15	Thioredoxin domain-containing protein 15	360	Membrane	153–296	CRFS?
24	TXD16	TXNDC16	Thioredoxin domain-containing protein 16	825	Secreted	392–495	?
25	TXD17	TXNDC17	Thioredoxin domain-containing protein 17	123	Cytosol	41–123	CPDC
26	TXNL1	TXNL1	Thioredoxin-like protein 1 (Txl1)	289	Cytosol	2–109	CGPC
27	TXN4A	TXNL4A	Thioredoxin-like protein 4A	142	Nucleus		DPTC?
28	TXN4B	TXNL4B	Thioredoxin-like protein 4B	149	Nucleus		DPVC?
			Protein disulfide isomerases				
29	ERP27	ERP27	Endoplasmic reticulum resident protein 27	273	ER	39–152	?
30	ERP44	ERP44	Endoplasmic reticulum resident protein 44	406	ER	30–138	CRFS
31	PDIA1	P4HB	Protein disulfide-isomerase	508	ER, membrane	18–134, 349–475	CGHC, CGHC
32	PDIA2	PDIA2	Protein disulfide-isomerase A2	525	ER	27–152, 367–496	CGHC, CTHC
33	PDIA3	PDIA3	Protein disulfide-isomerase A3	505	ER	25–133, 343–485	CGHC, CGHC
34	PDIA4	PDIA4	Protein disulfide-isomerase A4	645	ER	21–169, 158–301, 505–636	CGHC, CGHC, CGHC
35	PDIA5	PDIA5	Protein disulfide-isomerase A5	519	ER	134–261, 270–384, 378–506	CSMC, CGHC, CPHC
36	PDIA6	PDIA6	Protein disulfide-isomerase A6	440	ER	20–133, 154–287	CGHC, CGHC

(*continued*)

Table 1. (Continued)

			Glutaredoxin related				
37	GLRX	GLRX	Glutaredoxin 1	106	Cytosol, nucleus, secreted	3–106	CPYC
38	GLRX2	GLRX2	Glutaredoxin 2	164	Mitochondria	57–157	CSYC
39	GLRX3	GLRX3	Glutaredoxin 3	335	Cytosol, nucleus	2–117, 144–236, 237–335	APQC, CGFS, CGFS
40	GLRX5	GLRX5	Glutaredoxin 5	157	Mitochondria	42–145	CGFS
41	GRCR1	GRXCR1	Glutaredoxin domain-containing Cys-rich protein 1	290		127–234	CPSC (CSVC, CTAC)
42	GRCR2	GRXCR2	Glutaredoxin domain-containing Cys-rich protein 2	248			CFHC (CSLC, CPAC)
43	PGES2	PTGES2	Putative uncharacterized protein PTGES2	377	Cytosol, golgi, membrane	90–193	CPFC
44	TRXR1	TXNR-D1_v3	Thioredoxin reductase 1, cytoplasmic (TrxR1_v3)	649	Cytosol, nucleus	56–156	CTRC
45	TRXR3	TXNRD3	Thioredoxin reductase 3 (TGR)	754	Cytosol, nucleus, ER	167–267	CPHS
46	YD286		Glutaredoxin-like protein YDR286C homolog	115		1–115	CPLC
			Peroxiredoxins				
47	PRDX1	PRDX1	Peroxiredoxin-1	199	Cytosol, nucleus, Secreted	6–165	CPTE
48	PRDX2	PRDX2	Peroxiredoxin-2	198	Cytosol, nucleus, secreted	6–164	CPTE
49	PRDX3	PRDX3	Peroxiredoxin-3	256	Mitochondria	63–221	CPTE
50	PRDX4	PRDX4	Peroxiredoxin-4	271	Cytosol, secreted, ER	79–237	CPTE
51	PRDX5	PRDX5	Peroxiredoxin-5	214	Cytosol, mitochondria, peroxisomes	56–214	CSKT
52	PRDX6	PRDX6	Peroxiredoxin-6	224	Cytosol, vesicles, lysosomes	5–169	CTTE

TMX3 (10) and TXNDC5 (16), listed in the thioredoxin related group, likely belong to the protein disulfide isomerase group.
aa, amino acid; ER, endoplasmic reticulum; Trx, thioredoxin.

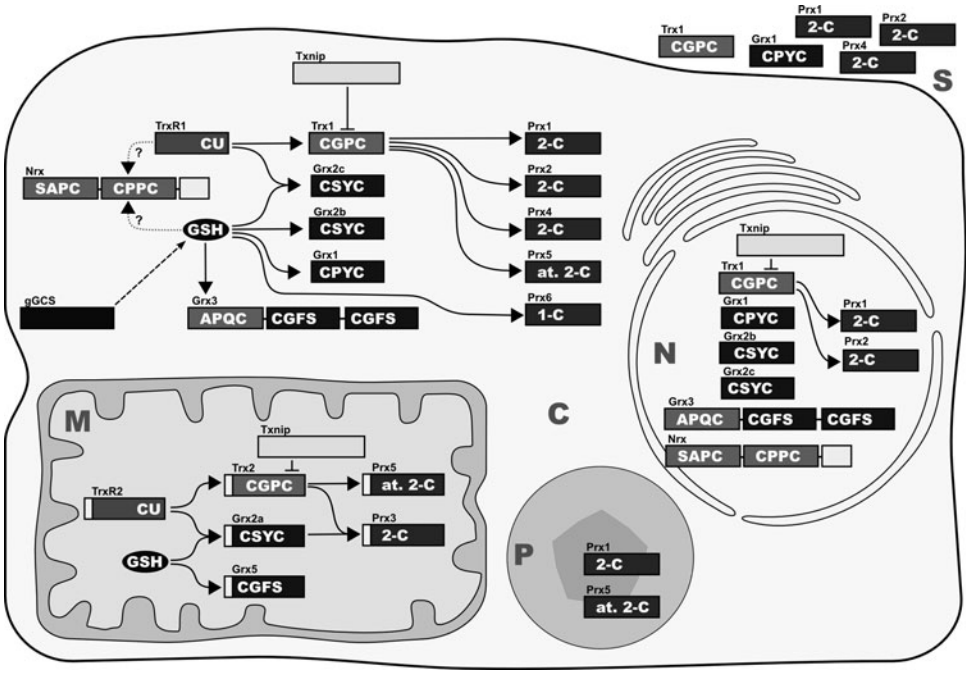


FIG. 5. Mammalian Trxs, Grxs, and Prxs. Isoforms, subcellular localization, and confirmed interactions between the various redox proteins discussed in this review. The active site sequences and the classes of proteins, respectively, are indicated in white. C, cytosol; M, mitochondrium; N, nucleus; P, peroxisome; S, secreted. The secretory compartments, that is, endoplasmatic reticulum, Golgi apparatus, and lysosomes, were excluded for reasons of clarity; however, these compartments contain Trx family proteins; see Table 1.

Prx1 is mainly localized in the cytosol, the nucleus, and peroxisomes, but it was also found in serum (112, 321). Prx2 is present in the cytosol and the nucleus and was shown to bind to cell membranes (109). Prx3 is exclusively located in mitochondria (98, 805). Prx4 is found in both the cytosol and the endoplasmic reticulum. It contains a leader peptide that is believed to be essential for protein secretion (558). Prx5 is localized in cytosol, mitochondria, and peroxisomes (98, 870). Prx6 is located in the cytosol, vesicles, and lysosomes (734, 735), reviewed in (195). Expression of some Prxs is regulated by hyperoxia (378, 379). Knockout mice for peroxiredoxins (Prx1–4, 6) generally showed increased ROS levels, but were viable; for details, see section II.A.1.

d. Trx-like proteins. Many multi-domain proteins contain at least one Trx fold domain. In fact, at least 723 proteins may contain at least one Trx fold domain, some with additional secondary structure elements that extend the common Trx motif (614). Various proteins share the active site motif Cys-X-X-Cys and were shown to possess oxidoreductase activity. However, there are Trx-like proteins that lack the active site and any oxidoreductase activity. Functions in disulfide bond formation, intracellular signaling, and protection from peroxides have been described (281). Until now, numerous proteins have not been analyzed thoroughly, the nomenclature is not clear, and physiological functions are rare; therefore, the impact of most of these proteins is generally not well understood.

In humans, there are various Trx-like proteins, including nucleoredoxin (Nrx), Thioredoxin-like protein (Txl) 1 and 2, the latter also known as thioredoxin domain-containing protein (TXNDC) 6, sperm-specific thioredoxin (Sp-Trx) 1–3, also known as TXNDC 2, 3, and 8 (Table 1). PDIs (180, 244, 405), GSTs (627, 673), and GPxs (199, 778) are also Trx-fold proteins, but are not a part of this review.

Nrx is characterized by two N-terminal Trx-like domains with the active site motif Cys-Pro-Pro-Cys and a C-terminal PDI-like domain without any redox active Cys residues (215). The 55 kDa protein is located in both the cytosol and the nucleus (Fig. 5), even though no nuclear localization sequence was identified. Nrx was shown to reduce insulin and seems to regulate distinct transcription factors, including NF-κB and AP-1 (279). It suppresses the Wnt/β-catenin pathway, essential for embryonic development, *via* redox-dependent associated interaction with Dishevelled (213), and regulates Toll-like receptor 4 (TLR-4) signaling (272) (see also section II.B.1). Moreover, Nrx-like protein 1 (Txl6) and 2 have been proposed (Table 1).

The ubiquitously expressed Txl1 is a two-domain protein, composed of a N-terminal Trx-domain and a C-terminal domain with unknown function (497), which was shown to receive electrons from TrxR1 (344). Due to the findings that (i) Txl1 expression is highest in tissues with high metabolic rate including stomach, testis, bone marrow (497), and the central nervous system (CNS) (344) and that (ii) Txl1 over-expression protects cells against glucose-starvation induced cytotoxicity, the protein might function in the cellular response to sugar deprivation (344). TXNDC6 (Txl2) is also ubiquitously expressed and possesses two domains, the N-terminal Trx-domain and a C-terminal domain, that are typical of the nucleoside-diphosphate (NDP) kinase family. The highest expression was detected in testis and lung. Interestingly, the protein was shown to be associated to microtubular structures, potentially regulating microtubuli physiology (664).

TXNDC2/Sp-Trx1 is exclusively located in spermatozoa. It reduces insulin in the presence of NADPH and TrxR (498). Moreover, TXNDC2/Sp-Trx1 can oxidize a specific substrate, in the presence of the electron acceptor selenite. Acting as an oxidase, TXNDC2/Sp-Trx1 might be essential for stabilizing different structures in the developing spermatid-tails *via* disulfide bond formation (343). TXNDC3/Sp-Trx2 is also a testis-specific protein, consisting of a N-terminal Trx-domain and three consecutive NDP kinase domains. Recombinantly expressed TXNDC3/Sp-Trx2 in *E. coli* does not show any oxidoreductase activity (663). TXNDC8/Sp-Trx3 comprises a

unique Trx domain, which is highly homologous to Trx1. The protein is exclusively found in male germ cells, where it is located in the Golgi apparatus, even though no transit sequence was found. The protein might regulate proteins *via* post-translational modifications, controlling germ-cell specific functions. However, no reduction of insulin was detected in enzymatic assays (345).

B. The concept of redox signaling

The concept of cell signaling was developed from the ground-breaking analysis of signal transduction of extracellular signals to intracellular effector molecules *via* G-protein coupled receptors by Martin Rodbell and Alfred Goodman Gilman (232, 646). In the first step, an extracellular signal activates a receptor protein or protein complex. In the second step, this activation promotes the conversion, production or release of second-messenger molecules. These molecules might act on transducer proteins, for example, protein kinases, activate the production or release of third messenger molecules, or directly activate effector molecules. In some cases, the receptor itself might act directly as the effector molecule.

Redox regulation of cellular processes has most commonly been characterized using redox potentials, for instance, by determination of the [GSH] (or more correctly, the $[GSH]^2$) to [GSSG] ratio. ΔE, the difference in redox potentials between products and reactants, is a measure of the change in free energy ΔG, as ΔG equals $-n \cdot F \cdot \Delta E$, with n being the number of electrons and F being the Faraday constant. In a biological system held at constant pressure and temperature, ΔG determines whether a chemical reaction or reaction sequence is thermodynamically favorable and, therefore, the direction of the reaction. However, ΔG does not determine the reaction kinetics, it leaves no clues whether and at what rate the reaction actually takes place. This rate is determined by the number of molecules in the transition state, which is dependent on the activation energy. Even thermodynamically favorable reactions cannot occur if the activation energy is too high. Enzymes accelerate reaction rates by lowering this activation energy. Therefore, ΔE values by themselves are not suitable to describe or model dynamic cellular redox processes, such as transient modifications of transducer proteins in signaling pathways. The activities of the enzymes that catalyze the generation of the signals and the modifications of the effector molecules determine the transduction of the information, as long as the reactions are thermodynamically favorable. By analogy, the action of protein kinases and phosphatases in signal transduction pathways such as the MAP kinase cascades cannot be described or modeled on the basis of the ΔG values of the phosphorylation and dephosphorylation reactions.

Redox signaling requires the active adjustment of the levels of redox active second messengers in response to the activation of a receptor or sensor molecule. Figure 6 summarizes potential pathways for the production, reaction, and breakdown of such redox active compounds, namely reactive oxygen, nitrogen, and sulfur species; for details, see, for instance, (311, 352, 738, 791). The key compounds, that is, the metabolites which hold the potential to induce reversible post-translational redox modifications on proteins, are H_2O_2, $\cdot NO$, peroxynitrite/peroxynitrous acid ($ONOO^-$/ONOOH), and, possibly, H_2S. These compounds are produced enzymatically, either as primary products of specialized enzymes, for instance, $\cdot NO$ produced by nitric oxide synthase (NOS) or as by-products of enzymes, such as superoxide ($O_2^- \cdot$) produced by complex I of the inner mitochondrial membrane and a number of other enzymes (see below). The decay of these compounds is controlled by other, independent enzymes, for instance, H_2O_2 and ONOOH are reduced by GPxs and Prxs. The levels of these redox-active second messengers are, thus, enzymatically regulated on both the production and the elimination side, similar to, for example, adenylate cyclases and phosphodiesterases whose combined activities determine the level of the second-messenger molecule cAMP.

In the next section, we will discuss how the redox second-messenger molecules mentioned earlier may transduce their information to effector proteins in the form of post-translational redox modifications and how the proteins from the Trx family might be involved in these processes.

C. Reversible post-translational redox modifications of protein thiols

Proteins can be regulated post-translationally *via* reversible redox modifications of susceptible amino acid side chains or cofactors. The thiol groups of cysteinyl side chains constitute the major targets, even though methionyl and selenocysteinyl residues undergo reversible redox modifications as well. Cysteinyl residues are often essential, for instance, in the form of active side residues, or for the tertiary and quaternary structure of proteins. The number of homologous proteins containing at least one cysteine expanded along with evolution, highlighting the importance of their signaling and regulatory functions in increasingly complex organisms (499).

Thiol groups can be oxidized in various ways (Figs. 6 and 7). Two protein thiols can be oxidized to a disulfide, forming a strong inter- or intramolecular bridge. A single protein thiol may also form a disulfide with GSH, termed glutathionylation, or free cysteine, termed cysteinylation or thiolation. Cysteinyl thiols may also react with H_2S to form persulfides, ROS or RNS to form sulfenic acids, or nitric oxide resulting in nitroso thiols, a process named S-nitrosylation. Not every surface-exposed, cysteinyl residue can undergo any or all of these oxidative modifications. It was repeatedly demonstrated that distinct thiol groups undergo specific modifications, such as glutathionylation, S-nitrosylation, or sulfenylation, in response to specific oxidants; see, for instance, (200, 202, 233, 257, 699, 765). In proximity to basic amino acids, the pK_a of the SH-group is lowered from usually eight to between five and seven. At physiological pH, these thiols with lower pK_a will be dissociated. The resulting thiolates are efficient nucleophiles, and their reactivity toward electrophilic targets increases by orders of magnitude. The susceptibility of cysteinyl side chains to undergo S-nitrosylation is determined by the electrostatic and hydrophobic environment of the thiol. Two motifs have been proposed that determine this specificity, the "acid-base motif," or the "hydrophobic motif"; for details, we refer to (278). It is thus the micro-environment of the cysteinyl side chains that determines their reactivity toward different redox compounds and, therefore, the specificity of redox signaling in general.

1. Sulfenylation. Oxidation of thiol groups to sulfenic acids may occur directly by a reaction of susceptible thiols/

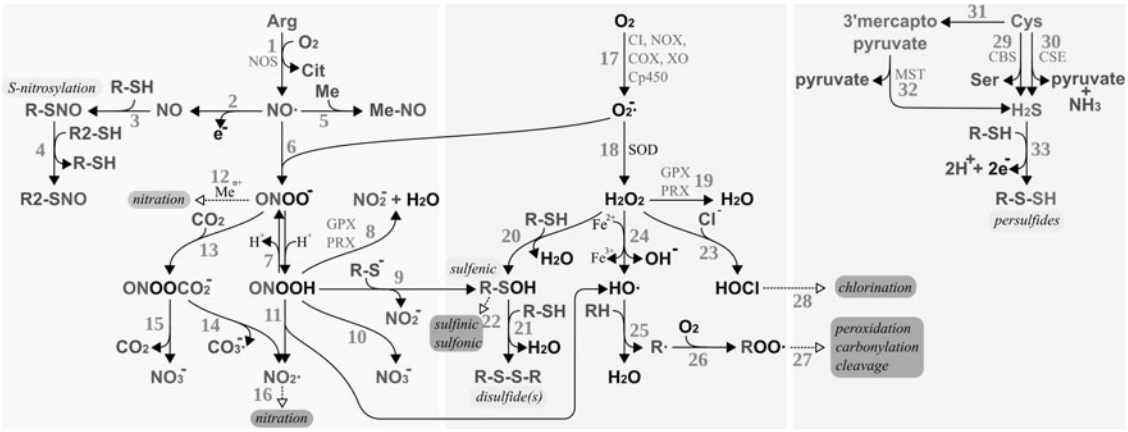


FIG. 6. Production and reactivity of reactive nitrogen, oxygen, and sulfur species. RNS (bio-)chemistry, *left side:* [1] Production of nitric oxide by nitric oxide synthase (NOS). [2–3] S-nitrosylation of protein thiols. [4] Trans-nitrosylation between protein thiols. [5] Reaction of nitric oxide with metals, for example, heme iron. [6] Nitric oxide reacts spontaneously with superoxide yielding peroxynitrite. [7] Reversible protonation of peroxynitrite to peroxynitrous acid. [8] Reduction of peroxynitrous acid by glutathione peroxidases (GPxs) or PRX. [9] Peroxynitrous acid reacts with protein thiolates, yielding protein sulfenic acids. [10] Spontaneous decomposition of peroxynitrous acid yielding nitrite anion. [11] Spontaneous decomposition of peroxynitrous acid to hydroxy radicals and $NO_2\cdot$. [12] Peroxynitrite can (metal catalyzed) lead to the nitration of, for instance, protein tyrosyl residues. [13] Peroxynitrite and carbon dioxide react spontaneously to nitrosoperoxycarbonate. [14] Spontaneous decay of nitrosoperoxycarbonate to carbonate radical anions and nitrite radicals. [15] Spontaneous decay of nitrosoperoxycarbonate to carbon dioxide and nitrate. [16] Nitration may also be initiated by $NO_2\cdot$. ROS (bio-)chemistry, *bmiddle:* [17] Production of superoxide by, for instance, mitochondrial complex I (CI), NADH oxidase (NOX), cyclooxygenases (COX), xanthine oxidase (XO), or cytochrome P450 enzymes (Cp450). [18] Superoxide is either reduced to H_2O_2 or oxidized to molecular oxygen (not shown) by superoxide dismutases (SOD). [19] H_2O_2 can be reduced to water by GPxs or PRX. [20] H_2O_2 may react directly with specific thiols, yielding sulfenic acids. [21] Sulfenic acids can react with other thiols, yielding disulfides. These disulfides are direct substrates of Trxs and Grxs (not depicted). [22] Sulfenic acids may be further irreversibly oxidized, for example, by H_2O_2, to sulfinic and sulfonic acids. [23] H_2O_2 may react with chloride anions, yielding hypochlorous acid. [24] The metal-catalyzed Fenton reaction yields hydroxyl anions and hydroxy radicals. [25] Hydroxy radicals remove hydrogen from volatile organic compounds, yielding water and alkyl radicals. [26–27] Alkyl radicals may react with molecular oxygen and other compounds, eventually resulting in the peroxidation, carbonylation, or cleavage of the organic molecules, for example, proteins. [28] Hypochloric acid may lead to the chlorination of organic compounds. RSS biochemistry, *right side:* [29–32] Hydrogen sulfide may be the product of cystathionine β-synthase [29, CBS], cystathionine γ-lyase [30, CSE], or *via* 3-mercaptopyruvate sulfurtransferase [31–32, MST]. [33] Hydrogen sulfide may react with thiols in the presence of an electron and hydrogen acceptor to persulfides. Modifications labeled with a light gray background are reversible and important in redox signaling, and modifications with a dark gray background are irreversible modifications; hence, "oxidative damage." ROS, reactive oxygen species; RNS, reactive nitrogen species; RSS, reactive sulfur species.

thiolates with H_2O_2, $ONOO^-$, or ONOOH (Fig. 6). Outside peroxisomes, H_2O_2 may primarily be the product of superoxide dismutases (SOD), metal cofactor-dependent enzymes that are present in the cytosol (SOD1, Cu/Zn-dependent), and the mitochondrial matrix (SOD2, Mn-dependent), catalyzing the alternate reduction and oxidation of $O_2^-\cdot$ to H_2O_2 and O_2 (212, 484, 859). $O_2^-\cdot$ is produced both actively and as by-product by numerous enzymes in the cell, for instance, complex I, complex III, NADH oxidases, cyclooxygenases, xanthine oxidase, or cytochrome p450 enzymes (73, 88, 208, 485, 547, 821). It may also be produced through the reaction of iron sulfur clusters with oxygen (560). $ONOO^-$ and ONOOH are the product of the, only diffusion limited, chemical reaction of $O_2^-\cdot$ and $\cdot NO$ (325), an RNS that is actively produced by three isoforms of NOS (358, 792).

The reactivity of most cysteinyl side chains toward H_2O_2 or $ONOO^-$/ONOOH is low; however, if present in the thiolate form, some may react with H_2O_2 or ONOOH to form the sulfenic acid intermediates. The formation of sulfenic acids on cysteinyl side chains is, *via* the formation and subsequent reduction of a disulfide formed with another thiol, a reversible reaction. However, in excess of H_2O_2 or $ONOO^-$/ONOOH, these intermediates may be oxidized further to sulfinic and sulfonic acids (Figs. 6 and 7) (606). With the exception of sulfinic acid formation on Prxs, these reactions are irreversible (see section I.A.2.c). Both H_2O_2 and ONOOH are substrates for peroxidases, that is, GPxs and Prxs (outside peroxisomes). During catalysis, these enzymes form sulfenic intermediates on their selenolate (GPx1–4 & 6) or thiolate (GPx5 & 7–8, Prx1–6) active site themselves, which are subsequently reduced to H_2O along with the formation of a disulfide, that is, GSSG or protein disulfides (199).

The topic of sulfenylation in redox regulation has been comprehensively summarized by others earlier, for example, (377).

