ANTIOXIDANTS & REDOX SIGNALING
Volume 2, Number 4, 2000
Mary Ann Liebert, Inc.

Review Article

Antioxidant Function of Thioredoxin and Glutaredoxin Systems

ARNE HOLMGREN

ABSTRACT

Selenium is an essential trace element with known antioxidant properties. Cytosolic thioredoxin reductase from mammalian cells is a dimeric flavin enzyme comprising a glutathione reductase-like equivalent elongated with 16 residues including the conserved carboxy-terminal sequence, Gly-Cys-SeCys-Gly, where SeCys is selenocysteine. Replacement of the SeCys residue by Cys in rat cytosolic thioredoxin reductase using site-directed mutagenesis and expression in *Escherichia coli* resulted in a functional mutant enzyme having about one percent activity with thioredoxin as a substrate through a major loss of K_{cat} and a shift in the pH optimum from 7 to 9. The truncated enzyme expected in selenium deficiency by the UGA mRNA codon for SeCys acting as a stop codon was also expressed. This enzyme lacking the carboxy-terminal SeCys-Gly dipeptide contained FAD but was inactive because the SeCys selenol is in the active site. These results show that selenium is essential for the activity of thioredoxin reductase, explaining why this trace element is required for cell proliferation by effects on thioredoxin-dependent control of the intracellular redox state, ribonucleotide reductase production of deoxyribonucleotides, or activation of transcription factors. The selenazol drug ebselen (2-phenyl-1,2 benzisoselenazol-3 (2*H*)-one) is a known glutathione (GSH) peroxidase mimic with antioxidant properties. The hydrogen peroxide reductase activity of human thioredoxin reductase was stimulated 15-fold by 2 μM ebselen. Glutaredoxins protect against oxidative stress by catalyzing reduction of protein mixed disulfides with GSH. The mechanism of glutaredoxins as efficient general GSH-mixed disulfide oxidoreductases may protect proteins from inactivation as well as play a major role in general redox signaling. Antiox. Redox Signol. 2, 811–820.

INTRODUCTION

THIOREDOXIN AND GLUTAREDOXIN are small proteins containing a redox-active disulfide (CXXC) and were both discovered from *Escherichia coli* as independent cofactors for the dithiol-dependent reduction of ribonucleotides to deoxyribonucleotides by the essential enzyme ribonucleotide reductase (Holmgren, 1985, 1989). Thioredoxin and glutaredoxin were subsequently shown to be general thiol-disulfide oxidoreductases and members of the thioredoxin superfamily of structures (see review by Martin, 1995). Thioredoxins are reduced by NADPH-dependent thioredoxin reductases, which are dimeric flavoproteins present in all living cells. In contrast, glutaredoxins are reduced by glutathione (GSH), the oxidized form of which is GSSG and is reduced by GSH reductase (Holmgren, 1989) or formed directly from the rapid synthesis by the enzymes gammaglutamyl-cysteine synthetase and GSH synthetase.

Medical Nobel Institute for Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, S-171 77 Stockholm, Sweden.

Antioxidant functions of thioredoxin and glutaredoxin are, e.g., as electron donors for ubiquotous methionine sulfoxide reductases participating in protein repair by reduction of methionine sulfoxide residues (Moskovitz *et al.*, 1999). Oxidation of methionine residues to the sulfoxide by reactive oxygen species (ROS) may impair protein function, and the methionine sulfoxide reductase restores the methionine side chain. Lately, a lot of focus has been on the antioxidant properties of thioredoxin-dependent peroxidases (peroxiredoxins), which reduce hydrogen peroxide with a low K_m value via cysteine residues and are ubiquitous with quite a large number of isoenzymes (Chae *et al.*, 1999).