2. Protein disulfides. "Thiol redox control" *via* the reversible formation of intra- and intermolecular disulfide bridges was first conceptualized by Bob Buchanan and coworkers, following their studies on the regulation of photosynthesis (81). In nonphotosynthetic organisms, disulfides (outside the secretory pathway) may be formed by the

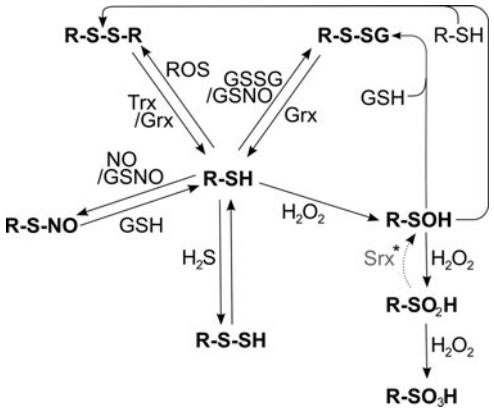


FIG. 7. Redox modifications at cysteinyl residues. Free thiol groups (R-SH) can be reversibly modified by ROS, leading to the formation of protein disulfides (R-S-S-R), which can be reduced by the Trx and Grx systems. Thiols can also be glutathionylated (R-S-SG) by oxidized glutathione (GSSG) or S-nitroso glutathione (GSNO). The de-glutathionylation is exclusively catalyzed by Grxs. GSNO or ·NO, in general, can lead to the nitrosylation of cysteinyl residues, which can be reversed by GSH or transferred to other thiols such as the active site of Trx1 (53) (trans-nitrosylation, not shown). Another modification, induced by peroxides, is the formation of sulfenic acid (R-SOH). In the presence of another free thiol, it can be modified to a protein disulfide. However, in the presence of excessive peroxides, it can be irreversibly over-oxidized to sulfinic ($R\text{-}SO_2H$) and sulfonic acid ($R\text{-}SO_3H$). *The reduction of sulfinic acids to sulfenic acids, catalyzed by Srxs, is specific for Prxs; in addition, Srxs have been reported to catalyze the de-glutathionylation of Prxs.

reaction of a cysteinyl thiol with the sulfenic acid of a second cysteinyl residue (Figs. 6 and 7), or by direct thiol-disulfide exchange reactions. Both Trxs and Grxs catalyze the reduction of protein disulfides and have been implied in numerous regulatory processes that rely on this post-translational redox modification (432, 434, 703).

In the context of redox signaling, the most efficient way of protein disulfide formation would be *via* specialized transducer proteins, that is, proteins which show a very high reactivity toward, for instance, H_2O_2, leading to oxidation and disulfide formation on the transducer protein. This disulfide could subsequently be transferred to effector proteins. Such disulfide relay systems have been described in bacteria and lower eukaryotes; for an introduction, see (77). Although experimental evidence is missing, it is tempting to speculate about similar functions for human Prxs and Trxs with their specificities for peroxides and target proteins, respectively.

3. Glutathionylation and cysteinylation. Cysteinyl side chains may not only form disulfides with other protein thiols, but some form disulfides with low-molecular thiol compounds, such as GSH or cysteine. These post-translational redox modifications have been termed glutathionylation and cysteinylation, or, more generally, thiolation. Hundreds of proteins have been reported to undergo glutathionylation at specific cysteinyl residues, and the topic has been reviewed extensively earlier; see, for instance, (142, 205, 495, 833). Similar to protein disulfides, these disulfides may not only form *via* sulfenic acid intermediates and subsequent reactions with the reduced low-molecular-weight thiol (Figs. 6 and 7), but they may also result from a nucleophilic attack of a cysteinyl thiolate on the low-molecular-weight disulfide, that is, GSSG or cystine. In addition, radical pathways have been suggested to result in thiolation. Grxs have a very high affinity for the GSH moiety. They catalyze the reduction of mixed disulfides, the de-glutathionylation, with very high efficiency (240, 703), as well as, if thermodynamically favorable, the forward reaction, that is, the glutathionylation of protein thiols (658). Therefore, Grxs are central for signal transduction *via* glutathionylation.

4. S-nitrosylation. ·NO is best known for its relaxing function in smooth muscle cells surrounding the vasculature, through the activation of guanylate cyclases by modification of their heme iron cofactor (607). In addition, it was recognized early on that ·NO leads to the reversible modification of cysteinyl residues by the formation of S-nitroso thiols (Figs. 6 and 7). By today, hundreds of proteins with susceptible cysteinyl residues have been identified; for detailed discussions on the topic, see, for instance, (203, 699). The reaction of ·NO with thiols to S-nitroso thiols is an oxidation that requires the transfer of one electron to an acceptor molecule, and thus catalysis, for instance, by protein-bound transition metals. Despite the direct modification of thiols by ·NO, redox signals may also be transduced by the transfer of S-nitroso groups between thiol groups, a process termed trans-nitrosylation (467). A source for such nitroso groups may be S-nitrosylated glutathione (GSNO). The formation of GSNO is catalyzed, for instance, by ceruloplasmin, the decay by GSNO reductases (203). Thus, GSNO may qualify as a second-messenger molecule in redox signaling (Fig. 7), although experimental evidence for this role is still incomplete. Trx and TrxR have been implied in trans-nitrosylation reactions, as well as in specific reductases of S-nitroso thiols and may thus take part in both the transduction and termination of such signaling events (697).

5. Other reversible redox modifications.

a. Persulfide formation. H_2S is, similar to NO, an endogenously produced gaseous signaling molecule. It is produced enzymatically by three different enzymes (Fig. 6), cystathionine β-synthase, cystathionine γ-lyase, and 3-mercaptopyruvate sulfurtransferase (MST), all of which depend on pyridoxal-5′-phosphate as cofactor (168, 241, 706, 740, 749), reviewed in (160, 382, 720). The formation of persulfides of protein thiols exposed to H_2S has been reported for ATP-sensitive K^+ channels, it leads to the inhibition of phosphodiesterases (801), and shows a number of additional physiological effects; see, for instance, (43, 157, 274, 650, 813). Recently, Francoleon *et al.* reported that protein persulfides are easily generated by a reaction of H_2S with disulfides and are relatively stable (204). It remains to be established as to what extent these modifications occur *in vivo*, whether they modify transducer or effector molecules, and whether Trx family proteins take part in persulfide reduction or "trans-persulfidation" reactions.

b. Methionine sulfoxidation. In addition to cysteinyl residues, ROS may also react directly with methionyl residues to form protein methionine sulfoxides. This oxidation is

reversible through the action of the Trx-dependent methionine sulfoxide reductases (Msr), reviewed in (739). This post-translational modification is discussed to be involved in metabolic regulation and cell signaling; for more elaborate discussions on this topic, we refer to Refs. (62, 519, 520, 739).

D. Oxidative stress in the concept of redox signaling

As outlined earlier, oxidizing second-messenger molecules, also known as "pro-oxidants," are produced both constitutively and in response to signals as primary or side products of specific enzymes and are eliminated by reactions with target or transducer proteins. How can these regulatory circuits be brought into accordance with the oxidative damage that was demonstrated in numerous pathological conditions? If the redox circuity was disturbed, for instance by continuous activation of such signaling pathways in response to a specific pathological condition, oxidative second-messenger molecules could accumulate to such a degree that biomolecules become irreversibly modified, as outlined in Figure 6. Excessive peroxynitrite might, *via* different pathways, lead to the nitration of, for instance, protein tyrosyl residues. Further oxidation of sulfenic acids will lead to sulfinic and sulfonic acids. Decomposition of peroxynitrous acid or the Fenton reaction of H_2O_2 with metal ions may lead to the formation of the hydroxyl radical. This molecule will, only limited by diffusion, subtract hydrogen atoms from various biomolecules; subsequent reactions of the radical products will lead to peroxidation, carbonylation, or decomposition of these molecules. Catalyzed by myeloperoxidase, excess H_2O_2 may also react with chloride ions, yielding hypochlorous acid that may lead to the chlorination of various building blocks of the cell. These irreversible modifications do not occur randomly, instead various proteomic screenings suggest both target and side chain specificity for them as well, summarized, for instance, in (114, 242, 458, 622, 788).

Although the concept of "oxidative stress" as damage that arises from disturbed redox signaling/regulation reactions is based on an overwhelming body of knowledge and evolved for a long time, it was not explicitly written out before 2005/2006 (227, 354).

II. Mammalian Trx Family Proteins in Health and Disease

A. Specific pathways

1. Apoptosis. Trxs, Grxs, and Prxs have been implied in many aspects of programmed cell death prevention and induction, as mentioned earlier and as exemplified next. Please see also section II.B.12 for their role in degenerative disorders.

a. Cytosolic pathways. ASK1 is a MAP kinase kinase kinase that leads to the activation of JNK and p38 MAP kinase pathways, for instance, during tumor necrosis factor (TNF) α-induced apoptosis (317). ASK1 is activated by ROS through signal transduction *via* Trx1 and/or Grx1. Reduced Trx1 and Grx1 bind to N- and C-terminal domains of ASK1, respectively, thereby inhibiting its kinase activity (Fig. 8). Oxidation of Trx1 or Grx1 leads to the dissociation of the complex and activation of the kinase (670, 731, 732). In addition, binding of reduced Trx1 to ASK1 targets the kinase for ubiquitination and degradation (443). In agreement with a function as endogenous Trx1 inhibitor, silencing of Txnip expression attenuated high glucose-induced apoptosis and activation of ASK1 in mouse mesangial cells (710) and dexamethason-mediated apoptosis of insulin-producing cells (631). Thus, Trx1 and Grx1 act as redox signal transducers for the induction of apoptosis *via* the JNK and p38 MAPK pathways.

Caspases, the executors of apoptosis, belong to the class of cysteine proteases, whose activity critically depends on the presence of a thiolate in their active site (72). This requirement makes them vulnerable to redox modifications such as S-nitrosylation and S-glutathionylation (307, 465). Trx1 catalyzes the trans-nitrosylation or denitrosylation of caspase-3, thereby regulating protease activity (53, 502). Silencing of Grx1 significantly inhibited TNF-α-induced endothelial cell death because of attenuated caspase-3 cleavage, for example, by caspase 8, concomitant with increased caspase-3 glutathionylation, apparently also of cysteinyl residues outside the active site (571).

Increasing evidence suggests diverse functions of the cytosolic Prxs in redox signal-induced apoptosis. Cisplatin is a chemotherapeutic that is effective in the treatment of several tumors. Prx1-deficient embryonic fibroblasts were sensitized to cisplatin-induced apoptosis, displayed an increased activation of p38 and JNK, and reduced extracellular signal-regulated kinase (ERK) activation. Thus, Prx1 modulated the cisplatin-induced MAP kinase activation that leads to apoptosis (459). Mammalian Ste20-like kinase-1 (MST1) mediates p53-dependent H_2O_2-induced cell death. Morinaka *et al.* showed that H_2O_2 generation by cisplatin caused Prx1 oligomer formation, dependent on the presence of p53, and subsequently MST1 activation (517). Inhibition of Prx1 by a recombinant antibody induced apoptosis in A549 lung carcinoma cells and sensitized these cells to radiation (248). Prx2 inhibited granulosa cell apoptosis during follicle atresia through the NF-κB pathway (844). Down-regulation of Prx2 expression contributed to angiotensin II-mediated podocyte apoptosis (304). Transgenic over-expression of Prx4 protected mice against high-dose streptozotocin-induced death of pancreatic β-cells (154). TNF-related apoptosis-inducing ligand (TRAIL) signaling repressed Prx4 at the transcriptional level, and over-expression of Prx4 suppressed TRAIL-induced apoptosis. Deficiency of Prx6 in lens epithelial cells evoked unfolded protein response and apoptosis (179) and over-expression attenuated cisplatin-induced apoptosis in human ovarian cancer cells (566).

b. Mitochondrial pathways. Cardiolipin is a phospholipid that is specific for energy transducing membranes such as the inner mitochondrial membrane and is important for the activity of the complexes of the electron chain (209, 282, 645). Importantly, cardiolipin anchors cytochrome c to the inner mitochondrial membrane (644); loss of this lipid causes the release of cytochrome c and to the induction of apoptosis as monitored by activation of distinct caspases (69, 330, 745). Short interfering RNA silencing of mitochondrial Grx2 in HeLa cells sensitized these cells to cell death induced by doxorubicin (50-fold) and phenylarsine oxide (40-fold), but the cells did not show signs of a general increase in oxidative damage, that is, protein carbonylation (435). HeLa cells over-expressing Grx2 were less susceptible to apoptosis induced by 2-deoxy D-glucose and doxorubicin. Grx2 prevented the loss of cardiolipin and, therefore, cytochrome c release and caspase activation (167). Corroboratively, transgenic mice over-expressing Grx2 displayed an attenuation of

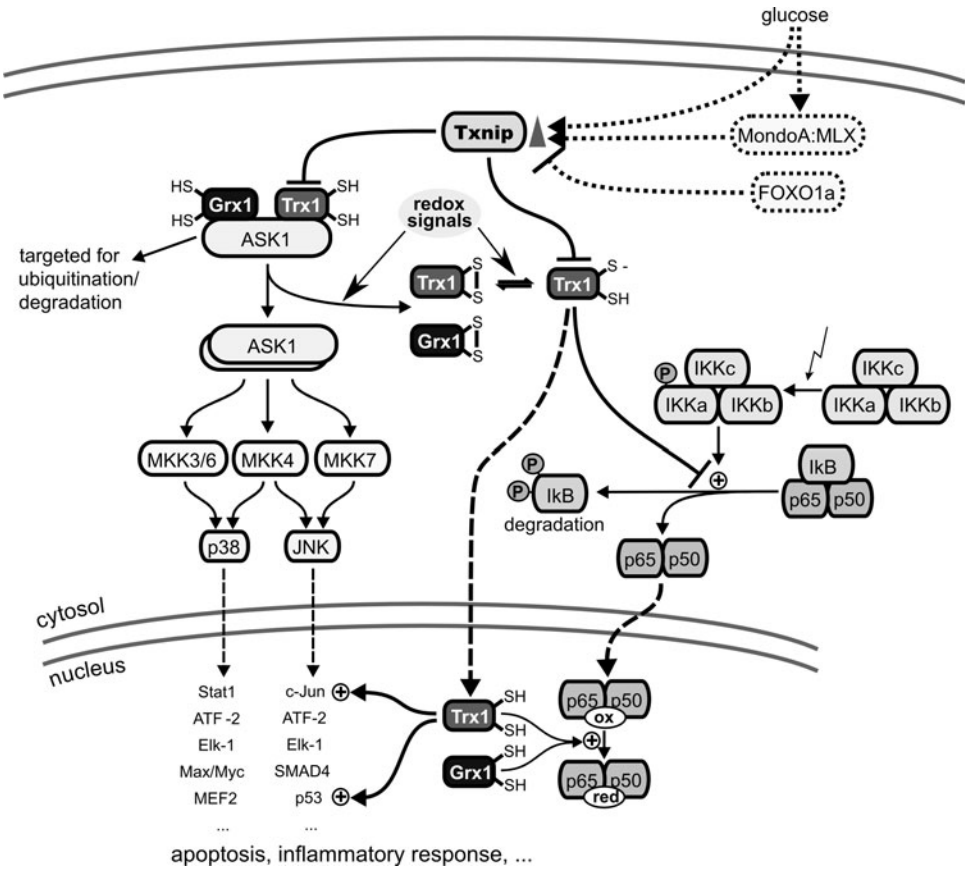


FIG. 8. Trx, Txnip, and Grx in MAP kinase and NF-κB signaling. Txnip, whose expression is promoted by glucose *via* MondoA:MLX signaling and repressed by FOXO1a, was suggested to be a negative regulator of reduced Trx1. *Left side:* Trx and Grx as negative regulators of apoptosis signal-regulating kinase 1 (ASK1)–ASK1 is a mitogen-activated protein (MAP) kinase kinase kinase that 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 Trx1 and Grx1 can bind to ASK1, leading to an inactive complex. Oxidation of Trx1 and/or Grx1 by various redox signals leads to dissociation of the complex and activation of ASK1. Moreover, the Trx1/ASK1 complex is targeted for ubiquitination and degradation. *Right side:* 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 not only promoted by phosphorylation of I-κB in response to a variety of signals but also inhibited by reduced Trx1, 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, Trx1, Grx1, and Nrx (not shown) have been reported to promote NF-κB binding to the κB site in the DNA. NF-κB, nuclear factor kappa B; Nrx, nucleoredoxin; Txnip, trx interacting protein.

doxorubicin-induced cardiac inquiry, which was accompanied by an increase in protein S-glutathionylation (155).

Trx2-deficient DT 40 cells derived from chicken undergo apoptosis mediated by cytochrome c release and subsequent caspase-9 and caspase-3 activation (759). $Trx2^{-/-}$ mouse embryos showed massively increased apoptosis at 10.5 days and died before day 12.5 along with the maturation of mitochondria. It should be noted that even embryonic fibroblasts cultured from $Trx^{-/-}$ embryos were not viable (552). WEHI7.2 thymoma cells with stable over-expression of Prx3 showed a marked resistance to hypoxia-, H_2O_2-, tert-butyl hydroperoxide-, and imexon-induced apoptosis (551). Over-expression of Prx3 also protected pancreatic β cells from apoptosis induced by pro-inflammatory cytokines or streptozotocin (820).

2. Proliferation. Both Trxs and Grxs were initially discovered as electron donors for RNR (Fig. 1), an essential enzyme for DNA synthesis and thus proliferation.

Dysregulated proliferation is one hallmark of tumor formation. Several members of the Trx family, that is, Trxs, Grxs, and Prxs, have been suggested to fulfill crucial functions during carcinogenesis, including promotion of proliferation and thereby tumor growth (see section II.B.12). This function as growth factor has been determined not only in cancer cells, but also in normal hepatocytes and lymphocytes as well as in murine fibroblasts (540, 555, 798). Proliferation of human adipose tissue-derived mesenchymal stem cells was increased by over-expression of both Trx1 and Trx2, whereas knockout of these proteins inhibited proliferation (733). However, treatment with recombinant Trx1 and high expression of Trx1 was also described to induce growth arrest in liver cells (656). Extracellular applied Trx1—alone or in concert with interleukins (ILs)—stimulated the proliferation of human B cells immortalized by the Epstein-Barr virus *via* activation of protein kinase C, indicating an important role of Trx1 not only in the permanent growth of Epstein-Barr virus-infected B cells,

but also for cell growth of Epstein-Barr virus negative cell lines (47, 63, 798). Trx1 might promote proliferation by increased expression and stimulation of different growth factors and proliferation-associated transcription factors such as ILs, FGF, ERK1/2, TNF-alpha, p53, NF-κB, AP-1, or Nrf2 (206, 480, 509, 609, 685, 733, 751, 787). Although it remains elusive whether all interactions with the listed factors are directly connected to the proliferative effect of Trx1, a crucial role of Trx1 during cell cycle progression appears likely (509).

Usually, Trx1 activity depends on the presence of TrxR1. Mouse hepatocytes lacking TrxR1 displayed normal supply of electrons to RNR to support DNA replication and normal proliferative growth, indicating that TrxR1 might be dispensable under certain conditions (649). In mouse liver lacking TrxR1, GSH was essential, indicating that the GSH- and TrxR1-dependent pathways constitute complementary systems of supporting RNR in this organ (611). The important role of GSH for the cellular proliferation was recognized decades earlier (403, 440); depletion of total GSH induced cell cycle arrest (171). GSH, when transported into the nucleus, seems to have a profound impact on cell cycle progression and gene expression; for details, see (153, 468).

Grx1 was suggested to be involved in controlling cell proliferation in mouse primary lens epithelial cells (445). Grx3-deficient mouse embryonic fibroblasts exhibited defects in cell cycle progression during late mitosis, one potential reason for early embryonic lethality of Grx3 knockout (116).

In human mammary epithelial cell lines, higher expression of Prx1 positively correlated with the proliferation rate (612). c-Abl and c-Myc were identified as interaction partners of Prx1, suggesting that Prx1 promotes proliferation *via* these important cell cycle regulating proteins (531, 810). Indeed, over-expression of Prx1 altered the transcription profile of c-Myc target genes (531). Moreover, it was proposed that phosphorylation of Prx1 by cyclin-dependent kinase 2 is an important regulatory mechanism during cell cycle progression, as the modified Prx1 was detectable during mitosis, but not during interphase (113).

Nrx inhibits activity of the Wnt/β-catenin pathway, a signaling pathway promoting proliferation. Not surprisingly, Nrx silencing accelerated proliferation (213).

3. Iron metabolism. Iron is an essential trace element that is required for a number of protein co-factors, including, for instance, heme and iron-sulfur centers. On the down side, ferrous iron in its free form is an efficient catalyst of the Fenton reaction, generating OH· radicals from H_2O_2. The reaction of OH· radicals with proteins, lipids, and nucleic acids generates other radical species that subsequently lead to peroxidation, carbonylation, or fragmentation of these biomolecules (Fig. 6). It is, therefore, not surprising that the dysregulation of iron metabolism was implied in the pathophysiology of various human diseases, including Alzheimer's disease (AD) (5, 460), Friedreich's Ataxia (570, 816), hemochromatosis (59, 94), and Parkinson's disease (PD) (60, 126).

a. Iron sulfur Grxs. Human mitochondrial Grx2 was the first Grx that was identified to complex a [FeS] cluster (433). This, in many aspects unusual Grx (active site Cys-Ser-Tyr-Cys), contains a redox inactive $[2Fe2S]^{2+}$ cluster that bridges two Grx2 molecules to form a dimeric holo Grx2 complex (Fig. 9). The [FeS]-bridged dimer lacks enzymatic activity, but degradation of the cluster and dissociation of the holo complex activated the protein. Slow degradation of the complex under aerobic conditions was efficiently prevented by GSH. GSSG promoted cluster degradation and thereby activation of Grx2 (433). The biochemical analysis of several mutants demonstrated that the iron-sulfur cluster is complexed by the two N-terminal active site thiols of two Grx2 monomers and two molecules of GSH which are bound noncovalently to the proteins and in equilibrium with GSH in solution (56). The structure of the dimeric holo Grx2 complex was solved by X-ray diffraction (Fig. 9A) (348). Astonishingly, hardly any direct molecular interactions between the two protein monomers could be identified. Besides one hydrogen bond and two small hydrophobic interactions, all molecular interactions contributing to the holo complex involve the GSH molecules. The two GSH molecules efficiently shield the iron from the solvent. Only one of the sulfur atoms of the [FeS] cluster is solvent exposed. Hence, the [2Fe2S] cluster may not be able to react with redox compounds that require direct molecular interactions with iron such as H_2O_2. Instead, degradation of the cluster in response to oxidative signals more likely occurs through the formation of GSSG (see above). Similar to human Grx2, many, if not all, monothiol Grxs (active site Cys-Gly-Phe-Ser) can form the dimeric holo [FeS] complex (Fig. 9B–D) (271, 490, 603). The properties that permit some Grxs to form the [FeS] bridged dimeric holo complex are likely due to the exchange of the active site Pro. This exchange allows a higher flexibility of the main chain in the active site area, providing enough room for the noncovalent binding of GSH and cluster coordination (181, 348). For human Grx2, a function as redox sensor of the [FeS] cluster was suggested, because redox-induced cluster decay activated the oxidoreductase (56, 433); the functions of the monothiol Grxs appear to lie primarily in iron metabolism (see below).

Another amino acid whose presence prevents metal binding in the active site of Trx family proteins is the cis-proline (743). Exchange of this prolyl residue not only in human Grx1, but also in human Trx1 resulted in a [FeS] cluster coordinating protein. Moreover, mutation of the Thr-X-X-Cys active site in a Prx, Prxs do not contain the cis-proline, to a Cys-X-X-Cys active site resulted in a [FeS] cluster coordinating protein as well.

b. Biogenesis of iron-sulfur centers. The biogenesis of iron-sulfur centers in eukaryotic cells is an essential function of mitochondria (436). Initially, iron-sulfur centers are synthesized on the scaffold protein Isu (IscU or NifU in bacteria). In the next step, these newly assembled [FeS] units are transferred to apo-proteins with the help of a DnaK- and DnaJ-type chaperone couple (437).

Knockout of mitochondrial monothiol Grx5 in yeast led to iron accumulation in the cell and inactivation of iron-sulfur center-containing enzymes (647). These defects could be suppressed by over-expression of the Hsp70/DnaK-type chaperone Ssq1 and the potential alternative [FeS] scaffold Isa2. Moreover, depletion of Grx5 led to an accumulation of iron loaded onto the scaffold protein Isu1, implying a function of Grx5 in the transfer of [FeS] clusters from the scaffold to apo-target proteins (521). A hypochromic anemia mutant of zebrafish (Shiraz) lacking Grx5 and a human sideroblastic-like microcytic anemia patient with reduced Grx5 levels provided strong evidence that this function of yeast Grx5 was conserved in vertebrate species; in both cases, impaired [FeS] cluster assembly resulted in defects in heme biosynthesis (95,

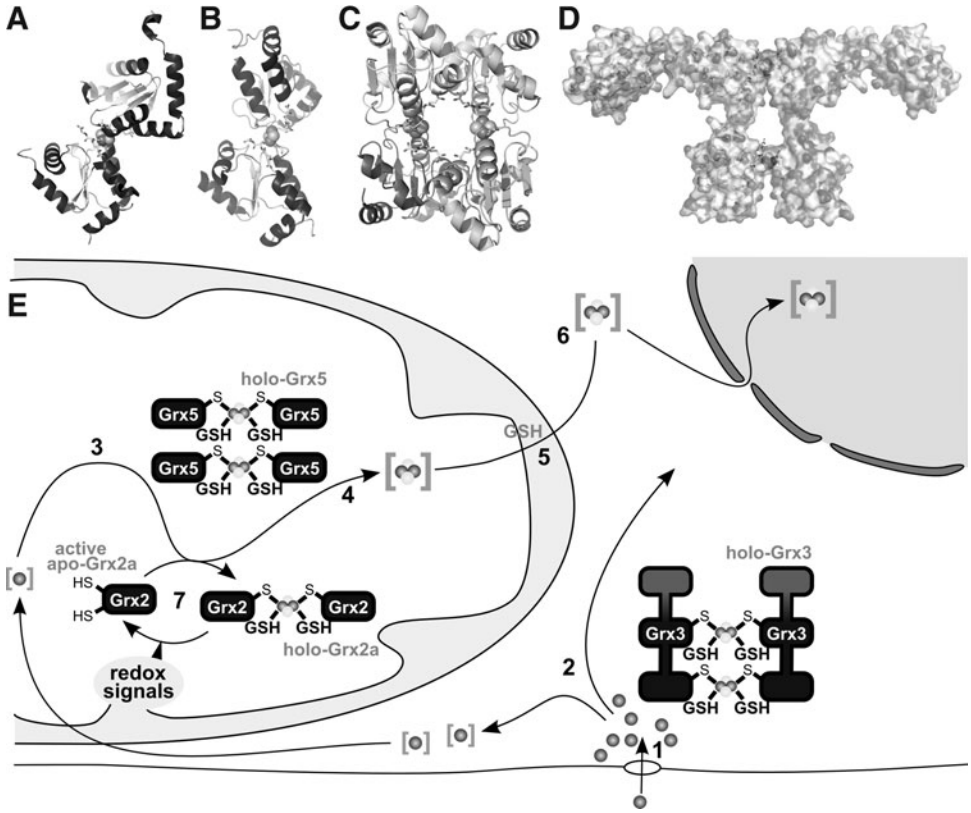


FIG. 9. [FeS]-Grxs in cellular iron metabolism. (A) Structure of the holo-Grx2 complex consisting of two monomers Grx2 (cartoon graphics), two GSH molecules (ball and stick model), and the [2Fe2S] cluster (calotte model), derived from PDB entry 2HT9 (348). **(B, C)** Structures of the holo-Grx5 complex depicted as dimer **(B)** and tetrameric holo complexes **(C)**, derived from PDB entry 2WUL (350). **(D)** Hypothetical model of the dimeric Grx3 holo complex (271). **(E)** Iron taken up into the cell, simplified in [1], is shuttled through the cytosol, presumably involving Grx3 [2]. Inside mitochondria, iron is used, for instance, for the biogenesis of iron-sulfur clusters [3] on a scaffold protein and transferred to target apo-proteins [4] in a reaction that requires Grx5. The export of iron-sulfur clusters in a hitherto unknown form requires GSH [5]. This compound X is used by the cytosolic iron-sulfur cluster assembly machinery for the synthesis of cytosolic and nuclear FeS proteins [6]. [7] Grx2 is usually present in the enzymatically inactive FeS-bridged dimeric holo form. On redox signals, the FeS cluster dissociates, yielding active monomeric Grx2.

817). The exact biochemical function of Grx5 in [FeS] center biosynthesis, however, remains to be established.

The lack of both mitochondrial Prx and mitochondrial/cytosolic dithiol Grx in yeast led to the induction the Aft1 iron regulon, despite optimal mitochondrial [FeS] biogenesis. A crosstalk between the dysfunction of mitochondrial redox homeostasis and the cytosolic iron regulation was thus suggested (486).

c. Regulation of iron metabolism. Vertebrate cells evolved a post-transcriptional regulatory mechanism for the expression of proteins involved in iron homeostasis and iron cofactor biosynthesis based on iron regulatory proteins (IRP) 1 and 2, reviewed for instance in Refs. (276, 572, 652). Loss of Grx5 in the zebrafish Shiraz mutant impaired mitochondrial [FeS] cluster assembly and promoted activation of IRP1. To some extent, knock-down of IRP1 restored hemoglobin synthesis in the Grx5 mutant, demonstrating a crosstalk between hemoglobin production and the mitochondrial [FeS] cluster assembly machinery (817) (Fig. 9E).

During exposure to nitric oxide the iron regulating function of both IRP1 and IRP2 is disrupted (161, 808). This dysregulation of ·NO-modified IRPs was restored by Trx1 *in vitro* and in cell cultures, indicating a crucial role of Trx as a modulator of IRP activity (559).

d. Intracellular iron distribution. As late as 2 years earlier, essentially nothing was known on how cells manage to passage iron safely to the various iron-dependent processes in the different subcellular compartments. Only recently, strong evidence was presented for an essential function of the cytosolic multi-domain monothiol glutaredoxins Grx3 and Grx4 in cellular iron trafficking in yeast (522). Combined depletion of Grx3 and Grx4 specifically impaired all iron-dependent reactions in the cytosol, mitochondria, and nucleus. These defects were caused by insufficient iron insertion into proteins and organelles, despite accumulation of cytosolic iron. Thus, in the absence of Grx3 and Grx4 iron, even though sufficient amounts were taken up into the cells, iron was not bioavailable. The ability of the monothiol Grxs to bind a [FeS] cluster themselves was an absolute requirement for this function (522).

B. Tissues, organ systems, and diseases

1. Development. Oxygen concentrations and ROS levels are known to affect cell fate and embryonic development. The

expression of proteins of the Trx family was also shown to be important, because protein deficiency is correlated with severe and often fatal phenotypes (Table 2). Trx1 knockout in mice was lethal due to its importance in early differentiation and morphogenesis. These mice died already at embryonic day E3.5 (474). Deletion of mitochondrial Trx2 was also lethal. Due to increased apoptosis, homozygous mice die between E10.5 and E12.5, which coincides with maturation of mitochondria (552). In contrast, Txnip, the suggested endogenous inhibitor of the Trxs, was not essential for embryonic development (856). Grx1 knockout mice were viable (301), while in zebrafish, Grx2 has an important impact on embryonic brain development. Knock-down inhibited the outgrowth of axons and leads to neuronal apoptosis and subsequent impaired formation of a functional neuronal network (75). Grx3 knockout is lethal between E12.5 and E14 (105, 116). Most likely, Grx3 deficiency induces defects in cell cycle progression during late mitosis (116). Grx3 was identified as a direct target of serum response factor, indicating that Grx3 is important during early embryonic development of cardiac tissue (865). The mitochondrial monothiol Grx5 is also important for embryonic development and essential for [FeS] cluster and heme biosynthesis (section II.A.3) (817).

Transgenic mice lacking Prx1–4 and 6 were viable, but showed signs of increased ROS levels (328, 422, 438, 545, 802). In addition, Prx1 controls motor neuron differentiation in the spinal cord of chick embryos *via* redox-dependent regulation of glycerophosphodiester phosphodiesterase 2 (GDE2) activity, a transmembrane protein that is essential for motor neuron differentiation (846).

Nrx knockout mice show skeletal and cardiovascular defects and die around birth (216). In Xenopus embryos, it was shown earlier that Nrx interacts with dishevelled to regulate both Wnt/β-catenin and Wnt/planar cell polarity pathways during embryonic development (Fig. 10) (213, 214). Wnt signaling is one of the central pathways during embryogenesis (750). In addition, Nrx also regulates *via* an interaction with Flightless-1 (Fli-1) TLR-4 signaling, another important pathway during embryogenesis (272).

The electron donors of both the Trx and Grx system, TrxR and GSH, were essential for embryonic development. Mouse embryos lacking TrxR1 died between E8.5 and E10.5 because of impaired cell proliferation or gastrulation, respectively (332). TrxR2$^{-/-}$ mice displayed a severe anemic phenotype and partial growth retardation and died between E13.5 and E15.5 (135). However, these phenotypes were less severe compared with Trx1 or Trx2 knockout mice (see above), indicating that Trx functions during embryonic development are not entirely dependent on the respective TrxR. GSH, the electron donor of Grxs, is synthesized in two steps. Mice lacking either γ-glutamylcysteine synthetase or GSH synthase died latest at E8.5 (711, 818). Lack of GSH resulted in failed gastrulation, impaired formation of the mesoderm, and death because of increased apoptosis rather than reduced cell proliferation (711), confirming earlier studies claiming crucial functions for GSH during early embryonic development (221).

2. Central nervous system.

a. Expression profile of Trxs, Grxs, Prxs, and related proteins in the CNS. Cells of the nervous system are particularly susceptible to oxidative damage due to their high oxygen consumption and metabolic activity that are accompanied by a reduced cellular regeneration capacity and the presence of redox sensitive molecules such as neurotransmitters and polyunsaturated lipids. Indicators of ROS-induced damage have been reported in the three most widespread neurodegenerative diseases, that is, PD (17, 146, 152, 684), AD (525, 620), and amyotrophic lateral sclerosis (ALS) (40, 188).

Trx family proteins are expressed in various areas of the mouse, rat, and human brain (for a more detailed comparison

Table 2. KnockOut Phenotypes of Trx Family (and Related) Proteins

Gene	*Protein*	*Embryonically lethal?*	*Phenotype(s)*	*References*
TXN1	Thioredoxin 1	Yes	Died before implantation	(474)
TXN2	Thioredoxin 2	Yes, E10.5–12.5	Massive apoptosis at the onset of respiration; open anterior neural tube	(552)
TRXR1	Thioredoxin reductase 1	Yes, E9.5–10.5	Reduced proliferation; reduced body size; cerebellar hypoplasia	(332, 552)
TRXR2	Thioredoxin reductase 2	Yes, E13.5–15.5	Reduced in size; anemic; reduced hematopoiesis; thinning of the ventricular myocardium, septum, and trabeculae; pleiomorphic and spongiform liver	(135, 298)
TXNIP	Thioredoxin interacting protein	No	Hypoglycemic; hypoinsulinemic; defects in the glucose metabolism of hepatocytes	(856)
NXN	Nucleoredoxin	No	Skeletal and cardiovascular defects	(216)
GLRX1	Glutaredoxin 1	No	No obvious phenotype	(301)
GLRX2	Glutaredoxin 2	No	Mouse—unpublished; loss of neurons and axonal scaffolds in zebrafish embryos	(75, 826)
GLRX3	Glutaredoxin 3	Yes, E12.5–E14.5	Reduced body size; hemorrhage in the brain	(105)
GLRX5	Glutaredoxin 5	(Yes in *D. rerio*)	Anemia; iron overload	(817)
PRDX1	Peroxiredoxin 1	No	Hemolytic anemia at 9 months; more oxidative damage; more malignant tumors	(393)
PRDX2	Peroxiredoxin 2	No	Splenomegaly; abnormal erythrocyte morphology	(369)
PRDX3	Peroxiredoxin 3	No	Reduced body weight	(438)
PRDX4	Peroxiredoxin 4	No	Atrophic testes; otherwise, no obvious phenotypes	(328)
PRDX6	Peroxiredoxin 6	No	No obvious phenotype	(802)

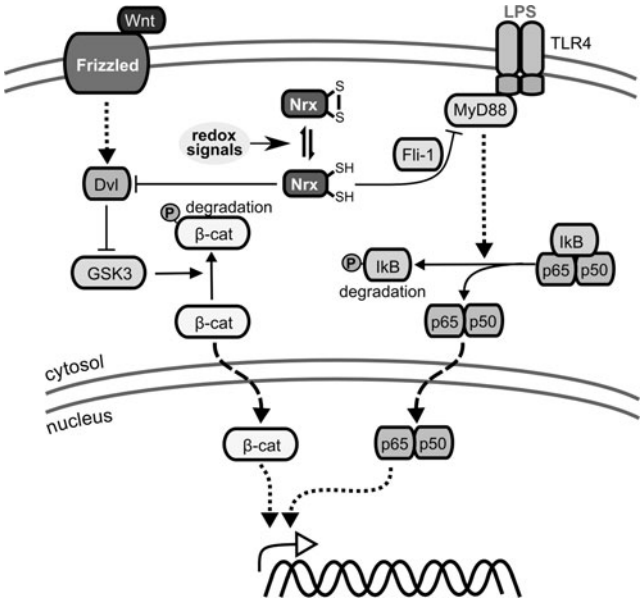


FIG. 10. Nrx in Wnt/Dvl and Toll-like receptor 4 (TLR4) signaling. Nrx was shown to suppress the Wnt/β-catenin pathway, which is involved in embryonic development and cancer. Secreted Wnt proteins bind to receptors of the Frizzled family and activate a signaling cascade. This process involves the cytosolic dishevelled (Dvl) protein, which inhibits the glycogen synthase kinase-3 (GSK3)-containing destruction apparatus and thereby phosphorylation and degradation of beta-catenin (β-cat). β-cat translocates into the nucleus and activates the transcription of Wnt-regulated target genes. Reduced Nrx binds to Dvl and suppresses Wnt/β-catenin signaling, whereas *via* "redox signals" oxidized Nrx does not. Similarly, reduced Nrx can inhibit TLR4 signaling, which is essential for embryonic development and the innate immune response. Lipopolysaccharide (LPS) stimulates the oligomerization of TLR4, inducing the recruitment of signal transduction adaptor proteins, such as myeloid differentiation primary response protein (MyD88). MyD88 activates a cascade of IKK and MAP kinases, leading to the phosphorylation and degradation of the inhibitor protein IκB, translocation of NF-κB (comprising subunits p65 and p50) into the nucleus, and activation of target genes. Reduced Nrx binds to Flightless-1 (Fli-1), forming an inhibitory complex with Myd88, suppressing TLR4-signaling.

of the expression patterns, see Table 3). With certain exceptions, for instance the mouse striatum, the redox proteins seem to be ubiquitously expressed in the murine and human brain. Certain redox proteins show strong nuclear staining in different brain regions, as described for Trx1, Grx1, Grx3, and Nrx in the mouse. Other proteins such as Prx2, Prx3, and, most notably, Prx6 show a typical astroglial staining in different areas of the brain (26, 143, 235). Prx1 was reported to be localized in glial cells of several human brain regions, whereas in neurons, it was essentially not present (678). The same study described a reciprocal staining pattern for Prx2, which was exclusively expressed in neurons but not in glia. Mizusawa *et al.* identified the localization of Prx1 to be restricted to oligodendroglia and Schwann cells, whereas most neurons appeared to be negative (508). In an earlier study, Prx1 immunoreactivity was detected in oligodendrocytes in several regions of the brain (347). Prx2 is highly expressed in the hippocampus and cerebral cortex of rats and humans (26, 143) and was previously reported to be present in NeuN-positive cells in the CA3 region of the hippocampus and thalamus, as well as in neurons of the gray matter in the hippocampus, cerebral cortex, and thalamus of the mouse (347). In the mouse CNS, Trx2 was specifically detected in axonal fibers in the cerebral cortex, striatum, and white matters of the cerebellum and spinal cord, in contrast to the functional-related protein TrxR2, which was present in the cell bodies (235). This observation may imply more specific functions of Trx2 independently of its reductase, for instance, in mitochondria that are distributed along axons. Using *in situ* hybridization, Lippoldt *et al.* demonstrated transcription of Trx1 in neurons of the cerebral cortex, the piriform cortex, the medial preoptic area, the CA3/CA4 region of the hippocampal formation, the dentate gyrus, the paraventricular nucleus of the hypothalamus, the arcuate nucleus, the substantia nigra pars compacta, the locus coeruleus, the ependyma of the 4th ventricle, and the epithelial cells of the choroid plexus (441).

Padilla *et al.* reported the immunolocalization of Trx1 and Grx1 in the hypophysis (563). Trx1 and Grx1 were prominently detected in the folliculo-stellatae cells of the adenohypophysis, while only a minor proportion of the glandular cells were stained. In the pituicytes and the clusters of synaptic terminals of the neurohypophysis, Trx1 was intensely stained. Grx1 immunoreactivity, in contrast, was detected in the neurosecretory terminals and Herring bodies.

In the dopaminergic neurons of the substantia nigra from mouse and rat, strong immunoreactivities were reported for Trx1, Trx2, Grx1, and Grx2 (26, 235). Using confocal microscopy, co-localization of these proteins with the specific marker tyrosine hydroxylase (TH) was demonstrated (Godoy and Lillig, unpublished data). The most notable observation was the high correlation between Grx2 and the cytosolic-localized TH, pointing out the presence of a cytosolic isoform of Grx2 in these neurons, likely Grx2c. By *in situ* hybridization and immunofluorescence, Grx2 was identified in both neurons and glia cells of mouse brain and co-localized with TH in the substantia nigra as well (371).

In the Purkinje cells as well as in different layers of the cerebellum, Trx1, TrxR2, and Prx1 were strongly detected (26, 143, 235).

Some of the Trx-related redox proteins were detected in areas of the central nervous system where active secretion takes place. In the plexus coroideus of the mouse, Grx3, Prx3, Prx5, Nrx, and Trx1 were notably expressed. Trx1 and Nrx are also strongly expressed in the ependymal cells of the cerebral ventricles (235). Active secretion of Trx1 was reported for a variety of cells (655), and increased Trx1 plasma levels have been detected in many diseases (342, 363, 542, 543). The putative presence of Trx1 in the cerebrospinal fluid might contribute to the defense of the central nervous system.

Trx1, Prx1, and Prx5 were strongly expressed in the motor neurons of the mouse and rat spinal cord (26, 235). In the mouse spinal cord, some of the proteins (*i.e.*, Grx1, Prx3, and Nrx) were abundantly present in both the gray and the white matter; whereas other, such as Trx2, showed a clear regional distribution, being most notably expressed in the white matter (235). Prx2 was detected in the cytoplasm, proximal dendrites, and nuclei of anterior horn neurons of human, rats, and mice (374).

Table 3. Distribution and Expression Pattern of Trx Family Proteins in the Mouse, Rat, and Human Brain

	Tissue or cell type																						
													Cerebellum										
	Hippocampus			*Substantia nigra*			*Striatum*			*Cerebral cortex*			*Purkinje cells*			*Granular layer*			*Mol. layer*			*Plexus coroideus*	
Protein / *Species*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*	*H*	*M*	*R*
Trx1	+*	+	+[a]	+*	++	n.a.	−	+	n.a.	+	++	+	++*	++	−	++	+	−	++	++	−	++*	n.a.
TrxR1	+	+	++[a]	−	+	n.a.	−	+	n.a.	+	+	++	+	+	++	+	+	+	+	+	++	+	n.a.
TrxR1-v3	n.a.	n.a.	++[a]	n.a.	n.a	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	++*	n.a.	n.a.	++	n.a.	n.a.	+*	n.a.	n.a.	++	n.a.	n.a.
Trx2	+	+	+[a]	+	++	n.a.	+[x]	++	n.a.	+[x]	+	+*	+	+	+	+	+	−	+	+	+	+	n.a.
TrxR2	+	+	+	+	+	n.a.	−	+	n.a.	+	+	−	++	++[d]	+	+	+	+	++	++	+	+	n.a.
Txnip	n.a	+	n.a	n.a.	+	n.a.	n.a.	+	n.a.	n.a.	+	n.a	n.a.	+	n.a	n.a.	+	n.a.	n.a.	+	n.a.	n.a.	n.a.
Nrx	+*	n.a.	n.a	+[*x]	n.a	n.a.	−	n.a.	n.a.	++*	n.a.	n.a.	+*	n.a.	n.a.	++	n.a.	n.a.	++	n.a.	n.a.	++	n.a.
Grx1	++*	++[a]	n.a	++*	+	n.a.	−	+	n.a.	++*	++	n.a	+*	+*	n.a	+	+	n.a.	+	+	n.a.	+	n.a.
Grx2	++	+	n.a	+	++	n.a.	−	++	n.a.	++	+	n.a	+	+*	n.a	+	+	n.a.	+	+	n.a.	+	n.a.
Grx3	+*	+	n.a	++[*x]	+	n.a.	+[x]	++	n.a.	+*	+	n.a	+*	+	n.a	+	+	n.a.	+	+	n.a.	++*	n.a.
Grx5	+	+	n.a	+	++	n.a.	−	++	n.a.	+	+	n.a	+	+	n.a	+	+	n.a.	+	+	n.a.	+	n.a.
γGCS	+	+	+[a]	+	+	n.a.	−	+	n.a.	+	+	+	−	+	+	−	+	+	−	+	+	−	n.a.
GR	n.a.	n.a.	+[a]	n.a.	n.a	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	n.a.	n.a.	+	n.a.	n.a.	+*	n.a.	n.a.	++*	n.a.	n.a.
Prx1	+	+	+[a]	+	+	n.a.	−	+	n.a.	+	++	+	++*	+	−	+	+	+*	+	++	+*	+	n.a.
Prx2	−	++[a]	++[a]	+	++	n.a.	−	+	n.a.	+	++	++[n]	−	++	++*	+	+	+*	+	++	++*	+	n.a.
Prx3	+[a]	+	++[a]	+	+	n.a.	+[a]	+	n.a.	+[a]	++	++	+	+	+	+	+	+	+	++	+	++*	n.a.
Prx4	−	++	+	+	++	n.a.	−	+	n.a.	+	++	+	−	+	+	−	+	+	−	++	+	−	n.a.
Prx5	+	++	+	+	++	n.a.	−	+	n.a.	+	+	++	+	+	+	+	+	+	++	+	+	++*	n.a.
Prx6	+[a]	++[a]	++[a]	−[x]	++	n.a.	+[a]	++[a]	n.a.	+[a]	++[a]	++*	−	+	+*	+	+	+	+	+	++*	+	n.a.