The early work on thioredoxin in *E. coli* and yeast showed that the thioredoxins are stable disulfide-containing proteins with the conserved active site (Cys-Gly-ProCys) being reduced by a 70-kDa dimeric thioredoxin reductase, which generally is species specific for its own thioredoxin (Holmgren, 1985). However, when research started around 1970 to isolate thioredoxin systems from bovine and rat, as well as human tissues (Engstrom *et al.*, 1974; Holmgren, 1977), some important differences were noted that are important for understanding the role of these proteins in antioxidant defense. Thus, thioredoxin was a protein that only could be purified to homogeneity in the reduced form, because it contains two (calf thymus) or three (rat and human) additional structural sulfhydryl groups that easily oxidize to generate inactive aggregated molecules, dimers, or even multimers (Holmgren, 1977; Luthman and Holmgren, 1982; Ren *et al.*, 1993; Weichsel *et al.*, 1996). This may be of significance for redox regulation and particularly in conditions of severe oxidative stress (Ren *et al.*, 1993). However, the major difference was seen in the molecular properties and activity of thioredoxin reductase (Holmgren, 1977; Luthman and Holmgren, 1982).

This review will focus on some recent developments in the structure and function of human and other mammalian thioredoxin reductases, in particular in relation to the requirement of selenium, a well-known antioxidant element.

MAMMALIAN THIOREDOXIN SYSTEMS

Mammalian thioredoxin systems comprise the same reactions as in all other living cells:

$$\text{Trx-S}_2 + \text{NADPH} + \text{H}^+ \xrightarrow{\text{TrxR}} \text{Trx-(SH)}_2 + \text{NADP}^+ \quad (1)$$

$$\text{Trx(SH)}_2 + \text{Protein-S}_2 \underset{\longleftarrow}{\overset{\text{spontaneous}}{\longrightarrow}} \text{Trx-S}_2 + \text{Protein-(SH)}_2 \quad (2)$$

Reduction of Trx-S_2 by thioredoxin reductase (TrxR) follows Michaelis-Menten kinetics with a K_m value of Trx-S_2 of about 2.5 μM and K_{cat} of about 3,000 per min (Reaction 1) (Luthman and Holmgren, 1982). Trx-$(SH)_2$ is a powerful protein disulfide reductase with a K_2 of 5×10^4 M^{-1} s^{-1} for insulin, a substrate used in assays (Reaction 2) (Holmgren, 1979a). However, Reaction 2 is reversible and dependent on the redox potential of the protein disulfide/dithiol pair. Via Reaction 2, thioredoxin may therefore catalyze general reactions between pairs of thiols and disulfides acting as a shuttle (Holmgren, 1979b).

Among the properties noted early for mammalian thioredoxin reductase was its ability to directly reduce 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) (Holmgren, 1977), which is used today as a convenient substrate in assays of the purified enzyme (Holmgren and Bjornstedt, 1995). Furthermore, quite a remarkable number of molecules have been shown to be reduced by mammalian thioredoxin reductase (Table 1). These include alloxan (Holmgren and Lyckeborg, 1980), which is known to be particularly toxic for pancreatic Langerhans islet insulin-producing B cells, where thioredoxin reductase may be participating in generation of toxic ROS leading to cell death and diabetes (Halliwell and Gutteridge, 1999). Thioredoxin reductase will also reduce the disulfide bond of thioredoxins from different species. In the case of *E. coli* thioredoxin, there is a 14-fold higher K_m value but almost identical K_{cat}. The growing large number of proteins with thioredoxin domains (Ferrari and Söling, 1999) including protein disulfide isomerases (PDI) and

TABLE 1. SUBSTRATES FOR DIRECT REDUCTION BY NADPH AND MAMMALIAN THIOREDOXIN REDUCTASE

Substrate	*Reference*
Thioredoxin-S_2	Holmgren (1985)
SeO_3^{2-} and selenocystine	Kumar *et al.* (1992)
S-Nitrosoglutathione (GSNO)	Nikitovic and Holmgren (1996)
Plasma glutathione peroxidase	Bjornstedt *et al.* (1994)
Lipid hydroperoxides	Bjornstedt *et al.* (1995)
Alloxan	Holmgren and Lyckeborg (1980)

analogues are substrates for thioredoxin reductase (Lundstrom and Holmgren, 1990; Lundstrom *et al.*, 1995). How this has physiological relevance remains to be established, but it could well be involved in oxidative stress related functions of calcium movements (Morad and Suzuki, 2000) and requires further studies.