Immunohistochemistry data adapted from Godoy *et al.* 2011 (mouse) (235), Aon-Bertolino *et al.* 2011 (rat) (26), and Dammeyer and Arnér 2011 (human) (143).

M, mouse; R, rat; H, human; −, absent, not detected; +, present, weak expressed; ++, strong expressed; n.a., not analyzed; a, glial staining; *, strong nuclear staining; x, axonal staining; n, neurofilaments; d, dendrites; Grx, glutaredoxin; GR, glutathione reductase; Nrx, nucleoredoxin; Prx, peroxiredoxin.

b. Trxs, Grxs, Prxs, and pathologies of the CNS. In this section, we summarized the role of Trx family members in cellular and animal models, as well as in patients suffering, from AD, PD, ALS, ischemia/stroke (see also section II.B.11 for details on hypoxic insults), and neuroinflammation.

Amyloid β treatment, a common model for AD, led to oxidation of Trx1 in the neuroblastoma cell line SH-SY5Y (16). Over-expression of Trx1 protected SH-SY5Y cells as well as rat primary hippocampal neurons against amyloid β-induced cell death (16, 450). Trx1 expression was suppressed in a rat pheochromocytoma cell line (PC12) after treatment with 1-methyl-4-phenylpyridinium (MPP^+), an active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes Parkinsonism (36). Over-expression of Trx1 attenuated MPP^+-induced neurotoxicity of PC12 cells (36). Trx1 is also induced after cerebral ischemia induced by middle cerebral artery occlusion (399), and mice over-expressing Trx1 showed attenuation of apoptosis and thereby neuroprotection after both permanent and transient focal ischemia (752, 868). Infarct volume and neurological deficits after transient focal ischemia were also ameliorated by an intravenous injection of recombinant human Trx1 in mice (269). In patients, during amnestic mild cognitive impairment, a transition stage between normal aging and AD, as well as in several regions of Alzheimer's brains, Trx1 protein levels were markedly decreased (16, 159, 450). In contrast, Cumming *et al.* reported no significant differences in Trx levels between control and AD patients (138). Trx1 levels were elevated in diseases associated with neuroinflammation, for example, in cerebrospinal fluid and blood of multiple sclerosis patients (592), and in spinal cords of ALS patients (462).

Although mitochondrial integrity is crucial for the progression of most of the neurological diseases, almost nothing is known about the role of the mitochondrial Trx2, except for the finding that Trx2 levels increased in hippocampus of gerbils after ischemia reperfusion (316). The electron donor of Trx2, TrxR2, is not essential for the development of the central nervous system. Mice lacking TrxR2 specifically in the nervous system developed normally, whereas nervous system-specific deletion of TrxR1 displayed massive malformation of the hippocampus and cerebellum, resulting in ataxia and tremor (724). Treatment of rat primary hippocampal neurons with TrxR1 attenuated amyloid β-mediated toxicity (450). In Alzheimer's patients, TrxR1 activity was generally enhanced compared with controls (450), whereas TrxR1 levels in the cerebrospinal fluid and blood of multiple sclerosis patients were decreased (592). Moreover, single-nucleotide polymorphisms of the TRNRD1 gene were significantly associated with familial ALS (503).

Amyloid β treatment of SH-SY5Y cells led to the oxidized of both Trx1 and Grx1. Over-expression of Grx1 protected SH-SY5Y cells against amyloid β-induced cell death (16). Several proteins have been described to be involved in PD development and progression. The expression of one of these proteins, DJ-1 (137), correlates with the expression of Grx1 (665). In a mouse model for PD based on MPTP toxicity, loss of dopaminergic neurons was associated with inactivation of mitochondrial complex I, a hallmark of the disease. Recovery of complex I activity correlated with an increase of Grx activity after MPTP treatment (376). Although knockout of both Grx1 and Grx2 inhibited this recovery (371, 376), over-expression of Grx2 diminished MPTP-nduced neuronal apoptosis *via* decreased complex I activity (371, 419). Aggregation of mutant SOD1 has been proposed as one reason for the degeneration of motoneurons during ALS. Over-expression of both Grx1 and Grx2 in immortalized motoneurons increased solubility of mutant SOD1, but only Grx2 protected against subsequent apoptosis (191). After induction of focal ischemia in rat brains, Grx1 levels decreased parallel to the rate of neuronal damage (752). In Alzheimer's brain tissue, Grx1 was up-regulated in healthy neurons of the hippocampus and the frontal cortex, but down-regulated in degenerating neurons (16).

De-/glutathionylation, specifically catalyzed by Grxs (see also section I.C.3), is associated with several aspects of neurodegeneration, such as apoptosis, mitochondrial function, and plaque formation, summarized for instance in (661). Several studies demonstrated the important role of GSH in pathologies of the central nervous system. Amyloid β treatment of SH-SY5Y cells decreased the total cellular GSH amount (16). In the substantia nigra of Parkinson patients, not only total GSH levels were decreased, but also GSH was virtually absent. This loss of GSH is one of the first signs of the disease (597, 598). Knock-down of GSH synthesis in PC12 cells, rat dopaminergic N27 cells, as well as in mice by catecholaminergic neuron-specific down-regulation of γ-glutamyl cysteine ligase, the rate-limiting enzyme in the *de novo* GSH synthesis, resulted in inhibition of complex I activity (127, 305, 340, 419). These data highlight the importance of the GSH/Grx system in the maintenance of mitochondrial function in the early onset of PD.

In amyloid β-resistant clones of the PC12 cell line, Prxs1, 2, and 6 expression was significantly increased. PC12 cells and primary neurons over-expressing Prx1 exhibited attenuated amyloid β and MPP^+/MPTP toxicity (138, 615). Treatment with 6-hydroxydopamine (6-OHDA) led to an oxidation of Prx1. Increased levels of Prx1 as well as Prx2 protected dopaminergic cells both *in vitro* and *in vivo* against 6-OHDA-induced apoptosis, whereas silencing of Prx1 sensitized the cells (315, 423). In addition, elevated Prx2 levels protected against amyloid β toxicity in a transgenic mouse model for AD (847). In whole brain samples, the expression levels of Prx1 and Prx2 were elevated in Alzheimer's patients (138, 381). Two other studies, however, could not confirm a higher Prx1 expression in Alzheimer's brains (406, 746). Prx2 levels were also increased in the hippocampus and the frontal cortex of AD patients (746), in substantia nigra of PD patients (44), and in motor neurons during ALS (374). Prx3 expression was decreased in the brains of Alzheimer's patients and in the motor neurons of ALS patients (381, 391). In addition, Prx4 was down-regulated in motor neurons during ALS (391). Prx6 was up-regulated in astrocytes of AD patients and familial ALS (608, 741). In PD patients, peroxidase activity of Prx2 was inhibited by S-nitrosylation (174) and phosphorylation (615). The redox states of Prx2 and Prx6 were more oxidized in the brains and serum of Alzheimer's patients (138, 853). In circulating endothelial progenitor cells of ischemia stroke patients, Prx1 was tenfold higher expressed than in healthy controls (76). Prx2, in rat brains down-regulated after cerebral ischemia (399), protected against stroke-related insults, such as ischemia and glutamate treatment *in vitro* and *in vivo* (70, 624). Prx3 was increased in the hippocampus of gerbils after cerebral ischemia reperfusion and protected against ischemic damage (316). Inflammation is known to be a characteristic for several neurological diseases such as multiple sclerosis, ALS,

and PD. Thus, the protection of Prx2 against neuroinflammation *via* suppression of pro-inflammatory signaling pathways in microglia (556) may be become helpful to combat these diseases. Based on the importance of the Trx family proteins in other inflammatory processes (see section II.B.8), it is likely that more of these proteins may protect against neuroinflammation.

3. Sensory organs.

a. Expression profile of Trx-related proteins in sensory organs. Sensory organs are directly exposed to various sources of ROS. In this section, we will discuss expression patterns and pathological implications of Trx family proteins in different sensory organs, with emphasis on the eye, which has been the most intensively studied so far. The ear, tongue, and olfactory part of the nose have up to now only been sparsely investigated with regard to the Trx, Grx, and Prx systems.

Both Trx1 and Grx1 were detected after E13.5 in the mouse lens and retina (396). Trx1 and TrxR1 expression was also demonstrated in neurons and photoreceptor cells in the developing rat retina (259). In adult rats, Trx1 was detected in the outer and inner plexiform layers with especially strong expression in the ganglionar cell layer but only faint staining in the photoreceptors. In contrast, TrxR1 was primarily observed in the photoreceptors (26). In the same study, no or only weak immunoreactivities were detected for Grx2 and Grx3 in photoreceptor cells. In the mouse eye, with the exception of γGCS, Trx family proteins were abundantly expressed in the corneal epithelium and stroma, the lens, ciliary body, retina, and the underlying pigmented epithelium (235) (Fig. 11A). In the retina, the layer of rods and cones showed clear differences in the localization of certain Trx-related proteins. The inner segment of the photoreceptors is rich in mitochondria and was intensely stained for Grx1, Grx5, Prx5, Trx2, and TrxR2. TrxR2 also displayed the strongest immunoreactivity in the outer photoreceptor segment (235). An eye-specific Trx-like protein, the rod-derived cone viability factor (RDCVF or Nrx-like protein 1, Nxnl1, see Table 1), was detected in photoreceptor outer segments and the interphotoreceptor matrix (428). The outermost layer of the retina, the retinal pigmented epithelium, functions in photoreceptor nourishment and contributes to the formation of the blood-retinal barrier (162). Several Trx-related proteins have been detected in this epithelium, with the strongest staining detected for Nrx (Fig. 11A). However, the high content of melanin in these cells makes qualitative analyses of immunoreactivities generally difficult.

Several Trx family proteins were detected in the mouse lens and cornea; Grx5 immunoreactivity was the strongest of all analyzed proteins in the lens fibers (Fig. 11A) (235).

Most Trxs, Grxs, and Prxs have been observed in the stratified squamous epithelium of the mouse tongue and the underlying skeletal muscles (235). Grx1 was also detected in the calf tongue by immunohistochemistry (653).

The olfactory epithelium of the developing mouse was intensely stained for Trx1 and Grx1 at E13.5 (396). With the exception of Prx2, proteins of the Trx family were abundantly distributed in both the olfactory and the respiratory epithelium of the mouse nose. An apparently nuclear staining was described for Trx1, Prx1, and Prx6 but only in the outermost cell layer of this epithelium (Fig. 11A). Protein expression of Prx3 and Trx1 appeared very strong in ganglion cells, whereas Prx4 and Prx6 were prominently stained in olfactory nerve bundles (Fig. 11A) (235). Immunoreactivities for both Trx1 and TrxR1 were seen in epithelial cells, glands, and vascular endothelium of human nasal mucosa and nasal polyps (421).

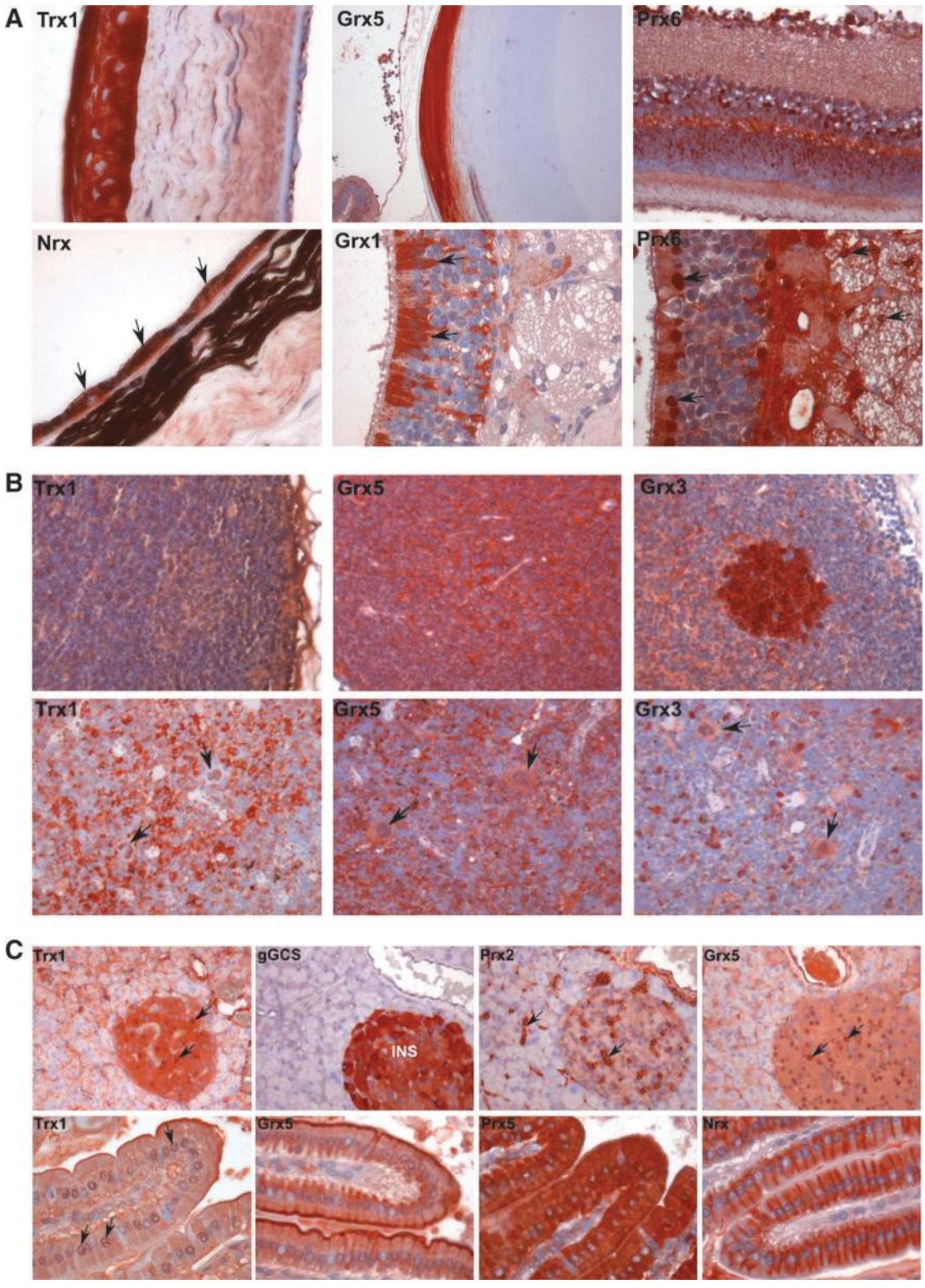
In the cochlea of guinea pigs, TrxR1 was expressed in the inner and outer hair cells of the organ of Corti as well as in the lateral wall and the neurons of spiral ganglion (275).

b. Pathologies of the eye. The next section focuses on the role of Trxs, Grxs, and Prxs in pathological features that are common for several diseases of the eye, for example, glaucoma, age-related macular degeneration (AMD), retinopathy, and cataract. Glaucoma is one of the leading causes of blindness in the world that is connected to selective death of retinal ganglion cells. The disease is characterized by an elevation in intraocular pressure (IOP), which leads to increased levels of glutamate and pro-inflammatory cytokines and subsequently to deleterious formation of ROS (771). Diabetic retinopathy and AMD are associated with hypertension-induced oxidative stress and inflammation, causing loss of vision (360, 448). Formation of cataracts, opaque areas of the

FIG. 11. Expression pattern of selected members of the Trx family in various organs of the mouse. (A) Sensory organs. *Upper panel:* In the mouse eye, Trx1 is highly expressed in the corneal epithelium; Grx5 is intensely stained the lens fibers. Prx6 immunoreactivities were detected in several layers of the retina (from the bottom up: layer of rods and cones, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, and ganglionar cells). *Lower panel:* Despite the high melanin content in the retinal pigmented epithelium, Nrx staining in this layer is evident (*arrows*). Grx1 and Prx6 were abundantly detected in the olfactory epithelium of the nose (*arrows*). Prx6 showed intense nuclear staining patterns in the outermost layer of the olfactory epithelium and also appeared distributed in the olfactory nerve bundles (*arrows*). **(B)** Lymph nodes and spleen. *Upper panel:* In contrast to the other members of the Trx family, which appear to be uniformly expressed in the lymph nodes (Trx1 was weakly expressed, and Grx5 particular strongly expressed), Grx3 yielded a strong immunoreactivity that was concentrated in the germinal centers. *Lower panel:* Trx1, Grx5, and Grx3 immunoreactivity suggests nuclear localization in the megakaryocytes of the mouse spleen (*arrows*). **(C)** Pancreas and duodenum. Trx1 and Grx5 show intense nuclear staining in the islets cells (*arrows*). Prx2 was abundantly detected in intercellular spaces of both endocrine and exocrine components of the mouse pancreas (*arrows*). In contrast to other tissues, where γGCS was weakly detected, the islets of Langerhans show intense immunoreactivities. Note that this enzyme is absent from the exocrine part of the pancreas. In the duodenal epithelium, Trx family proteins show a high variability in the compartmentalization. Trx1 and Prx5 appear homogenously distributed within the cells, Whereas Grx5 and Nrx immunoreactivities seem to be concentrated in specific areas of the cells, that is, the apical pole for Grx5 and the lateral sides for Nrx. As in the pancreas, Trx1 also shows a consistent nuclear staining pattern in the duodenal epithelium (*arrows*). All pictures are derived from the freely accessible redox atlas of the mouse (www.lillig.de/redoxatlas). INS, islets of Langerhans.

lens, is mainly based on oxidative stress that is induced by intrinsic factors such as hypertension, or by extrinsic factors such as UV light exposure (782).

In the retina of albino rats, as well as in mice exposed to cell-damaging high light, Trx1 and TrxR1 were increased (762, 764). In line, Trx1 expression and activity were increased in the lens of a mouse model for human cataract after the induction of photochemical oxidative stress (630). Over-expression of Trx1 in mice, as well as an intravitreous injection of recombinant human Trx1, suppressed the reduction of photoreceptors and the apoptosis induced by high light exposure in mice retina (401, 763). Trx1 was down-regulated



after IOP in a rat glaucoma model. Consistently, over-expression of Trx1 attenuated cell death after IOP (526). Administration of N-methyl-D-aspartate (NMDA) to mammalian eyes stimulated glutamate receptors and induced retinal damage, mimicking retinal ischemia and glaucoma (717). An intravitreous injection of Trx1 effectively attenuated NMDA-induced retinal cell damage (323). An NMDA injection into the rat retina increased the levels of Txnip, the proposed Trx1 antagonist, which may contribute to inflammation and subsequent apoptosis (19). Moreover, decreased levels of Txnip attenuated early signs of diabetic retinopathy (595), and Txnip expression levels increased after IOP (528). Over-expression of Trx2 in the retina and the optic nerve attenuated degeneration after intra-ocular pressure (526, 527).

The absence of Grx1 worsened cataract morphology in mouse lens after exposure to ultraviolet radiation (409, 493). Knockout of Grx1 in rat Müller cells exposed to hyperglycemia increased the pro-inflammatory response. Corroboratively, over-expression showed the opposite effect. Grx1 may, thus, be important for the protection against diabetic retinopathy by regulating both autocrine and paracrine pro-inflammatory responses (704, 705). In general, knockout of Grx1 (445) and Grx2 (826, 827) in human lens epithel cells increased oxidative stress-induced apoptosis; over-expression of Grx2 protected the cells (185, 827).

GSH was implied in several pathologies of the eye. GSH levels were decreased in the retina of mice exposed to damaging light (764), in rats with glaucoma (514), and both decreased and oxidized in the cataractous lens (107). Plasma and whole blood of patients with AMD displayed reduced levels of the total GSH pool and an increase of the GSH/GSSG redox potential (136, 674); GSH treatment of cultured retinal endothelial cells protected against oxidative damage (91).

In patients with diabetic retinopathy (see also section II.B.9.a), Prx1 was increased in the vitreous (219). Nipradilol and timolol, two drugs used in glaucoma therapy, induced the expression of Prx2, thereby protecting cells of the tabecular meshwork, the tissue surrounding the base of the cornea, against H_2O_2-induced apoptosis (506). Prx3 was induced in human and mouse lens cells after treatment with H_2O_2 (420). Over-expression of Prx5 in *Xenopus* embryos reduced alcohol-induced eye malformation, indicating that Prx5 might be involved in protection against alcohol-induced fetal ocular injury (590). Over-expression of Prx6 attenuated hypoxia-induced retinal ganglion cell death (784), and treatment of retinal ganglion cells with Prx6 decreased glutamate and TNF-α induced cell death (177). In primary human cells of the tabecular meshwork, Prx6 levels were enhanced in glaucoma patients with increased signs of inflammation (178). Prx6 levels were 10-fold decreased in cataractous lenses of rats and mice (410). In addition, in patients, a negative correlation between severity of cataracts and Prx6 expression was reported (266, 567). Prx6-deficient lens epithelial cells were sensitized to apoptotic cell death that was induced by UV-B exposure, a major cause of the development of cataracts (411). Over-expression of Prx6 delayed development of cataracts in rat and mouse lenses (410).

c. Pathologies related to tongue, olfactory system, and ear. Trx1 was significantly increased in tongue squamous cell carcinoma tissue (773, 871). TrxR1, as well as Prx1 and Prx6 levels were also elevated in this type of malignancy (306, 842, 871). For more details on Trx-fold proteins in cancer, see section II.B.12.a.

No significant change of expression of Trx1 and TrxR1 was detected in nasal polyps compared with normal human nasal mucosa (421), whereas Grx1 was reported to be over-expressed in nasal polyps, that is, in the surface epithelial cells and the submucosal glandular cells (823). Levels of Trx1 were positively correlated with the respiratory disturbance in patients with obstructive sleep apnea. After nasal continuous positive airway pressure therapy, Trx1 levels significantly decreased (754).

Several anticancer drugs induce ototoxicity. Cisplatin is strongly ototoxic to cochlea hair cells in a guinea pig model, likely by targeting TrxR1 (275). In these cochlea hair cells, ototoxicity is induced not only by cisplatin, but also by gentamicin. The toxicity was increased after depletion of Prx3 (128). Ménière's disease is characterized by fluctuating hearing loss and tinnitus. In patients with this disease, decreased levels of Trx1 and the GSH/GSSG ratio were reported (93). In families with sensorineural autosomal-recessive non-syndromic hearing impairment, a splice-site mutation was found, which leads to an impaired expression of the GRXCR1 gene (see Table 1) and that resulted in a protein with partial or complete loss of its Grx domain (686). Interestingly, a mutation in the same gene region was determined as a reason for hearing loss in the pirouette mouse mutant (557).

4. Cardiovascular system.

a. Expression pattern of Trxs, Grxs, and Prxs in cardiovascular tissue. In 1978, Trx1 was detected in hearts and erythrocytes from a calf by a radioimmunoassay (292). Seven years later, both Trx1 and TrxR1 were detected by immunohistochemistry in the cytosol of epithelial cells in adult rats (654). More recently, investigations revealed that as early as embryonic day E8.5, Trx1 and Grx1 are detectable in the heart and great vessels of the mouse embryo, whereas most tissues were still negative for these proteins. The myocardium and the wall of great vessels showed strong immunoreactivities for Trx1 and Grx1 and remained positive until adulthood (396). Recently, several members of the Trx family have been detected in the adult mouse and human heart (143, 235). In the mouse cardiomyocytes, Trx1 and Grx3 showed a typical nuclear staining pattern, whereas Prx2 and TrxR2 were localized in the intercellular space of cardiomyocytes, most probably in the connective tissue (235). In the human heart, this expression pattern of TrxR2 was not confirmed. The mitochondrial reductase, as well as Prx1, was the only redox protein out of the 14 proteins analyzed as being absent from heart muscle cells (143).

b. Trxs, Grxs, and Prxs in pathologies of the cardiovascular system. The anti-apoptotic functions of Trx1 (see section II.A.1) are related to its role in protecting cardiac tissue against ischemia/reperfusion injury (see section II.B.11). This function is inhibited by nitration of Trx1 (769) as detected in diabetic (849) and aged hearts (864). In contrast, S-nitrosylation of Trx1 increases protective effects (767). Since Trx1 knockout is embryonically lethal for mice (see section II.B.1), the group of Sadoshima decreased the activity of Trx1 in mice *via* expression of a dominant negative form of Trx1 in the cardiovascular system (838). These mice displayed cardiac hypertrophy, a risk factor for sudden death caused by heart failure, already

without induction of this disease. In contrast, mice with cardiac-specific over-expression of wildtype Trx1 were protected against hypertrophy. Recently, the same group described that Trx1 modulates cardiac hypertrophy *via* up-regulation of miR98 transcription, which down-regulates cyclin D2, an essential mediator of angiotensin II-induced cardiac hypertophy (845). Trx1 activity potentially depends on the presence of the endogenous inhibitor Txnip. Not surprisingly, modulation of Txnip has opposite effects on the development of cardiac hypertrophy as described for Trx1 (856, 857), although Txnip-dependent regulation of cardiac hypertrophy is not only related to Trx1 inhibition (856). Besides attenuated cardiac hypertrophy, Txnip knockout mice display reduced infarct size after reversible coronary ligation (855, 856). Interestingly, a recent genetic study revealed that individuals carrying polymorphisms up-regulating Txnip expression show increased susceptibility to hypertension (190). After infarction, Trx1 is important for neovascularization, as seen not only in over-expressing mice (6), but also in infarcted myocardium in diabetic rat hearts in which Trx1 was increased *via* intramyocardial administration of an adenoviral vector encoding for Trx1 (675). This Trx1 gene delivery also protected rats against cardiac failures associated with hypertension (400). Over-expression of human Trx1 in mouse hearts conferred protection against doxorubicin-induced cardiotoxicity (707). It is important to mention that doxorubicin (Adriamycin) is one of the most effective drugs in the treatment of several types of cancers; however, its therapeutic use is limited due to its high cardiotoxicity (873). Moreover, Trx1 prevented damage of cardiac tissue *via* inhibition of pro-inflammatory cytokine expression, adhesion of neutrophils (see also section II.B.8), and subsequent inflammatory injury of hearts occurring in response to ischemia/reperfusion (166). In addition, severity of myocarditis, an inflammation of the heart most likely due to virus infection (395), is correlated to Trx1. In mouse models and patients, Trx1 was up-regulated in the acute stage (505, 708) and enhanced in plasma in more severe forms of myocarditis, respectively (129, 546). Temocapril treatment of rats in the beginning of experimental autoimmune myocarditis ameliorated the severity *via* up-regulation of Trx1 in the acute phase (858). As described earlier, increased levels of Trx1 protect against several pathological conditions in the cardiovascular system. Even though Trx1 was down-regulated after ischemia/reperfusion in isolated rat hearts, it is up-regulated in adapted hearts after ischemic preconditioning (IPC) (786) (see also section II.B.11), potentially explaining the protective effects of this powerful technique for cardioprotection (166, 530). In line with this aspect, it is not surprising that treatment with human recombinant Trx1 attenuated several pathological processes affecting the cardiovascular system. It attenuated cardiac hypertrophy in aged mice (9), reduced infarct size after reperfusion in mice and rats (768, 829), lowered inflammatory cell infiltration in rats (829), diminished severity of myocarditis (442), and protected against reperfusion-induced arrhythmias in isolated rat hearts (27). Recent studies related the protective effect against arrhythmias with Trx1-dependent regulation of expression of ventricular K^+ channels (429, 444, 760). Trx1 levels in blood and serum of patients with dilated cardiomyopathy, acute coronary syndrome, or chronic heart failure were higher compared with controls, which correlated to the severity of the diseases (335, 392).

Surprisingly, knockout of TrxR1 had no effect on heart formation. TrxR1 seemed to be essential for development of most tissues, except for the heart, as heart-specific deletion of TrxR1 resulted in normally developed and viable mice (332). However, cardiac-specific knockout of mitochondrial TrxR2 resulted in embryonic lethality due to dilated cardiomyopathy and congestive heart failure (135). Moreover, knockout of TrxR2 attenuated myocardial protection after ischemia/reperfusion (298). Recently, it was described that mutations in the TXNRD2 gene may correlate with dilated cardiomyopathy in patients. The resulting proteins were not able to restore TrxR2 function in mouse fibroblasts lacking TrxR2 (713).

Although the role of Trx1 in cardiovascular pathology has been extensively investigated, only little is known about mitochondrial Trx2. Mice over-expressing Trx2 were protected against angiotensin II-induced cardiac hypertrophy and hypertension (814), generated less arteriolosclerotic lesions (863), and displayed enhanced arteriogenesis as well as angiogenesis (141).

In Grx1 knockout mice, attenuated cardiac hypertrophy was detected after induction *via* angiotensin II infusion (35). Grx1 knockout inhibited functional recovery and increased infarct size in coronary occlusion/reperfusion models of heart infarction (464); whereas in an earlier study, no role of Grx1 in this animal model was identified (301). In agreement, Grx1 over-expressing mice exhibited a reduced infarct size, as seen for increased Grx1 expression after IPC or gene therapy (426, 464). In addition, over-expression of Grx2 in myocardial mitochondria reduced infarct size (535). Similar to Trx1, over-expression of Grx2 protected mice against doxorubicin-induced cardiotoxicity (155). Grx3 over-expression in cardiomyocytes inhibited cardiac hypertrophy induced by treatment with enthothelin-1 and phenylephrine (337). In hearts of adult rats as well as in neonatal rat cardiomyocytes, Grx3 was up-regulated after treatment with enthothelin-1 and phenylephrine (337). This effect was mediated by interference of Grx3 with calcineurin-nuclear factor of activated T cells (NFAT) signaling (338). Using $Grx3^{-/+}$ gene-targeted mice as well as Grx3 over-expressing mice as models, this specific function was confirmed *in vivo* (105, 338). A patient with reduced levels of Grx5 exhibited sideroblastic-like hypochromic anemia (95) (see also section II.A.3).

Both Prx1 and Prx2 knock-out mice developed hemolytic anemia (422, 545), and exacerbate formation of atherosclerotic plaques (393, 575). Prx2 deficiency suppressed angiogenesis during tumor development, supporting the important role of Prxs in cancer progression (see also section II.B.12) (368). In mice over-expressing Prx3, cardiac failure after myocardial infarction was inhibited (476); a similar phenotype was observed in Prx6 knockout mice. In an ischemia-reperfusion model, mice lacking Prx6 were more susceptible to ischemia-reperfusion injury such as increased infarct size (534). In contrast, neither mice with elevated Prx6 levels nor those with reduced Prx6 levels yielded hints for an involvement of this protein in the development of atherosclerosis (601, 803).

Mice with the targeted disruption of the Nrx gene displayed several cardiovascular defects, for example, a ventricular septal defect and persistent truncus arteriosus (216).

5. Skin. The skin is exposed to several chemical and physical injuries. Oxidative equivalents in the skin are produced, among others, by gaseous airborne environmental

pollutants, UV radiation, cosmetic products, drugs, and certain food constituents/contaminants (32, 61). Trx-related proteins are already present in the skin of the fetal organism, even though they are not detectable in the surface ectoderm from mouse embryos at E8.5 and only faintly in the epidermis at E10.5. Trx1 and Grx1 immunoreactivities become very prominent in the epidermis and hair follicles of mouse fetuses at E16.5 (396). Later, in the adult mouse, 16 members of the Trx family of proteins have been identified in the different layers of the epidermis (235). In the outermost layer of the epidermis, the stratum corneum, Trx1 is the most abundantly detected Trx family protein. The three layers underneath the stratum corneum (*i.e.,* stratum granulosum, stratum spinosum, and stratum basale) were uniformly and strongly stained for Grx2, Grx5, Nrx, Prx3, Prx4, Prx6, and Trx1. In the hair follicles and sebaceous glands, Grx2 and Grx5, Prx5 and Prx6, and Trx1 displayed strong immunoreactivities (235). In the epidermal cells of the human skin, Trx1 and TrxR1_v3 were strongly expressed; whereas mitochondrial Trx2 displayed low or no staining (143). In bovine, Grx1 was prominently detected in the epithelium, and the expression pattern suggested functions during differentiation (653).

6. Skeletal muscle. ROS and RNS are continuously generated in skeletal muscle cells and increased during contraction and fatigue (189, 267, 397). In older rats, skeletal muscles are the main sources of ROS and RNS generation (404). With the exception of Trx1 and TrxR2, all Trxs and Prxs are present in the human skeletal myocytes; the strongest expression was detected for Prx2 (143). In mouse skeletal muscle, Grx2, Nrx, Prx1, and Prx5 displayed the strongest staining. Prx5 imunoreactivity was localized in the periphery of the myocytes, close to the plasma membrane; whereas Prx2 and TrxR2 were more diffusely detected in the intercellular space, which was reported as a characteristic attribute for these proteins in several tissues (235). Supported by the findings in other tissues (for instance, mammary gland), localization of Prx2 and TrxR2 was detected in the connective tissue. In the case of TrxR2 and in contrast to other analyzed members of the Trx system, a significantly reduced expression in aging skeletal and cardiac muscle was demonstrated, which could be renormalized by caloric restriction (648).

Trx family proteins have been implied in muscular and joint diseases. Protein levels of Trx1 and Prx3 were decreased in the late phase of disuse muscle atrophy in rats. In the same study, the mRNA level of Txnip was significantly increased before the muscle loss and the concomitant decrease in Trx1 levels (478).

Human chondrocytes constitutively express Prx5, an expression that was increased in osteoarthritis (800). The cytosolic Trx system seemed to be more implicated in rheumatoid arthritis than in osteoarthritis. Trx1 was significantly increased in the synovial fluid of rheumatoid arthritis patients, and also along with TrxR1 in synovial tissues of the same patients (481). In rheumatoid arthritis patients, Trx1 was detected on the surface of the synovial lining layer and in mononuclear cells of the synovial sublining layer. Trx1 levels in synovial fluids from rheumatoid arthritis were significantly higher compared with those from osteoarthritis patients and were correlated with inflammatory indicators in the serum and synovial fluid (342).

7. Respiratory system.

a. Expression of Trx family proteins in the respiratory system. The airway system is the main oxygen delivering interface between the host and the environment and is, consequently, especially susceptible to oxygen-mediated injury. The constant and combined exposure of airborne gases and particles and endogenously produced ROS and RNS requires sophisticated lines of defense. GSH plays a vital role here. The first and probably most important protective barrier is the highly heterogeneous layer of respiratory-tract lining fluid covering the respiratory epithelium. An about 100-fold higher concentration of GSH compared with serum levels underlines its general importance, combined with GSH-dependent oxidoreductases, that is, Prx6 and/or GPx3 (253). In fetal mice, Trx1 and Grx1 were detected in the epithelial cells of the airway (future bronchial and alveolar epithelia) and the lung parenchyme at E13.5, increasing at later developmental stages (396). Postnatal exposure to oxygen induces elevated expression of Trx and TrxR (148). In combination with the ROS-evoked chronic rise of intracellular buffer capacity, it supports the role of Trx and related molecules as key activators for oxidative stress-inactivated proteins and during development of the human lung (186). In the human lung, Trx1 is detected from week 35 onward and is located in the bronchial epithelium, alveolar macrophages, chondroid cells, and cells of the bronchial glandular epithelium (361). However, in the mature, adult lung, Trx1 and TrxR1 immunoreactivities were reported to be weak or moderate only in pneumocytes, macrophages, and bronchial epithelial cells (774). In a recent study, some redox proteins were detected in alveolar cells (*i.e.,* TrxR1, GR, Prx2, and Prx6) as well as in macrophages of human lungs (*i.e.,* Trx2, TrxR1, TrxR1_v3, TrxR2, Prx2, and Prx3) (143). Grxs have not been intensively investigated in the human lung. In a study analyzing Grx1 and Grx2 expression, only the former showed strong immunoreactivities in the alveolar macrophages and weakly positive signals in the bronchial epithelium (589).

In the adult mouse and rat, only the mitochondrial Trx system along with the cytosolic peroxiredoxins, Prx2 and Prx6, were detected in pneumocytes; whereas Grxs and Trx2 were either not or only weakly expressed (235, 359, 654). In the upper respiratory tract of the mouse, only Prx6 was highly expressed in the pseudostratified epithelium of the trachea (235).

b. Trxs, Grxs, and Prxs in pathologies of the lung—interplay between ROS and inflammation. Many airway-related disorders, including acute lung injury, asthma bronchiale, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis, display an alteration of the cellular redox profile (71, 147). Asthma has an approximate prevalence of 5% of the worldwide population and is one of the most common chronic inflammatory airway diseases (809). In several studies, a direct correlation between oxidative damage as a fundamental consequence of characteristic-reversible airway obstruction and airway hyper-responsiveness and the severity of asthma was found (532, 662, 672).

GSH was attributed a key role in the maintenance of the integrity of the epithelial barrier. Not surprisingly, inflammatory airway diseases such as asthma or COPD show

altered ratios of GSH to GSSG (198, 617) and its biosynthesizing enzyme γGCS (261, 618). An increase of γGCS, especially in the epithelium, might be a counter-regulation of ongoing inflammatory responses in pulmonary diseases (626), and an external augmentation of GSH levels in the lung appears to be a logical therapeutic approach to combat COPD or asthma (74).

Asthma is a mainly a type-2 helper T-cell (Th2)-driven disease that is characterized by eosinophilia and the activation of a broad array of inflammatory cells such as macrophages, neutrophils, and mast cells. GSH depletion in mouse T-cells and macrophages leads to an impaired interferon-gamma production and favors a Th2 response, underlining its vital importance in the polarization of the immune system (599). High concentrations of circulating Trx1 were found in infectious and inflammatory diseases, inhibiting monocyte and neutrophil responses to chemokines by acting downstream of the chemokine receptors eotaxin and CCR3 (538, 564). In patients, Trx serum concentrations correlated with increasing serum eosinophil cationic protein concentrations and were conversely proportionate to the expiratory peak flow rate during asthmatic attacks (835). Mouse models demonstrated that both exogenous application of Trx1 and transgenic over-expression suppress asthmatic key features such as airway hyperresponsiveness and inflammation. The combined role as regulator/transducer of ROS and regulator of the macrophage inhibitory factor (MIF) (see also section II.B.8.b) might be the key to maintaining the integrity of the epithelial cell and, subsequently, of the healthy lung (318, 779), reviewed in (327). In addition, an intraperitoneal injection of recombinant human Trx 1 suppressed bleomycin-induced or inflammatory cytokine-induced acute interstitial pneumonia in mice, suppressed lipopolysaccharide (LPS)- or bleomycin-induced acute lung injury (539), and was also shown to efficiently prevent elastase-induced emphysema (390).

In the case of COPD, which is highly induced by smoking, an up-regulation of Trx1 and TrxR1 in epithelial cells was detected (251, 604). Grx1 was up-regulated during monocytic differentiation and highly expressed in macrophages (589, 755). The expression in sarcoidosis and allergic alveolitis patient samples is decreased, implying further functions in both inflammatory and fibrotic lung diseases. In an ovalbumin-induced murine model of allergic airway disease, an increased amount of Grx1 and total Grx-activity was detected (636). Prxs exert a broad spectrum of peroxidase activity in the lung and show a cell-type specific expression (389). Prx1 was induced in mouse peritoneal macrophages exposed to oxidative stress and in endothelial cells, fibroblasts, and leukocytes (324, 326). It functions not only as a mere ROS scavenger in the Th2-driven asthmatic phenotype, but also by suppressing the IL4 cytokine. High expression of Prx1 and Prx3 in granulomas and alveolar macrophages of sarcoidosis parenchyma suggest a significant role in the control of the oxidant burden and the progression of lung injury (389). KO-mice of Prx2 displayed an increased asthmatic phenotype along with a decreased expression of the LPS-detecting TLR-4 (512). In addition, Prx3, Prx5, and Prx6 were abundantly expressed in the bronchial epithelium, protecting epithelial cells from oxidative stress-induced cell death (34, 389). COPD patient lungs appear to express all Prxs at equal levels, and only Prx6 was found to be induced in sputum supernatant (424).

8. Infection, inflammation, and immune response.

a. Expression pattern of Trx-related proteins in lymphoid tissues. The cytosolic Trx system has been detected in lymphoid cells of human lymph nodes (143). In mouse lymph nodes, Trx1 was not so strongly present, compared with the spleen, where it appeared in both functional areas: the white and the red pulp (235). In contrast, certain Trx-related proteins showed more intense immunoreactivities in defined areas. Grx2 and TrxR2 signals were more pronounced in the red pulp than in the white pulp; whereas Grx1, Grx3, Grx5, and TrxR1 immunoreactivites were more significant in the white pulp. Moreover, a difference in the subcellular localization in both zones was reported. Using confocal microscopy, Grx2a was demonstrated in the mitochondria of red pulp cells; whereas in white pulp cells, mainly cytosolic Grx2c was detected (310). In mouse lymph nodes, the expression of 16 Trx family proteins has been described (235). Grx5 and Prx2 were strongly expressed in the cortex and medulla. Grx3 was the only protein of the family that showed a specific staining pattern in the germinal centers of the lymph nodes (Fig. 11B).

b. Immune system. An adequate host immune response to viral, bacterial, and parasitic infections and airborne macromolecules is vital to regulate effector mechanisms. A proper activation of cells of the innate immune system *via* their so-called pattern recognition receptors has been demonstrated to play a crucial role in early shaping of the immune system. A fine balancing of Th1, Th2, and regulatory T-cell responses triggered by altered or missing innate immune cell activation depends on the reduction–oxidation equilibrium of tissues, and disturbances are implied in a broad array of diseases (231). The phagocytic cells of the innate immune system, including macrophages, monocytes, dendritic cells (DCs), and neutrophils, destroy pathogens *via* the NADPH oxidase-dependent formation of ROS. NADPH oxidases are membrane-spanning enzyme complexes that transfer electrons from NADPH across biological membranes to molecular oxygen, forming superoxide and its downstream metabolite H_2O_2 (414), as well as other radical species in the presence of myeloperoxidase, nitric oxide, or iron. Potential mechanisms killing pathogens involve changes in the phagosomal pH and ion concentrations as well as the inactivation of virulence factors, for instance, redox-sensitive elements, as described for bacterial pheromones (651), reviewed in (51). ROS can activate an increased immune response *via* redox-sensitive signaling pathways, including, for example, NF-κB-activation and expression of pro-inflammatory cytokines such as IL-1β and TNF-α (494, 687). This is especially important for the activation of the adaptive immunity, established by antibody-producing B cells and T cells, which depends on the binding of the T-cell receptor to a peptide bound to the major histocompatibility complex on antigen-presenting cells and additional co-stimulating and pro-inflammatory signals (139, 336). In addition, it was shown that ROS levels increase in T cells in the presence of mitogenic stimuli and during activation, for example, on antigen presentation. On the contrary, in the presence of ROS-scavenging enzymes, T cells lose their ability to respond to cytokine- or receptor-mediated signaling (473, 783). Similarly, DCs also produce ROS during antigen presentation, which is essential for cytokine production (473). Moreover, they generate cysteine from imported cystine after LPS- or TNF-α-stimulation and secrete Trx1 on interaction

with T cells. Interestingly, DC activation can be inhibited by glutamate, prohibiting cystine uptake, or antagonistic antibodies against Trx. The authors hypothesized that DCs may activate T cells, which lack cystine transporters, by creating a reducing milieu in the immunological synapse, providing them with free thiols (25). This is especially important, because intracellular GSH, which is generated from cysteine, is essential in the response to mitogenic and antigenic stimuli (491). This is also valid in the case of polymorphonuclear leukocytes, reviewed in (780). GSH can inhibit the binding of NF-κB to DNA by specific glutathionylation of the p50 (605) and the p65 subunit (613).

Cytosolic proteins of the Trx family have been shown to be secreted in various cell and animal models as well as in various clinical conditions. This section summarizes these findings and discusses potential functions in the modulation of the immune response. The extracellular environment is more oxidizing than the intracellular room; the GSH plasma levels, for instance, range between 2 and 20 μM compared with cellular levels in the millimolar range (353). Therefore, the redox state of the individual proteins is believed to be rather oxidized than reduced; which is also underlined by the lack of sufficient electron donors such as NADPH or TrxR. However, a few studies show that the latter can also be secreted by some cell types (23, 722).

Besides the missing information on the specific redox state of the individual proteins and thereby their enzymatic activity, not many specific targets and mechanisms have been revealed and analyzed. It is possible that extracellular functions are not based on the reduction of disulfides, but rather the transfer of disulfides to target-soluble proteins or surface-exposed cellular structures.

Trx1 was shown to be secreted by various cell lines, including primary and cancer cells, following a secretory pathway independent from ER and the Golgi apparatus (655). The oxidoreductase was detected in blood plasma in various clinical conditions, such as cancer (541), rheumatoid arthritis (342), type-2 diabetes (363), and HIV infection (543). Indeed, Trx, secreted from human T-lymphotropic virus-1 transformed T cells, was originally identified as T-cell leukemia-derived factor, inducing the expression of the IL-2 receptor (751). B and T cells secrete detectable levels of Trx1 when activated by specific compounds. Ericson and coworkers demonstrated that activated B cells, isolated from B-type chronic lymphocytic leukemia patients and healthy donors, strongly increased the expression of Trx1, with two thirds being secreted (169). Potential functions include the reduction of ROS, which can freely pass or leak through the membranes of phagosomes, *via* endogenous GPx3 (66) or Prxs. Extracellular Trx1 was also shown to act as a cytokine or chemokine, that is, signaling molecules, which can either alter the cellular expression of distinct genes and transcription factors or attract and activate immune cells, respectively. Even though no specific receptor has been identified so far, exogenous administered Trx1 was shown to induce the expression of antioxidant genes, including Grx1, Grx2, SOD2, and Prx4 in human lens epithelial cells (848), of various cytokines, such as TNF-α, IL-1, IL-2, and IL-8 in monocytes and dose dependently of IL-6 in fibrosarcoma and endothelial cells (685). Furthermore, Trx regulates NF-κB activation. Trx1 translocates from the cytosol into the nucleus on TNF-α treatment and was shown to suppress NF-κB activation induced by TNF-α, phorbol myristate acetate (PMA), or IL-1 (279, 757).