Of specific interest was the discovery that lipid hydroperoxides (HPETE) are direct substrates for NADPH and thioredoxin reductase using either the human or the bovine enzymes and that free selenocyst(e)ine was shown to enhance this reaction (Bjornstedt *et al.*, 1995).

REACTIVITY OF SELENIUM COMPOUNDS WITH THIOREDOXIN REDUCTASE

The first studies on the reactivity of thioredoxin reductases with selenium compounds (Holmgren and Kumar, 1989) were aimed at understanding the reported inhibitory effects of inorganic selenium compounds like selenite on the growth of mouse tumor cells (reviewed by Ip, 1998). When we tested selenite (1–10 μM), it was surprisingly found to be a direct substrate for the mammalian thioredoxin reductase (Kumar *et al.*, 1992) (Reaction 3):

$$SeO_3^{2-} + 3NADPH + 3H^+ \xrightarrow{TrxR} Se^{2-} + 3H_2O + 3NADP^+ \quad (3)$$

The product selenide (Se^{2-}) generated anaerobically is required for selenocysteine synthesis. Under normal aerobic conditions, the reaction between selenite and mammalian thioredoxin reductase is redox cycling by oxygen resulting in nonstoichiometric oxidation of large amounts of NADPH (Kumar *et al.*, 1992). This is true also for selenodiglutathione (GS-Se-SG) (Bjornstedt *et al.*, 1992). Selenocystine is also a substrate for thioredoxin reductase with a K_m value of 6 μM and a K_{cat} of 3,000 $\times$ min^{-1} (Bjornstedt *et al.*, 1997). In the presence of 10 μM selenite, a strong inhibition of the ribonucleotide reductase reaction (85%) as well as general protein disulfide reduction was observed (Bjornstedt *et al.*, 1992). These results showed that selenite is toxic to particularly tumor cells because of the redox cycling and potential generation of free radicals via thioredoxin reductase. Selenide (Se^- and HSe^-) is readily autooxidized and generates DNA-damaging free radicals as observed in model studies (Whiting *et al.*, 1980; Seko and Imura, 1997). Many tumor cells express 10-fold higher levels of thioredoxin reductase, with up to 0.5% of total protein (Gladyshev *et al.*, 1996; Gallegos *et al.*, 1997; Berggren *et al.*, 1997). Cells do not contain a free pool of selenocysteine, as this would prohibit using oxygenated lipid intermediates like prostaglandins or leukotrienes (Bjornstedt *et al.*, 1995), and it would furthermore redox cycle by oxygen by thioredoxin reductase and thioredoxin (Kumar *et al.*, 1992). As will be discussed below, selenocysteine synthesis utilizes a cotranslational machinery for the proteins having this rare 21st amino acid encoded by TGA in DNA and UGA in mRNA (Böck *et al.*, 1991; Low and Berry, 1996).

STRUCTURE OF MAMMALIAN THIOREDOXIN REDUCTASE

Thioredoxin reductase from rat liver cytosol was purified to homogeneity in 1982 and shown to have subunits of M_r 58,000 (Luthman and Holmgren, 1982). The enzyme contained