Controversially, Trx1 was also shown to reduce a general inflammatory response (58). Wu and coworkers showed that the injection of recombinant Trx1 in a rat model for myocardial ischemia (see also section II.B.11), significantly reduced the number of infiltrating immune cells after 24 h of reperfusion (829). The anti-inflammatory function could be explained by regulating or rather inhibiting the macrophage migration inhibitor factor, a pro-inflammatory protein released from immune cells. MIF is characterized by the active site motif Cys-Ala-Leu-Cys and exhibits disulfide reductase activity in the insulin and the HED assay (394). Various studies have analyzed Trx1 and MIF, demonstrating potential regulatory mechanisms. Son and coworkers, for instance, showed a direct association between the two proteins (730), inhibiting the release of MIF or directly regulating protein expression, thereby inhibiting, for example, a general inflammatory response against cigarette smoking (537, 681).

The third described function as a chemoattractant in the nanomolar range also depends on the redox-active cysteine residues and was revealed as a receptor- and G protein-independent process in monocytes, polymorphonuclear leukocytes, and T cells. Trx1 might act as a redox sensor on a yet unknown substrate protein, promoting the transmigration of immune cells by its disulfide isomerase activity or generally amplifying the cellular response at a site of inflammation (58). Higher chemokine levels potentially have the oppositional effect, leading to impaired leukocyte migration and an enhanced infection rate, as described for IL-8 (718), human monocyte chemoattractant protein 1 (660), or murine CXC chemokine KC (815). Bertini and coworkers discuss that elevated, exogenous Trx levels might inhibit leukocyte migration and enhance the general infection rate, which could explain the early mortality rate of HIV patients with elevated, plasma Trx levels (>30 ng/ml), compared with patients with similar symptoms, but regular Trx levels (58, 543).

The truncated Trx80 comprises the N-terminal first 80–84 amino acids of the cytosolic Trx1 and was originally described as an eosinophil cytotoxicity-enhancing factor, which was detected in the plasma of humans infected with chronic schistosomiasis mansoni infection (150). Trx80 was detected in human B and T lymphocytes, monocytes, granulocytes, and melanomas (667), and it was shown to be secreted by monocytes and transformed leukocytes (666, 716), but is preferably localized or rather incorporated into the plasma membrane, which is externally oriented. Only minor levels of Trx1 are located to the membrane (667). The truncated protein differs from the full-length protein, because it is not a substrate for TrxR, lacks parts of the active site, and, thus, does not exhibit oxidoreductase activity (587). Nonetheless, both proteins share similar functions, such as proliferative effects on peripheral blood mononuclear cells (PBMCs) and monocytes (586, 587), induction and secretion of pro-inflammatory mediators into the plasma, role as a chemoattractant for monocytes and polymorphonuclear cells (65), and the activation of MAPK signaling pathways (585). It furthermore induces the expression of numerous "cluster of differentiation" (CD) surface antigens (584) and is involved in the production of the anti-inflammatory cytokine IL-10 (585).

The Trx-like protein Nrx functions in the innate immune response *via* the stabilization of the interaction of flightless

homolog 1 and myeloid differentiation primary response protein MyD88, suppressing LPS-induced NF-κB activity (272). In addition, potential regulatory functions of gene expression were determined. Nrx over-expression in HEK293 cells led to an increased NF-κB activation, following stimulation by TNF-α or PMA (279).

Prx1, Prx2, and Prx4 were extracellularly detected. Prx1 was secreted from lung cancer adenocarcinoma cells and was also detected in the serum of patients suffering from nonsmall cell lung cancer, as well as through specific antibodies against the peroxidase (112). Prx2 was detected in plasma, potentially due to endogenous hemolysis or secretion by T cells, of patients suffering from multiple sclerosis with severe acute respiratory syndrome (118). Prx1 and Prx2 are also known under the name "natural killer cell enhancing factors A and B," because they increase the cytotoxicity of natural killer cells, which belong to the innate immune system (682, 683, 701). Prx4 possesses a leader peptide and is processed and secreted from the cell *via* the ER and Golgi apparatus within minutes. The secreted form is potentially enzymatically active and might act in scavenging extracellular ROS or regulating biological processes *via* binding heparan sulfate attached to cell surfaces or the extracellular matrix (558). It regulates H_2O_2-induced signaling pathways, for instance, the H_2O_2-mediated activation of NF-κB *via* modulation of the inhibitory protein IκB, modulating specific gene expression and the immune response (346). Macrophages with depleted levels of Prx6 displayed increased levels of H_2O_2 and an elevated apoptosis rate (804).

In addition, the cytosolic Grx1 was demonstrated in the extracellular compartment. Lundberg *et al.* detected Grx1 in human plasma and demonstrated that the protein was secreted by unstimulated PBMCs, suggesting general extracellular functions (453). Peltoniemi *et al.* showed that alveolar macrophages expressed Grx1 and that Grx1 levels were decreased in homogenates of the lung and increased in the sputum of patients with COPD, with the levels correlating to the stage of the disease and lung function (588). $Grx1^{-/-}$ mice were characterized by lower levels of pro-inflammatory markers, after LPS stimulation, potentially due to a disruption of redox signaling *via* de-glutathionylation of specific proteins and signaling pathways (8). On the contrary, over-expression of Grx1 in HEK293 cells led to an increased TNF-α-and PMA-induced NF-κB activation (279). Furthermore, intracellular Grx1 was shown to affect the NF-κB-dependent expression of intercellular adhesion molecule 1 (ICAM-1), an adhesion molecule in endothelial- and immune cells, that facilitates cell-cell interactions and leukocyte transmigration into tissues. Furthermore, over-expression of Grx1 increases the secretion of IL6. Administering IL6 itself to the medium of cells also induces Grx1 and ICAM-1 expression, revealing pro-inflammatory functions in both autocrine and paracrine signaling (704). Another proposed function includes the decomposition of peroxides *via* the reduction of plasma GPx3 (66). Unlike Trx1, Grx1 does not seem to act as a chemokine (58).

Grx3 was identified as an interaction partner of protein kinase C-θ (819), which regulates TCR-mediated signaling and the activation of transcription factors, including NF-κB and AP-1 in antigen-stimulated T cells, reviewed in (747). Over-expression of Grx3 in T cells led to decreased phosphorylation and activation of c-Jun N-terminal kinase (JNK) and NF-κB (819). In another study, Grx3 over-expressing RBL-2H3 cells were characterized by increased degranulation, elevated activation of the transcription factor NFAT and the expression of IL-4 and TNF-α, a decreased phosphorylation state of JNK, and no changes in the phosphorylation state of ERK and NF-κB activation, implying new functions in FcεRI-mediated mast cell activation (373).

Down-regulation of Grx3 in HeLa cells affected the expression of numerous genes involved in the organization of the cytosceleton, cytokine secretion, and processes, including apoptosis, differentiation, and migration; that is, for instance, ICAM-1, IL-8, IL receptor 4, or the dual-specific phosphatases DUSP4 and DUSP6, which regulate MAP kinase signaling (unpublished data, P. Haunhorst and C.H. Lillig).

c. Infectious diseases. Infectious diseases arise from the presence of pathogenic organisms such as bacteria, fungi, parasites and viruses, or pathogenic agents called prions. Consequently, human defense mechanisms such as the formation of ROS, pore-forming immune toxins (PFTs), and pathogen-binding immunoglobulines evolved. To overcome continuous ROS exposure by the infected host and to maintain their own intracellular redox conditions, many bacterial and parasite-specific Trx systems have developed, reviewed, for instance, in (616, 860). The pivotal role of GPx1 in viral and bacterial infections was summarized in (49). It is worth mentioning that parasitic protozoa of the order *Kinetoplastida*, such as trypanosomes and leishmania, lack the eukaryotic (GSH)/GR and (Trx)/TrxR system and have instead developed a tryparedoxin/trypanothione [bis(glutathionyl) spermidine; $T(SH)_2$]/trypanothione reductase system (407, 550). However, trypanosomatids contain not only the parasite-specific tryparedoxin (451, 629), but also prominent levels of GSH and various monothiol and dithiol Grxs (101, 193, 407, 469).

Trx secreted by the host performs a variety of physiological and pathophysiological functions (see also section II.B.8.b). In addition, its role as an antibiotic agent, on the one hand, and species-specific expression as a counter-measurement to adapt to changing environmental conditions, on the other hand, are quite diverse, affecting the outcome of an infection. Numerous bacteria that multiply extracellularly, including *Staphylococcus* species, secrete PFTs to alter host cell membranes. Extracellular TrxR and Trx can modulate the activity of the pore-forming cysteine-containing NK-lysin, an effector peptide of T-lymphocytes (23, 722). Furthermore, secreted Trx exerts differential regulatory functions on circulating immunoglobulins by reducing intermolecular disulfides between heavy and light chains, thereby affecting the adaptive immune response (461). The potent antimicrobial peptide human β-defensin 1 is activated by Trx (688), which shows that secreted Trx from both host and intruding agents is being used to counteract respective defense mechanisms. Intracellular bacterial Trxs function as hydrogen donors, affect DNA synthesis in cell division, and regulate the transcriptome, phage assembly, and propagation (860). For instance, *Mycobacterium tuberculosis* resides in mononuclear phagocytes and, as most bacteria, has developed an individual set of Trxs to counteract intracellular oxidative killing (15). Prxs can detoxify cells from ROS and RNS. In *M. tuberculosis*, the alkyl hydroperoxide reductase AhpC and a thioredoxin peroxidase appear to play leading roles in the detoxification process (331). In the case of the diphteria toxin, secreted by

Corynebacterium diphteriae, TrxR1 is essential as a part of the so-called "cytosolic translocation factor complex," which enables receptor-mediated endocytosis of the A domain of the toxin (625). Due to the central role of TrxR as an effector enzyme for bacteria, parasites, and cancerous cells, a vast number of inhibitors was developed to trigger lethal effects (28, 48, 616).

As for viral infections, the Trx and Grx systems play a major part in both life cycle and virus-host interaction. Species-specific Grxs function in viral DNA biosynthesis when levels of the corresponding host cell proteins are depleted (619). The cytoplasmic vaccinia virus encodes its own Grx, which functions as a redox shuttle between membrane-associated enzymes that play an essential role in virion morphogenesis, assembly, and growth circle (11, 811, 812). An unusual monothiol Grx has been found in the Chlorella virus PBCV-1 genome; the fact that it is expressed throughout the entire virus life cycle implies its importance in viral replication (197). Moreover, Trx is relevant for DNA replication as a subunit of the T7 bacteriophage DNA polymerase and filamentous phage assembly (308, 659). The infection of bacteria by viruses or so-called "bacteriophages" was reviewed in (659).

Enzyme expression involved in GSH homeostasis affects host susceptibility and progression of many diseases such as cancer, neurodegenerative diseases, cystic fibrosis, and human immunodeficient virus (HIV) (780). GSH levels of HIV-infected individuals and in AIDS patients are depleted in plasma, epithelial lining fluid, PBMCs, and monocytes (83). Decreased GSH levels in viral-affected $CD4^+$ T lymphocytes and NF-κB-dependent HIV gene activation underlines the importance of a specific GSH/GSSG ratio in HIV-positive cells (737). Oral application of N-acetyl cysteine (NAC) provided beneficial effects for HIV-infected patients and might be a sufficient tool to counteract virus-related apoptosis in lymphocytes (230). HIV has a major impact on Trx expression and distribution. Decreased expression of the Trx system correlated with a decreased rate of activated macrophages and DCs and a general higher apoptosis rate of $CD4^+$ cells (22, 238), thereby preventing an effective immune mounting against virus-infected cells. An initial down-regulation of the pro-apoptotic Bcl-2 and Trx allows a replication boost; subsequent up-regulation might reflect a way of inducing a persistent infection (13). Innate immune mechanisms are further compromised by elevated Trx serum levels that impair $CD4^+$ cell survival by blocking pathogen-induced chemotaxis (542). Concordantly, TrxR was found to negatively regulate HIV-1 encoded transcriptional activator Tat in human macrophages (364). Grx1 was identified at the HI-virus surface, and a regulation and/or maintenance of protease activity in HIV-1 infected cells was suggested (149). Lundberg and co-workers have demonstrated that the interaction between the viral glycoprotein gp120 and the host cell receptor CD4 is modulated by both Grx1 and Trx1. Blocking antibodies could reduce the disulfide-dependent HIV-1 entry and could, therefore, constitute novel pharmacological therapeutic targets (33, 633). Prx1 and Prx2 can be up-regulated in activated $CD8^+$ T cells and are found in the plasma of HIV-infected patients. However, the secretion seems to be independent of the state of T cell activation (223). T cells over-expressing either Prx1 or Prx2 were resistant to HIV-1 infection, and HIV-1 replication was inhibited by the presence of the recombinant proteins in HIV-1 cultures (223, 501). This could be explained by the peroxidase function, because H_2O_2 promotes the NF-κB-dependent expression and replication of HIV-1 in Jurkat cells, which has been shown for cytoplasmic Prx4 and its effects on HIV infection (346).

9. Metabolic and digestive system. In the mouse liver, both Trx1 and Grx1 are already detectable by immunohistochemistry at E11.5. In contrast to Grx1, which is expressed continuously in the liver during the adult life, Trx1 expression was reported to decrease (396). Sixteen members of the Trx family were detected in the adult mouse liver. Trx1 and Grx5 were abundantly distributed in the cytosol of hepatocytes (235). In this study, clear differences in immunoreactivities between the areas surrounding the portal and central veins were reported, with the latter stronger stained for the majority of the analyzed proteins (*e.g.,* Trx2, Grx1, Grx3, and Prx3). Other Trx family proteins, such as Grx2, Prx4, and TrxR2, appeared to be uniformly distributed in both areas. In the Kupffer cells, the specialized macrophages of the liver, Grx1, Grx3, and Prx5, were significantly stained. Prx6 was also detected in hepatocytes, Kupffer cells, and endothelial cells in the mouse liver (802). Prx6 along with Prx2, Prx3, and Trx2 were also detected in human hepatocytes (143).

During embryonic development, Trx1 and Grx1 were not detectable in acini and islet cells of the pancreas before E16.5. Both proteins are distributed through the nucleus of acinous and islet cells and also in the cytoplasm of islet cells (396). γGCS, which was weakly detected in most tissues of the adult mice, including the exocrine component of the pancreas, showed the strongest staining in the endocrine cells of the Langerhans' islets (Fig. 11C). Trx1 was detected in the cytoplasm but not in nuclei of endocrine and exocrine cells. In the same study, TrxR1 staining was more pronounced in the endocrine cells of the islets. Both Trx1 and TrxR1 expression was affected in starving mice (260). In our expression analysis of the mouse pancreas, Trx1 along with Grx3 and Grx5 showed clear nuclear staining patterns. Prx2 and TrxR2 were detected in the intercellular spaces in both the endocrine and the exocrine components of the pancreas (see Fig. 11C) (235). In the human exocrine part of the pancreas, Trx2, TrxR1, GR, and Prx2, Prx4, and Prx6 showed the most evident staining. TrxR1 and its transcript variant v3 displayed reversed expression patterns. TrxR1_v3 showed a stronger staining in the central part of the acinus cells, whereas TrxR1 staining was weak (143).

The intestinal epithelium represents a barrier between the body and the luminal environment and is exposed to oxidants generated both in the intestinal mucosa and in the lumen (*e.g.,* ingesta and bacterial metabolites/toxins) (52, 133). Although faintly positive in the mouse intestinal epithelium at E11.5 (Trx1) and E13.5 (Grx1), immunoreactivities of Trx1 and Grx1 were very strong in the villous epithelium of the fetal intestine at E16.5 (396). Trx family proteins have been intensively analyzed in the gastrointestinal tract of adult mice (235). Since Trx family proteins are abundantly present in the different layers along the gastrointestinal tract (for details please see Table 4 and Fig. 11C), we will focus on the intestinal epithelium, where interesting expression patterns were observed (Fig. 11C). This epithelium harbors different populations of specialized cells, and the redox protein levels seem to be especially strong in some of them. Probably the most evident staining pattern has been observed in the enteroendocrine

Table 4. Distribution and Expression Pattern of Trx Family Proteins in the Gastrointestinal Tract from the Mouse

	Esophagus					*Stomach*					*Duodenum*					*Jejunum*					*Ileum*					*Colon*				
Protein	*E*	*LP*	*SM*	*MM*	*ME*	*E*	*LP*	*SM*	*MM*	*ME*	*E*	*LP*	*SM*	*MM*	*ME*	*E*	*LP*	*SM*	*MM*	*ME*	*E*	*LP*	*SM*	*MM*	*ME*	*E*	*LP*	*SM*	*MM*	*ME*
Trx1	+	+	+	+	+	+^{n}	+	+	+	+	+^{n}	+	+	+	+	+^{P}	+	++	+	+	+^{Pn}	+	+	+	+	+	+	+	+	+
TrxR1	+	+	−	+	+	+	+	+	+	+	++	+	+	+	+	++	−	−	+	+	+	+	−	+	+	+	−	−	+	+
Trx2	+	+	+	+	+	++^{e}	+	+	+	+	++	+	+	+	+	++	+	+^{M}	+	+	+	+	+	+	+	++	+	+	++	+
TrxR2	++	+	+	+	+	++^{e}	+	+	+	+	+	+	+	+	+	+^{P}	+	+^{M}	+	+	+	+	+	+	+	+	+	+	+	+
Grx1	+	+	+	++	++	++^{e}	+	+	+	+	+^{e}	+	+	+	+	+	+	+	+	+	+^{e}	+	+	+	+	+	+	+	++	+
Grx2	+	+	+	+	++	++^{e}	+	+	+	+	++	+	++^{B}	++^{MA}	++	++^{P}	+	+	+	+	++	+	−	+	+	+	+	+	+	+
Grx3	++	+	+	+	++	+	+	+	+	+	+^{al}	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Grx5	+^{s}	−	−	−	+	+	+	+	+	+	+^{ea}	+	++^{B}	++	++	+	+	+	+	+	++^{n}	+	−	+	+	++	+	+	+	+
γGCS	+	+	+	++	+	+	+	+	++	++	+^{e}	+	+	++	++	+	+	+^{M}	+	+	+	+	+	+^{A}	+	+	+	+	++	+
Prx1	+	−	−	+	++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prx2	−	++	++	+	+	++^{e}	+	+	+	+	+^{e}	++	+	+	+	+	+	−^{M}	+	+	+	++	+	+	+	+	+	+	+	+
Prx3	++	+	+	++	+	++^{nm}	+	+	+	+	+	+	++^{B}	+	+	+^{e}	+	+	+	+	++	+	+	+	+	++	+	+	+	+
Prx4	++	+	+	+	+	++^{m}	+	+	+	+	+^{a}	+	+	+	+	++	+	+	+	+	+	+	+	+	+	++	+	+	+	+
Prx5	++	+	+	+	++	++^{P}	+	+	+	+	++	+	+	+	+	+	+	+^{M}	+^{A}	+	++	++	+	+	+	++	+	+	+	+
Prx6	++	+	+	+	+	+^{n}	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	++	+	−	+	+
Nrx	+	+	+	+	+	++^{e}	+	+	+	+	++^{l}	+	+	+^{A}	+	++^{e}	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Within each gastrointestinal segment, different layers (E, epithelial layer; LP, lamina propria; SM, submucosa; MM, muscularis mucosae, ME, muscularis externa) were analyzed separately for each redoxin. Immunohistochemistry data adapted from Godoy *et al.* 2011 (235).

−, absent, not detected; +, present, weak expressed; ++, strong expressed; n.a., not analyzed; s, squamous cell layer of esophageal epithelium; m, surface mucous cells; p, parietal cells; e, enteroendocrine cells; n, nuclear staining; a, apical localization; l, lateral localization; B, Brunner's glands; P, Paneth cells; M, Meissner's plexus; A, Auerbach's plexus.

cells. These hormone-secreting cells were found to be strongly stained for Trx2, TrxR2, Grx1, Grx2, Prx2, and Nrx in the mouse stomach epithelium (235). In the duodenal enterocytes, strong immunoreactivities were detected for Grx2, Nrx, Prx5, Trx2, and TrxR1. Especially interesting is the localization pattern of certain Trx-related proteins in the intestinal epithelium (see Fig. 11C). Grx5 and Prx4 accumulated in the apical membrane, whereas Nrx was the only analyzed protein that was located at the lateral side of the enterocytes (Fig. 11C). The implication of such a "polarization" in the intestinal epithelium has to be investigated, as well as potential secretory pathways and extracellular functions of the proteins should be explored.

Serum Trx1 levels are significantly higher in patients with inflammatory bowel disease compared with controls, and over-expression of Trx1 ameliorated dextran sulfate sodium-induced colitis (758). Grx3 was reported to be strongly expressed in colon and lung cancer cells. mRNA and protein levels of Grx3 in colon cancer were the highest among several analyzed Grxs, Trxs, and Prxs (108).

a. Diabetes mellitus. The chronic disease diabetes mellitus is an increasing health issue with 220 million cases worldwide as stated by the World Health Organization in 2010. Type-I or juvenile diabetes is an autoimmune disease (207). The immune system attacks pancreatic β-cells, attenuating the synthesis and release of the hormone insulin into the portal vein. Type-II diabetes arises from constant glucose uptake and emerging insulin resistance, a condition in which insulin cannot be efficiently used anymore and β-cells progressively die from metabolic stress (721). The pivotal role of ROS/redox signaling was highlighted by the development of type-II diabetes in mice over-expressing GPx1; for an overview and details, see (425).

Consequently, both conditions prohibit the regulation and cellular uptake of glucose and lead to hyperglycemia. Long-term, chronic hyperglycemia or "glucose toxicity" can affect various tissues, manifesting, for instance, in increased susceptibility to infections, micro-vascular complications as in retinopathy and neuropathy, atherosclerosis, and cardiovascular and neurological damage (375, 850). Generation of ROS potentially *via* the reduction of sugars (366), the hexosamine pathway (367), and/or the mitochondrial respiratory chain (671) seems to be correlated to chronic hyperglycemia and the establishment of diabetes (78, 375) and diabetic complications (388). Moreover, mitochondrial dysfunction plays an essential role. Increases in mitochondrial ROS levels seem to lead to morphologically and functionally altered mitochondria, attenuating ATP production, glucose-dependent insulin secretion and potentially lead to apoptosis and β-cell mass reduction, reviewed in (483, 851).

Insulin secretion was shown to be inhibited by ROS; a process that could be restored by treatment with N-acetylcysteine (475) and GSH (247). In addition, NADPH was shown to stimulate exocytosis of insulin in pancreatic β cells. Cytosolic Grx1 increased this effect, whereas Trx1 counteracted the secretion (329). Knock-down of Grx1 inhibited glucose-mediated insulin secretion in distinct β-cell models, whereas knock-down of Trx1 did not do so. Furthermore, the authors showed that the excitatory effects of NADPH depended on the expression of Grx1 (632).

NADPH levels were decreased by 32%, and the general NADPH/NADP was significantly lower in streptozotocin-induced diabetic rats even though the pentose phosphate shunt did not seem to be affected. Streptozotocin is a β-cell toxin that is experimentally used to induce a phenotype resembling type-1 diabetes. Within this study, the total GSH level and the GSH/GSSG ratio were also significantly decreased (246). However, there are studies showing the opposite or no significant effect on GSH (691, 719). The Langerhans' islets of the pancreas showed the highest expression of γGCS, compared with all other analyzed mouse tissues (235). In diabetes patients, the GSH synthesis itself did not seem to be impaired; however, a lack of the GSH precursors cysteine and glycine was detected. Dietary supplementation of these amino acids or N-acetylcysteine restored GSH synthesis in platelets of diabetic patients and decreased ROS levels and, accordingly, oxidative modifications (228, 692). The expression of GR is especially high in islets and inhibition of the enzyme sensitizes β-cells to streptozotocin-induced diabetes (533). Furthermore, it was shown to be increased in diabetic patients (691, 719).

Grx1 expression and activity were decreased in platelets of diabetic patients (691, 719). Over-expression of Grx1 *via* gene therapy, that is, lentivirus-mediated over-expression in mice, attenuated diabetes-related cardiac pathologies in diabetic hearts exposed to ischemia-reperfusion (I/R) (426). Grx1 is known to regulate NF-κB *via* deglutathionylation, a hallmark in the generation of insulin resistance (712) and in various diabetes-related diseases, implying regulatory functions for Grx1 in various diabetic complications (96, 704). For instance, Grx1 was shown to be induced by glucose in rat retinal Müller cells, inducing NF-κB activation, ICAM-1 expression, and potentially diabetic retinopathy (705). Various other proteins have been shown to be regulated *via* de-/glutathionylation and were implicated in diabetes, for instance, aldose reductase, a substrate for Grx1, which catalyzes the conversion of glucose to sorbitol, or potassium and calcium channels, reviewed in (495).

Over-expression of Trx1 in models for type-I and type-II diabetes minimized cellular damage and improved the survival of β-cells (300, 837). Moreover, it reduced and prevented associated conditions such as diabetic embryopathy (365) and diabetic osteopenia (255). An intravenous administration of recombinant Trx1 into nonobese diabetic (NOD) mice protected islets and prevented the development of type-1 diabetes by modulating or inhibiting aberrant reactions of the immune system (125). In addition, administering recombinant Trx1 to diabetic mice exposed to myocardial I/R reduced apoptosis, infarct size, and had a positive impact on the overall cardiac function (849). This was confirmed in a different study by myocardial over-expression of Trx1 using a specific adenoviral vector in diabetic rats. Over-expression of Trx1 induced heme oxygenase (HO)-1, VEGF, and p38 MAPK-β expression; decreased the levels of phosphorylated p38 MAPK-α and JNK; and reduced the overall apoptosis rate of cardiomyocytes and endothelial cells (675). So far, not much is known about the role of the mitochondrial Trx-system. Development of diabetes induced in rats by streptozotocin led to a reduction in Trx2 mRNA in the aorta after 2 weeks, which was normalized *via* insulin treatment. In addition, human umbilical vein endothelial cells (HUVEC) cultured at high glucose concentrations showed around 20% reduced Trx2 mRNA levels. Knock-down of Trx2-sensitized

HUVEC to glucose-induced cellular alterations, including decreased levels of free thiols, increased lipid peroxidation and increased cytochrome c expression, probably due to elevated glucose transporter 1-mediated glucose uptake and metabolism (430). Mice with the impaired ability to incorporate selenocysteine in proteins, for instance TrxR, did not seem to exacerbate streptozotocin-induced nephropathy (67).

Generally, decreased intracellular levels or inactivation of Trx1 has been correlated to increased diabetes susceptibility. Increased secretion of Trx1 or rather elevated plasma levels were detected in patients with increased glucose tolerance and manifested diabetes (507), with the latter correlating to increased nonesterified fatty acid levels (363). Nitrative inactivation of the oxidoreductase sensitives streptozotocin-induced diabetic mouse hearts to myocardial I/R injury (849). In addition, a genetic analysis revealed distinct Trx1 polymorphisms correlating with the development of diabetes (319). Especially the endogenous inhibitor of Trx1, Txnip, has gained a lot of attention in the diabetes field. Txnip has been shown to be dramatically induced by glucose, a process that is p38 dependent and mediated *via* inhibition of the PI3-kinase/Akt pathway during hyperglycemia (690), suppressed by insulin (700), and strongly up-regulated in diabetic animal models and patients, inhibiting Trx activity (573, 690). It is not induced by the presence of fatty acids (117). Txnip was actually the highest changing transcript in models of diabetes (623). Glucose-induced Txnip expression was associated with increased transcription of IL-1β and its precursor, as well as an elevated secretion rate (398) and induction of the intrinsic mitochondrial apoptosis pathway (120). Deletion of the protein enhanced insulin sensitivity and glucose-mediated insulin secretion, promoting adipositas but protecting against diabetes (119, 132, 621, 854). Txnip expression was moreover induced and involved in diabetic complications such as diabetic retinopathy (595, 596), diabetic nephropathy (7, 623, 766), and by glucocorticoid hormones used as treatment of numerous inflammatory and immune diseases, which in the long run can lead to glucose intolerance and diabetes (631).

Streptozotocin, H_2O_2, and cytokines induce the transcription of Prx1 and Prx2 mRNA in the rat insulinoma cell line INS-1 (45). Furthermore, Prx1 protein levels were shown to be elevated in erythrocytes of type-2 diabetes patients (510). Wolf and colleagues stated that down-regulation of Prx3 in rat insulinoma cells led to insufficient insulin secretion, while overexpression protected the cells against various agents, including H_2O_2, NO, proinflammatory cytokines, and the β-cell toxin streptozotocin (820). Transgenic mice over-expressing Prx3, on the other hand, were characterized by lower mitochondrial H_2O_2 concentrations and were protected against hyperglycemia and glucose intolerance (122). Prx4 over-expressing mice were generally less susceptible to streptozotocin-induced diabetes, showed less hyperglycemia and glucose tolerance, down-regulation of various inflammatory-related proteins, less infiltration of $CD3^+$ lymphocytes, and a lower apoptosis rate (154).

It is known that not only several transcriptional and signaling pathways which are important for islet cell development, including PI3K, Wnt/β-catenin, PDX-1, TGF/Smad, and notch [for an overview on the topic see, for instance, (357)] can be redox modified, but also protocols for β-cell culture and differentiation depend on redox control; for instance, by adding reductants to the cell medium. The formation of definitive endoderm is controlled by TGF-β. By defining conditions of β-cell differentiation, it might be possible to improve the promising therapeutic strategy of β-cell transplantation. However, ROS are generated during islet isolation and transplantation, as well as general inflammation reactions, which may prevent long-term survival and regeneration of β-cells and the restored insulin secretion. Chou and Sytwu transfected healthy mouse islets with a lentivirus vector coding for Trx1, before transplantation into NOD mice. Trx1 over-expressing islets were resistant against inflammatory processes and significantly prolonged islet survival after transplantation, without showing any differences in the glucose-dependent insulin secretion *in vitro* (131).

Regular exercise is a preventive and, in a way, therapeutic strategy against diabetes. General exercise training was shown to affect GSH levels and enzyme activities in a tissue-dependent way in various animal- and disease models, including catalase, GPx, GR, and SOD (151, 416, 729). Trx1 levels were also shown to be increased in healthy animals on exercise, an effect that was attenuated in diabetic animals, potentially due to the increase in Txnip mRNA (417). Furthermore, exercise was shown to significantly increase Prx2 expression in obese type-2 diabetes patients (510).

10. Urinary tract and reproductive systems.

a. Kidney. The kidney exhibits a high complexity due to different functional areas and segments of the nephron that execute special functions. Described expression patterns of Trx family proteins reflect this complexity; several of the oxidoreductases show segment-specific distributions. In the glomeruli of fetal and adult mice, both Trx1 and Grx1 immunoreactivities could not be detected (396). In calf, Grx1 imunoreactivity was also absent from the glomerulus, but strong staining of juxtaglomerular cells was reported, suggesting functions in the renin-angiotensin system (653). Kasuno *et al.* analyzed the effects of Trx1 in a renal ischemia and reperfusion model (372). In sham-operated mice, Trx1 showed strong immunoreactivity in the cortex, but weak staining in the medulla. The same expression pattern was observed while analyzing Trx1 mRNA and protein in rat and human kidneys, with a strong expression in the cortex, particularly in the proximal tubules, compared with the distal segments of the nephron (7). Txnip mRNA and protein levels were, in contrast to Trx1, most abundantly expressed in the glomeruli and in the distal nephron of rats and human kidneys. Recently, an exhaustive expression analysis of the Trx family in the mouse kidney confirmed this expression profile (see also section II.B.11). Although Trx1 staining was abundantly distributed over the whole mouse kidney, it was particularly strong in the cortex, specifically in the proximal tubule cells (235). Such a regional strong distribution was also observed for Grx2 and Prx3 in the cortex and the medulla. In contrast, Prx2 was more abundant in the medulla, and γGCS immunoreactivity was especially strong in the outer medullary area. Prx2 and TrxR2 immunoreactivites were described as the strongest in glomeruli and renal connective tissue. Prx2 was also detected in podocytes of rat kidneys (304). All proteins were present in the proximal tubule cells, where Grx3 and Prx1 display strong nuclear localization. In the human kidney, several Trxs and Prxs have been detected in glomeruli and tubule cells. Prx5 was found in endothelial cells, forming

the lining of the Bowman's capsule (143). Prx6 was abundantly detected in renal cells (802).

The clinical involvement of Trx family proteins in the kidney has been analyzed in renal ischemia and reperfusion (236, 372); see section II.B.11, in diabetic nephropathy (7, 256) and in angiotensin II-induced podocyte injury (304). The Trx system seems to play a role in the progression of diabetic nephropathy, because the over-expression of Trx1 in mice led to the suppression of pathophysiological changes after streptozotocin-induced diabetes (see also section II.B.9.a) (256). The increased mRNA levels of Txnip after the induction of diabetes in rats supports these findings (7). The podocytes are essential components of the glomerular filtration barrier. In rats, angiotensin II treatment and podocyte-specific over-expression of angiotensin II type-1 receptors led to a decrease in Prx2 expression, implying a role of the peroxidase or rather increased H_2O_2 levels in angiotensin II-induced podocyte injury (304).

b. Urinary bladder. Members of the Trx family are also significantly expressed in the urinary bladder. The epithelial cells of uriniferous tubules express Trx1 and Grx1 from day E11.5 onward up to adult age (396). In the urothelium, most Trx family proteins showed stronger immunoreactivities in the basal cells as compared with the superficial cells, where only Grx2 and Grx5 showed strong immunoreactivity (235).

c. Male reproductive system. Tissues of the reproductive system are generally diverse due to distinct functions, hormonal status, high differentiation rates, and the stage of cellular development of primary reproductive cells. Interestingly, reproductive organs, especially testis, are equipped with distinct sets and even specific isoforms of antioxidants and Trx family proteins (see Table 5). However, not much is known about the specific functions of these proteins in the testis, even though disulfide formation and isomerization are important during sperm development and maturation (744). Selenium was shown to be essential for this process, which was confirmed by the findings that the selenoproteins GPx4 and TrxR3/TGR function in the disulfide-dependent sperm formation (549, 744, 794), thereby being essential for fertility. In addition, TXNDC2/Sp-Trx1 might also play a role in disulfide formation (343); whereas TXNDC8/Sp-Trx3 seems to regulate proteins *via* post-translational modifications, controlling germ-cell-specific functions (345).

The seminiferous tubules of the testis show a high of rate cell division, and Trx family proteins are present in these tubules in mice, as well as in the interstitial cells. The Trx fold proteins display a high variability in the testicular tissue, as several testis-specific proteins have been detected in distinct cell types. In Leydig cells, which function in the testosterone production, several proteins were strongly expressed, that is, Grx2, Prx2, Prx3, Prx5, Trx1, Trx2, and TrxR2 (235). Trx1 was highly expressed in these cells, showing a strong correlation with nuclei; a similar strong Trx1 immunoreactivity was also reported for calf Lydig cells (653). In contrast, virtually no signals were detected for the analyzed proteins in Sertoli cells, a specialized cell type that harbors the spermatogenesis. In contrast, strong staining for Grx1 was reported in bovine Sertoli cells (653). In mice, Grx1 displayed a strong staining mainly in the nuclei of progenitors cells, that is, spermatogonia. The developing spermatocytes abundantly express Grxs, Trxs, and Prxs. In early spermatids, Grx2 staining is characterized by a cup-like pattern capping the nucleus (235, 309). Further analyses will have to define the localization of Grx2 in this cellular stadium, for instance, in the acrosome, the anterior end of the head of a spermatide, which is essential for ovum penetration during fertilization. Grx3 also showed a notably strong nuclear staining in the early spermatids. In elongated spermatids, Prx5 and Trx2 were highly expressed in the mitochondrial rich tail region; whereas Grx2 and TrxR1 signals were situated in the acrosomal region (235).

In the human prostate, only TrxR1, GR, Prx3, and Prx6 were reported to display strong staining in both glandular cells and stroma (143). Malignant transformation of cells from the reproductive system displayed characteristic alterations of the redox systems (795). The invasiveness of human prostate carcinoma cell lines was shown to correlate to levels of ROS/RNS and the GSH/GSSG ratio. The invasive PC3 cells were characterized by a comparably lower amount of ROS/RNS, lower lipid peroxidation, and an increased GSH/GSSG ratio

Table 5. Testis-Specific Proteins and Isoforms from the Trx Family

Protein isoform	*Cell types*	*Specific properties*	*Reference(s)*
mouse Grx2c and Grx2d	Spermatogonia, spermatids	Unlike Grx2c, Grx2d is inactive and does not form iron-sulfur cluster bridged dimers	(310)
human Grx2b and Grx2c	Spermatids, Sertoli cells, cancer cells	Unlike Grx2c, Grx2b does not form iron-sulfur cluster bridged dimers	(447)
TXNRD1_v3	Leydig cells, cancer cells	TXNRD1_v3 guides actin polymerization in relation to cell membrane restructuring	(144)
TGR and TGR-1	Elongating spermatids	CUG serves as an inefficient start codon in mouse and rat	(224, 744)
TXNDC2/Sp-Trx1	Spermatids	Nucleation center in fibrous sheath (suspected)	(498)
TXNDC3/Sp-Trx2	Spermatids	Structural component of fibrous sheath (suspected)	(663)
TXNDC8/Sp-Trx3	Spermatids	Likely required in later steps of spermiogenesis or mature spermatozoa	(345)
Txl-2	Mainly associated with cilia and flagella	Novel regulator of microtubule physiology (suspected)	(664)
snGPx	Spermatocytes and early spermatids	Restricted to late stages of spermatogenesis	(515)
Prx4 31kda	Membrane bound in the elongating spermatid and the residual body	Acrosome formation during vesicular reorganization in spermiogenesis	(558, 679)

during cell growth (523). An up-regulation of the Trx system may play important roles in prostate cancer progression and responses to personalized cancer therapies. The majority of androgen-independent or hormone refractory prostate cancers expressing androgen receptors and Prx1–4 were up-regulated, regulating the receptor's activity (46, 578, 709).

d. Female reproductive system. As mentioned earlier, ROS are essential for reproductive processes. It was shown that ROS play an important role during ovulation and that suppression of an inflammatory response, as well as SOD or catalase, inhibit ovulation (210). Several members of the Trx family of proteins have been identified in the stroma and follicles cells of the mouse ovary as well as in the oviduct (235), with the highest expression detected for Trx1 and TrxR2. TrxR2, as well as Prx2, which was absent in these cell types, was expressed in the extracellular matrix of the ovarian stroma and the corpus luteum. In calf, Trx1, but not Grx1, was demonstrated immunohistochemically in follicular cells in the ovary. Grx1 immunoreactivity was particularly strong in both bovine and rat oocytes (237, 653). Grx1 was also suggested to play a role in corpus luteum regulation, because it was detected at different periods of the luteal phase in the human corpus luteum (220).

Trx family proteins have been shown to correlate with poor prognosis in ovarian cancers. A low cytoplasmic expression of Trx correlated significantly with better progression-free survival (824). In ovarian carcinomas, cytoplasmic Prx4 expression was associated with a better prognosis, whereas cytoplasmic Prx5 and 6 were associated with a higher stage (370).

In the mouse uterus, the expression pattern of 16 Trx family proteins was described in the endometrium (235). Several proteins showed stronger expression signals in specific areas, such as the uterine gland epithelium (Grx3, Prx3, Prx4, Prx6, and Trx1) compared with the surface epithelium. In term pregnant women, both Trx1 and Grx1 expression was increased in the cervix compared with nonpregnant individuals; the proteins are believed to be involved in cervical ripening (457, 668).

11. Ischemia and hypoxia. Conditions of insufficient oxygen supply to the whole organism or to single organs or tissues, for instance by insufficient blood supply, were implicated in various pathologies due to the general inhibition of proliferation and induction of apoptosis. However, oxygen concentrations are especially important in the regulation of embryonic development, often determing cell fate. Hypoxia regulates the survival and promotes proliferation and differentiation of some cell types, including neural crest stem cells (518) and CNS precursors (742). Human embryonic stem cells cultured under low oxygen concentrations proliferate, but do not differentiate, a process that in this case depends on hyperoxia (172). The same is valid for placental development (3). The formation of the vascular system is also oxygen dependent, because the proliferation of endothelial cells (602) and hematopoietic progenitors (145) depends on low oxygen concentrations. Of course, oxygen levels also regulate the development of the fetal and postnatal lung. Hypoxia modulates the expression of angiogenic factors and potentially affects lung microvascular development and lung morphogenesis (696). Transitional changes that occur in the pulmonary blood vessels at birth and with the postnatal adaptation to the extra-uterine environment are accompanied by an abrupt increase of NOS activity (30) and the Trx/TrxR system (148), as well as the differential regulation of Prxs (211, 378).

Cells have developed response mechanisms to cope with low oxygen concentrations. Hypoxia-inducible factors (HIF) 1 and 2 constitute transcription factors that regulate the expression of more than 180 genes under hypoxic conditions. HIF comprises two subunits, HIF-1α and the nuclear translocator HIF-1β. On normoxia, the α-subunit is degraded by the proteasome after hydroxylation of oxygen-sensing prolyl hydroxylases (PHD); while HIF-1β is constitutively expressed. On hypoxia, PHDs are inhibited, preventing HIF-1α ubiquitination and degradation, and the protein accumulates. The α-subunit translocates into the nucleus, dimerizes with HIF-1β, forming HIF-1, which can then regulate gene expression by binding to hypoxia-responsive elements, regulating angiogenesis, erythropoiess, vasomotor control, energy metabolism, and cell survival (4, 492, 694, 695). The HIF-1 target anti-TNFa-induced-apoptosis was shown to protect cells against hypoxia-induced apoptosis *via* Trx2 and the generation of ROS (130). Moreover, hypoxia-induced mitochondrial ROS are essential for stabilizing HIF-1α and HIF-1β, ensuring HIF activation (466, 677). Among others, they also regulate inflammatory responses *via* IL-6 production (581) and apoptosis *via* p38 phosphorylation (412). Increasing mitochondrial ROS, as well as exposing cells to H_2O_2, induced an activation of HIF-1 under normoxic conditions (111). Controversial reports state that nitric oxide is involved in the regulation of HIF-1, either by inhibiting HIF-1 activation (725) or by stabilizing and increasing the levels of the active HIF-1α subunit and the DNA binding capacity of HIF-1 under oxygen deprivation (38, 383) and normoxia (569), with the latter being potentially important on inflammation (676). NO potentially inactivates PHDs *via* nitrosylation, as seen in HEK293 cells treated with S-nitroso glutathione (492), or can nitrosylate HIF-1α at a Cys residue within the degradation domain, preventing its destruction (431). Another regulatory mechanism of HIF-1 is the generally increased translation due to phosphorylation of essential proteins such as by phosphatidylinositol 3 kinase/Akt-dependent or MAPK signaling pathways (695). Stress- and MAP kinase pathways represent cellular mechanisms to cope with altered O_2 levels. Over-expression of Trx1 led to elevated HIF-1α levels in cells cultured under normoxic and hypoxic conditions, whereas inhibition of TrxR1 activity blocked the activation of HIF-1α (513). Zhou and coworkers confirmed these data, showing that Trx1 increased the levels of HIF-1α by activating Akt-dependent translation. Trx1 might also be involved in depleting HIF-1α levels on reoxygenation (339). Over-expression of mitochondrial Trx2, on the other hand, either prevented or diminished hypoxia-induced HIF-1α accumulation (869). In addition, there are mechanisms regulating hypoxia-induced gene expression, independently from HIF. For instance, Txnip mRNA and protein levels rapidly decreased on hypoxia, potentially due to a cascade of changes preventing the activation of the MondoA:Mlx transcription factor and the binding to the carbohydrate response elements in the Txnip promoter. The authors hypothesized that down-regulation of Txnip is essential for cancer cells, adjusting their metabolism to the hypoxic conditions (106).

Tumors develop due to elevated cell- or tissue growth, exceeding the general blood supply; with tumor hypoxia correlating to poor prognosis, increased tumor growth, and resistance to drug and radiation therapy (264). In addition, over-expression of HIF-1α was accompanied by an elevated mortality rate in patients suffering from distinct cancer types (695). Many Trx family proteins show distinct expression patterns in cancer (see also section II.B.12). Prx1, for instance, was over-expressed in several cancer cell lines (840, 841) and up-regulated in A549 cells, after 4 h of hypoxia and 2–24 h of reoxygenation (385). Knock-down of Prx1 protein levels in lung carcinoma cell lines generally impaired cell growth, and transplantation of xenografts into nude mice resulted in delayed formation of tumors and metastasis and higher sensitivity toward irradiation therapy (123); see also section II.B.12. These proliferative and anti-apoptotic functions of the peroxidase Prx1 were confirmed in human lung cancer 1170i cells and explained by the inhibition of the JNK-signaling pathway *via* an interaction with the GST-JNK complex (385, 386). Both HIF-1α and Prx1 were appointed potential targets in cancer therapy. In addition, Prx3 stably over-expressing thymoma cells were also more resistant to hypoxia-induced production of H_2O_2 and apoptosis (551). On the contrary, retinal ganglion cells cultured in a hypoxic atmosphere showed reduced Prx6 levels, increased levels of ROS, NF-κB-activation, and induction of apoptosis. This potential dysregulation of redox signaling events can be prevented, by over-expressing the peroxidase, resulting in reduced hypoxia-induced cell death and neuroprotection. The authors speculate that Prx6 could be used in the clinic, intervening with the progression of hypoxia-related disorders such as glaucoma (784). Moreover, treatment with recombinant Trx1 protected retinal ischemia-reperfusion injury in rats (673)

Wound areas are susceptible to hypoxia as a result of tissue damage. Due to the loss of microcirculation and the presence of transmigrating inflammatory cells, the wound gets hypoxic, with an oxygen gradient being present between the last perfused capillary and the wound space. Angiogenesis, the formation of new blood vessels, is also induced by hypoxia and promoted in wound healing (602). Trx1 has been analyzed in burn injuries, demonstrating, among others, a potential function in wound healing (2), which is also seen for N-acetylcysteine (20).

Other pathological conditions, including cerebral stroke (please see also section II.B.2) and heart infarction (compare with section II.B.4), are triggered by hypoxic insults, induced by the blockage or general reduction of the blood flow, resulting not only in the lack of oxygen but also ATP and other nutrients. The return of blood, although necessary, leads to dramatic consequences in the injured tissue. This process, called ischemia-reperfusion injury, induces molecular and cellular changes, affecting cell morphology, cell polarity, osmoregulation, protein synthesis, and, for example, in the brain, release of neurotransmitters (156, 351). The reoxygenation phase can be divided into (i) an early, acute phase, induced by O_2, $O_2^{-}\cdot$, and rapid changes in the redox properties of the affected tissue and (ii) the late, subacute phase, induced by increased cytokine and chemokine levels and the infiltration of immune cells (173). Not surprisingly, members of the Trx family have been described to protect against ischemic injuries. Increased levels of Trx1, Grx1, Grx2, and Prx2 by either over-expression or treatment attenuated ischemic damage of neurons (70, 752, 868) and cardiac cells (426, 464, 535, 768, 829), respectively (see also sections II.B.2 and II.B.4).

Besides the pathological conditions, I/R injury is also induced surgically and during cell and organ transplantation. Lung transplantation in patients with progressive pulmonary diseases is limited by early graft dysfunction and rejection, implicated with I/R injury and elevated secreted Trx1 levels in the bronchoalveolar fluid (580). Even though Trx1 is a potential marker protein for graft rejection, a different study has demonstrated that pretreatment of rat donor lungs with Trx1 decreased tissue rejection, due to inhibition of I/R injury, NF-κB activation, and the inflammatory response (see also section II.B.8) (312). Hepatic I/R injury is induced by liver transplantation. The expression of Prx1 and Prx2 was shown to be induced by I/R in transplanted organs (702). Moreover, over-expression of Prx5, which among other organelles is located in mitochondria, decreased hepatocellular injury in a rat model for liver transplantation (828). Hepatic I/R injury was shown to affect mitochondrial function; indeed, the expression of 234 proteins was altered in a mouse model for I/R, detected by a proteomic analysis of liver mitochondria. Interestingly, Prx6 was shown to translocate from the cytosol into mitochondria after I/R. The peroxidase seems to function in the degradation of mitochondrial H_2O_2, because Prx6 knockout mice demonstrated increased levels of the second messenger, mitochondrial dysfunction, and hepatocellular injury (164). The important role of Prx6 in I/R injury was confirmed in a different study using Prx6 knockout mice in a model for myocardial I/R injury. Compared with wildtype organs, knockout hearts showed reduced recovery of the left ventricular function, increased myocardial infarct size, and elevated levels of apoptotic cardiomyocytes (534).

We have recently analyzed the expression of 16 Trx-related proteins in a mouse model for renal ischemia-reperfusion injury, revealing nephron segment-specific responses of Trx family proteins to the ischemic insult (236). I/R kidneys showed significantly increased levels of Trx1, Trx2, and Grx5 and decreased levels of Grx1, which might have resulted from specific secretion of the protein into the urine. Moreover, an analysis of contralateral kidneys revealed increased Grx5 and Prx6 levels and decreased protein levels of TrxR2, Prx4, and Prx5. We believe that these differences contribute to the distinct susceptibilities of different parts of the nephron toward the I/R insult; the glomeruli and the inner medulla cells, for instance, have been described to be very resistant, while medullary thick limb cells are extremely susceptible (234, 314). Moreover, Trx family proteins probably function in a systemic inflammatory response, due to their versatile extra- and intracellular functions (see also section II.B.8.b).

Trx1 and Trx2 are expressed in mTAL cells, and Kasuno *et al.* analyzed Trx1 over-expressing mice demonstrating attenuated reperfusion-induced mTAL injury (372). Induced by I/R, protein levels of Grx2, Prx3, and Prx6 were significantly increased in proximal tubule cells (236), a cell type that is characterized by the ability to regenerate after an I/R insult (511, 553). Over-expression of these proteinss in HeLa and HEK293 cells attenuated oxidative damage to the DNA and led to a higher cell survival and proliferation rate, compared with controls, implying functions in the regeneration process of cells after I/R (236). In addition, Yang and coworkers demonstrated that Prx5 is essential for the regulation of kidney homeostasis under hypoxic conditions, for

example, in terms of mitochondrial function and fatty acid metabolism (843).

So far, no effective therapeutic approaches to prevent or treat the damage caused by the hypoxia/ischemia insult are available. However, since the middle of the twentieth century hypothermia has been used as a clinical approach to reduce I/R injury, for instance, of the brain (487, 496) or the cardiovascular system (322, 402). The mechanisms underlying the protective effects are not fully understood. However, it was shown that hypothermia reduces ROS levels (99), NF-κB activation, and inflammation (806). In a proteomic approach, 1089 proteins were shown to be differently expressed in human coronary artery endothelial cells when cultured at 25°C, compared with at 37°C. These proteins were assigned to different categories, including oxidoreductase activity, cell redox homeostasis, and response to stress. Grx1, Prx2, Prx4, Prx6, and mitochondrial SOD showed changes. However, only Trx1, TrxR1 isoform 5, TrxR3, Prx1, GST π, and GST ω-1 were significantly increased; whereas protein-glutamine γ-glutamyltransferase 4, PDI 1, and PDI 4 were decreased. The reduction of the temperature to 25°C did not seem to affect the ratio of GSH/GSSG or the levels of reduced protein thiols and glutathionylation. These cold-adapted cells, as well as cells grown constantly at 37°C, were exposed to 0°C, which was followed by a rewarming period. Cold-adapted cells showed increased levels of glutathionylated proteins, higher levels of reduced protein thiols, due to higher activities of Trx, TrxR, and GSTs (872). Hypothermal preconditioning can be compared with general IPC, where resistance to I/R damage is induced by exposing a tissue to several ischemic episodes (516). IPC induced ROS, which are believed to alter various cellular targets including transcription factors, explaining the potential cyto- and tissue-protective role of this approach; for a detailed review, see Ref. (669). In a cardiovascular rat model, IPC increased Trx1 levels and the translocation from the cytosol to the nucleus, where it binds to Ref-1 and induces NF-κB and Akt1. Suppression of Trx1 by shRNA in rat hearts diminished cardioprotective effects of the preconditioning (463). IPC also induced production of $\cdot$NO, increased mitochondrial function, and altered the expression levels of various proteins, including mitochondrial SOD; see Ref. (524) and references within. Another approach is the so called "postconditioning," which is defined as brief intermittent cycles of ischemia alternating with reperfusion applied after the ischemic event. This approach is important for the treatment of patients, when the reperfusion period is induced and has been proved to have protective effects on the affected tissues, for instance, cardioprotection. Both approaches were discussed and compared in Ref. (797).

12. Cancer.

a. Carcinogenesis. Malignant transformation is the consequence of numerous dynamic changes in the genome, regulation of transcription, signaling pathways, proliferation, cellular architecture, and cell-cell interactions. Since essentially all of these cellular functions are at some level controlled by redox signaling, it comes as no surprise that Trx protein family members play a pivotal role in the process of carcinogenesis. Many aspects of the potential role of Trx family members both as oncogenes and as tumor suppressor genes have been extensively analyzed and reviewed earlier; for the Trx system, see, for instance, (29, 84, 362, 541, 693); for the Grx system (432); and for Prxs (87, 544, 728, 830). The various roles of the proteins in tumor development and progression are as complex as the multiple redox-regulated signaling pathways that contribute to malignant transformation. It is, thus, not possible to plainly classify Trx family proteins as oncogenes or tumor suppressor genes.

Trx1 was up-regulated in various cancers investigated, that is, from liver (540), lung (222), and colon (54). Trx may promote the growth of tumors, and its levels are negatively correlated with apoptosis in cancer cells (243). On the other hand, mice transgenically over-expressing human Trx1 do not show an increase in malignant diseases; instead, their life expectancy is increased (see also section II.B.13) (504, 594, 752, 852). The DNA-binding activity of the tumor suppressor p53 is controlled by the redox state of some critical cysteinyl side chains in its DNA-binding domain (252, 577). The redox state of these residues appears to be regulated by both Ref-1 and Trx. Trx can stimulate the DNA binding activity of p53 and potentiate Ref-1-stimulated p53 activity both *in vitro* and *in vivo* (789). In yeast, TrxR mutants failed to induce p53-dependent gene activation (100, 582).

Cytosolic Grx1 and mitochondrial Grx2a expression showed a significant correlation with the degree of differentiation in adenocarcinomas and an inverse correlation with proliferation (183). By mechanisms of alternative transcription initiation and alternative splicing, two nonmitochondrial Grx2 isoforms, Grx2b and Grx2c, are generated, whose expression in humans could so far only be demonstrated in testis and various tumor cells (447). Contradictory to a potential role as oncogene, Grx2c reduces the proliferation rate in stably transfected cells (183).

In many aspects, Prxs appear to qualify as tumor "preventers"; for an elaborate discussion on this topic, see (544); however, many cancer cells showed increased levels of Prxs, and their expression sometimes correlated with progression. Epigenetic down-regulation has been demonstrated for Prx1 in 1p/19q-deleted oligodendroglial tumors (158), Prx2 in acute myeloid leukemia (10), and Prx4 in acute promyelocytic leukemia (568). Prx1 interacted with a region of the c-Myc transcriptional regulatory domain that is essential for transformation. Therefore, c-Myc-mediated transformation was inhibited, implying a tumor suppressor role for Prx1 (163, 531). Moreover, Prx1 inhibits tumorigenesis *via* regulating phosphatase and tensin homolog (PTEN)/AKT activity; binding of Prx1 protected PTEN from oxidation-induced inactivation (97). Corroboratively to these findings, Prx1 knockout mice showed a higher rate of age-dependent malignancies (163). On the contrary, increased levels of Prxs have, for instance, been described for Prx1 in ovarian cancer proximal fluids (299), and Prx3 in lung cancer (387). Srx and Prx4 promoted the progression of human lung cancer (807).

13. Aging.

In the 1950s, Denham Harman hypothesized that the aging process is linked to species-specific metabolic activities, which depend on heritage and various stress factors. He proposed the so-called "free radical theory of aging," depicting the production and over-time accumulation of ROS and the irreversible macromolecular damage, as main reasons for the aging process (262). The special contribution of mitochondria was demonstrated later in 1972 (263). This theory was supported by a body of evidence, including that (i) cells

grown in hypoxia have a prolonged lifespan (562), while cells grown under hyperoxia have a reduced lifespan (861); (ii) cells treated with extracellular H_2O_2 undergo rapid, senescence-like growth arrest (124); and (iii) caloric restriction was shown to enhance the lifespan in a wide range of organisms from yeast to mammals (194, 472). Moreover, various studies in distinct cell and animal models have demonstrated an age-related increase in the intracellular ROS levels (134, 726), mitochondrial dysfunction (427, 635, 680), accumulation of oxidative-damaged mitochondrial (192, 834) and nuclear DNA (50), oxidized lipids, and protein-mixed disulfides (68, 628), with the latter also being the result of disturbed degradation and repair mechanisms of oxidatively modified proteins (176, 790). Intracellular as well as plasma GSH/GSSG ratios are known to decrease with age (628) and in age-related diseases such as atherosclerosis (31), macular degeneration (see also section II.B.3.b), and type-2 diabetes (674) (see also section II.B.9.a). The expression and/or activity of various mammalian Trx family and related proteins is also known to be reduced during aging, including, for instance, Trx1 (21, 832, 864), Trx2 (439), TrxR1 (832), TrxR2 (37), GR (68), Grx1 (69, 832), and Prx3 (439).

Mutations in various genes that interfere with the aging process have been characterized. These encode for proteins functioning either in the regulation of energy use or in redox regulation and signaling, including, for instance, catalase (770) and Prx (194, 775). Various model organisms, including *Sacharomyces cerevisiae*, *Cenorhabtitis elegans*, *Drosophily melanogaster*, or *Mus musculus*, depleted from SOD (446), Trx (748), TrxR Prx, and PDIs (250), were characterized by a reduced lifespan, reviewed in (334). *Vice versa*, protein over-expression can lead to a prolonged lifespan, which is especially significant in the case of Trx1, where protein over-expression led to a 35% increase in median and a 22% increase in maximum lifespan (504, 594). However, the absence of individual genes or proteins not always leads to a life-shortening phenotype; for instance, in $SOD2^{-/-}$ (634), $SOD2^{-/-}$ and $GPx1^{-/-}$ (866), or $Trx2^{+/-}$ mice, reviewed in detail in (334), which might be explained by compensatory effects of their functional homologs. Similarly, the over-expression of these antioxidants does not necessarily lead to an elongated lifespan (593). Despite all this supporting evidence, the contribution of ROS to organismic changes is highly controversial (574), because, first of all, ROS formation is very complex and verification procedures are difficult; and second, numerous studies did not confirm Harman's theory, which originally implied that the targets of ROS were random, indiscriminate, and cumulative (194)—which, as we know more than half a century later, is not true.

A different hypothesis suggested that mitochondrial mutations are created during replication errors during embryogenesis and then undergo clonal expansion in adult life, leading to mitochondrial and age-related diseases (574). The so-called "mutator mouse" expresses a proofreading-deficient mitochondrial DNA polymerase, leading to the accumulation of point mutations in the mitochondrial DNA, impaired respiratory chain functions, and premature aging (574). This phenotype was shown not to be associated with significant increased levels of ROS or a cellular anti-stress response (781), confirming the findings of the comparable Tfam knockout mice (799). However, even though these models disagree with the "free radical theory of aging," they do not exclude redox regulation. Many aging-related proteins are specifically redox regulated, including the lifespan regulator p66Shc (225, 226), MAP kinases (90, 94, 302, 303), the Trx-dependent Msr (89, 520, 600), as well as processes including protein folding and degradation (57, 470, 536). Furthermore, recent findings correlate specific oxidative changes to the aging process, demonstrating that these changes are distinctly redox couple-, subcellular compartment-, and tissue-specific. Using genetically encoded redox probes in *Drosophila melanogaster*, the authors showed that age-dependent pro-oxidants were not equally distributed throughout the organism, but rather restricted to specific regions. Moreover, they showed that the increased lifespan of the $chico^{1/+}$ mutant strain, carrying a mutation in the insulin/IGF signaling pathway, is correlated with increased oxidant levels (18), confirming previous data supporting a potential beneficial role for free radicals in longevity, reviewed in (593) and (415).

In the future, we might be able to assess oxidative changes during aging, elucidate critical mechanisms, and understand the impact of these modifications on the aging process as well as on age-related pathological conditions.

C. Therapeutic approaches

As described earlier, proteins of the Trx family show specific alterations in various pathological conditions, including changes in protein expression, enzymatic activity, tissue distribution, and intra- and extracellular localization. In the future, we might be able to use these findings in the clinic and apply Trxs, Grxs, and Prxs as specific biomarkers in early diagnosis, disease progression, or in order to determine the state of a disease, allowing for a more precise prognosis and choice of treatment.

The secretion of specific Trxs, Grxs, and Prxs has been described in various clinical disorders (see section II.B.8.b), and the analysis of, for example, sputum, blood, or urine samples for specific proteins has been done through a well-established and noninvasive approach to confirm potential pathological changes in patients. Elevated levels of Trx1 in HIV-infected patients have been correlated with a reduced immune response, an increased progression of the infection, and an early mortality rate (543). Grx1 was only detected in the urine of mice after I/R. This specific secretion of the oxidoreductase into urine has to be confirmed in patients; but might be applied as a marker for renal I/R injury in the future (236). Moreover, specific auto antibodies against Trx-related proteins could be used as diagnostic markers (112).

The specific expression and distribution of Trxs, Grxs, and Prxs is especially obvious in various cancer pathologies, with elevated protein levels of Trx1 or even the presence of cancer-specific Grx2 isoforms (see section II.B.12). These potential tumor markers could help determine the state of the disease and establish a patient- and disease-specific treatment. Even though Prxs are also highly expressed in various cancers, they cannot be implicated as medical biomarkers, due to the general high cellular abundance of these peroxidases. However, clinical information on the expression of Prxs might help determine the best medical care and improve the outcome of radiation therapy (825, 862).

Targeting the proteins that increase the proliferation or differentiation of cells and which are implicated in the development and progression of cancer cells (see section II.B.12)

has been an ongoing challenge. So far, no inhibitors for Grxs have been found, but various drugs were shown to affect proteins of the Trx family. Here, a prominent role is attributed to TrxR—the key enzyme of the Trx system, which also bears unique functions of its own (see also section I.A.2.a). Various drugs, foremost electrophilic compounds that target the selenocysteinyl residue in TrxR, have been developed, inhibiting the oxidoreductase activity. For an indepth discussion on this topic, we refer to the following articles: (29, 92, 591, 610, 693, 777, 793). Due to the finding that the mammalian reductase differs dramatically from the bacterial or parasitic enzyme, numerous inhibitors have been developed to counteract infectious diseases; for instance, affecting the malaria parasite *Plasmodium falciparum* (24, 48, 616). In addition, specific substrates for TrxR have been subjected to clinical trials. For instance, ebselen, reviewed in (175, 452), a "chemical mimic of GPx," which was shown to reduce H_2O_2 levels and oxidize Trx (867), was analyzed as a potential drug, for example, for cerebral ischemia (579) and stroke (836). Another target of TrxR is motexafin gadolineum. The drug has been suggested as a radiosensitizer in cancer therapy due to its tumor-specific uptake and its induction of ROS (201, 268). In the future, a strategy might be developed to specifically target Prxs in cancer cells, which contribute to resistance against radiotherapy (862).

It has been shown that the induction of protein expression, the addition of recombinant proteins, or over-expression *via* gene therapy is beneficial in various pathological conditions in distinct cell- and animal models, as well as in medical patient-based studies. Especially the treatment with recombinant Trx1 was described to decrease several pathological conditions affecting, for instance, the cardiovascular system, reviewed in (477) (see also section II.B.4.b), retinal cell damage (323) (see also section II.B.3.b), diabetes (125, 131, 849) (see also section II.B.9.a), and pathologies of the lung (see also section II.B.7.b). It was also shown to have a positive impact in the therapeutic approach of transplantation (see also section II.B.11). Pretreatment or preconditioning of rat donor lungs with the cytosolic oxidoreductase abolished tissue rejection (312) and transfection of mouse donor pancreatic β-cells with a Trx1 lentivirus vector extended cell survival after transplantation (131). Interestingly, Trx also bears functions in reducing allergenicity to, for instance, milk by reduction of its major whey protein β-lactoglobulin (756, 796). In addition, major protein wheat fractions (gliadins, glutenins) are enzymatically reduced (80). Trx may, thus, be useful for the production of hypoallergenic and more digestible food. Notably, breast milk concentrations of Trx during the early postpartum stage are highly increased, supporting this role (776). Elevated Grx1 protein levels in mice also diminished cardiac pathologies in diabetic hearts suffering from I/R-induced injury (426). Moreover, oral applications of GSH and precursor amino acids, including NAC, provide some degree of protection for HIV patients (230) (see also section II.B.8.b) and diabetes patients (228, 692) (see also section II.B.9.a). The activity of Prx2 was enhanced by obovatol, a compound extracted from the medical plant *Magnolia obovata*, revealing Prx2 as a new target protecting microglia against neuroinflammation (556). Two drugs, nipradilol and timolol, used in glaucoma therapy, increase the protein levels of Prx2, thereby protecting cells of the tabecular meshwork, the tissue surrounding the base of the cornea, against H_2O_2-induced apoptosis (506). Another potential target in the clinic is Prx6. Over-expression of the peroxidase could be used to prevent the progression of hypoxia-dependent disorders, such as glaucoma (784).

III. Concluding Remarks

The importance of redox signaling is increasingly recognized, despite the highly transient and volatile nature of the redox modifications that makes them very difficult to access for broad indepth investigations. The various redox modifications are highly target- and site specific, and the Trx, Grx, and Prx systems are pivotal players in redox signal transduction both as transducers and as regulators of second-messenger levels. One of the most striking findings of the last years was that these events might have to be defined individually for each tissue, each cell type within, and the condition of interest. Among others, our joint approach mapping Trxs, Grxs, and Prxs in physiological tissues of human, mouse, and rat "Human and murine redox atlases" highlighted the complexity of redox regulatory networks and implied more specific functions and interactions between the proteins themselves and with other proteins than those previously assumed. What will the future bring? Even though numerous open questions are awaiting bold hypotheses and brilliant new strategies, we should also continuously reassess previous findings and opinions. New issues involve the dynamics of subcellular localization—how can Trx fold proteins be secreted through the plasma membrane or taken up into cells? How do the proteins shuttle into and out of the nucleus? More targets and interactions will have to be defined. The molecular mechanisms of redox signal transduction are worthy of closer attention. Will we see more redox circuits with specific oxidases and reductases? Do redoxins transduce oxidative signals from, for instance, H_2O_2 to target proteins? […] Undoubtedly, the redoxin and redox signaling research field will continue to grow, and biological understanding will contribute to the development of clinical applications.

Acknowledgments

The authors' work was funded by the Deutsche Forschungsgemeinschaft (SFB593-N01), Karolinska Institutet, the P.E. Kempkes Foundation, and the von Behring-Röntgen Foundation.

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Date of first submission to ARS Central, March 5, 2012; date of final revised submission, February 1, 2013; date of acceptance, February 7, 2013.

Abbreviations Used

6-OHDA = 6-hydroxydopamine
aa = amino acid
AD = Alzheimer's disease
ADF = adult T-cell leukemia-derived factor
ALS = amyotrophic lateral sclerosis
AMD = age-related macular degeneration
AP-1 = activating protein 1
ASK1 = apoptosis signal-regulating kinase 1
CBS = cystathionine β-synthase
CD = cluster of differentiation
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
COX = cyclooxygenases
Cp450 = cytochrome P450 enzymes
CSE = cystathionine y-base
DCs = dendritic cells
ER = endoplasmic reticulum
FAD = flavin adenine dinucleotide
Fli-1 = Flightless-1
GPx = glutathione peroxidase
GR = glutathione reductase
Grx = glutaredoxin
GSH = glutathione
GSNO = S-nitrosylated glutathione
GSSG = glutathione disulfide
H_2O_2 = hydrogen peroxide
HIF = hypoxia-inducible factors
HIV = human immunodeficient virus
HUVEC = human umbilical vein endothelial cells
ICAM-1 = intercellular adhesion molecule 1
IL = interleukin
INS = islets of Langerhans
IOP = intraocular pressure
IPC = ischemic preconditioning
IRP = iron regulatory proteins
JNK = C-Jun N-terminal kinase
LPS = lipopolysaccharide
MAP = mitogen-activated protein
MIF = macrophage inhibitory factor
MPP^+ = 1-methyl-4-phenylpyridinium
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Msr = methionine sulfoxide reductases
MST = 3-mercaptopyruvate sulfurtransferase
NDP = nucleoside-diphosphate
NFAT = nuclear factor of activated T cells
NF-κB = nuclear factor kappa B
NMDA = N-methyl-D-aspartate
·NO = nitric oxide
NOD = nonobese diabetic
NOS = nitric oxide synthase
NOX = NADH oxidase
Nrf2 = nuclear factor E2-related factor 2
Nrx = nucleoredoxin
P = protein
PBMCs = peripheral blood mononuclear cells
PC12 = pheochromocytoma cell line
PD = Parkinson's disease
PDI = protein disulfide isomerase
PFTs = pore forming immune toxins
PHD = prolyl hydroxylases
Prxs = peroxiredoxins
RNR = ribonucleotide reductase
RNS = reactive nitrogen species
ROS = reactive oxygen species
RSS = reactive sulfur species
SOD = superoxide dismutases
SP-Trx = sperm-specific thioredoxin
Srx = sulfiredoxin
TBP2 = thioredoxin binding protein 2
TGR = thioredoxin glutathione reductase
TH = tyrosine hydroxylase
TLR = Toll-like receptor
TNF = tumor necrosis factor
TRAIL = TNF-related apoptosis-inducing ligand
Trx = thioredoxin
TrxR = thioredoxin reductase
TSA = thiol-specific antioxidant
Txl1 = thioredoxin-like protein 1
TXNDC = thioredoxin domain-containing protein
Txnip = trx interacting protein
VDUP1 = Vitamin D up-regulated protein 1
XO = xanthine oxidase