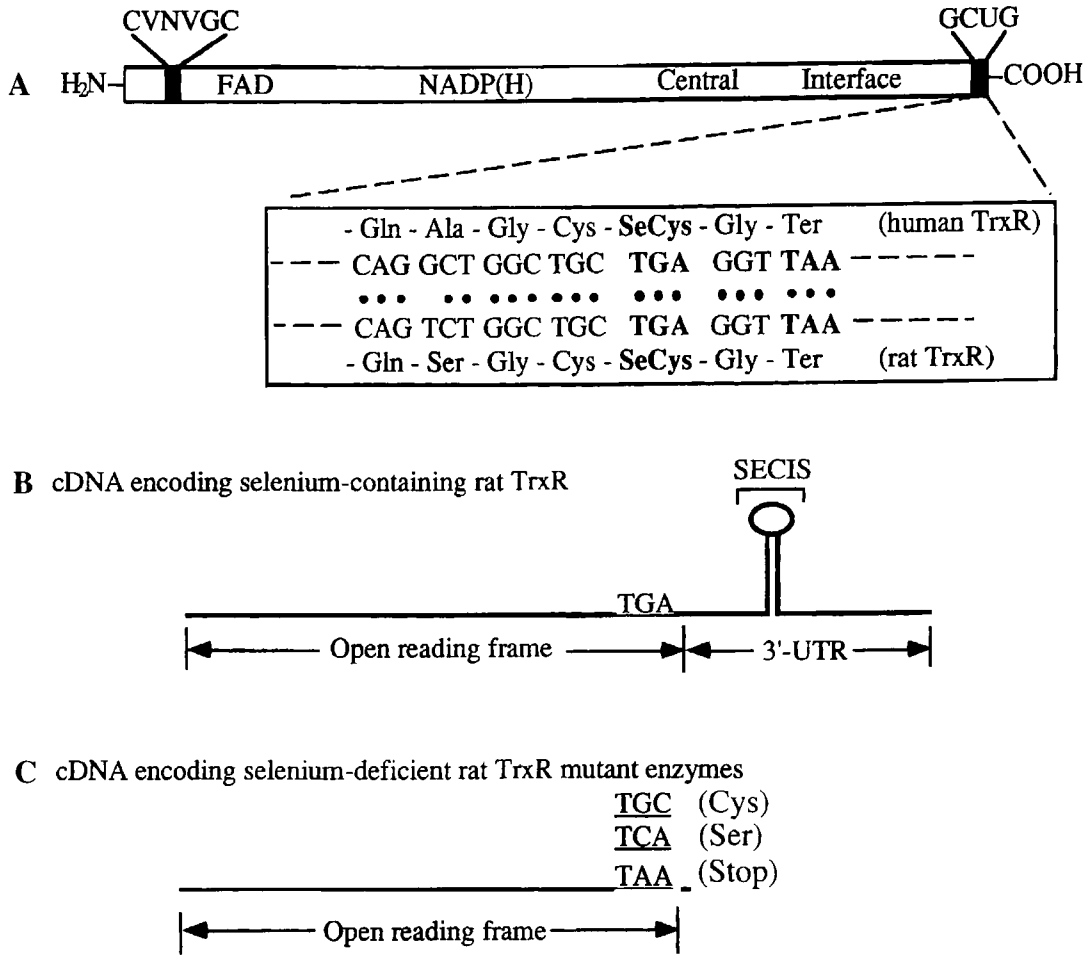

FIG. 1. (a) Schematic structure of rat and human cytosolic thioredoxin reductase based on the homology to GSH reductase, with the conserved active site redox active disulfide in one-letter abbreviations and the nucleotide and protein sequence of the carboxyl terminus of the proteins. (b) Native rat TrxR cDNA with the TGA codon for selenocysteine and the SECIS element in the 3'-untranslated region. (c) Engineered cDNA for expression of rat TrxR mutants replacing the SeCys residue by Cys, Ser or by a stop generating the Des-SeCys-Gly mutant protein (Zhong and Holmgren 2000). Structures are not drawn to scale.

two moles of FAD, and titration with NADPH resulted in a spectral change similar to that of glutathione reductase (Arscott *et al.*, 1997). The enzymes from calf thymus and liver as well as the human placenta enzyme purified by a different method had similar activity (Holmgren and Bjornstedt, 1995; Gromer *et al.*, 1998). These enzymes generally cross-react with the cytosolic thioredoxins from human, bovine, or rat with full activity (Ren *et al.*, 1993).

The sequence of cloned human thioredoxin reductase was reported by Powis and co-workers (Gasdaska *et al.*, 1995), who found a protein homologous to glutathione reductase. However, the cloned protein was a putative thioredoxin reductase because expression in *E. coli* resulted in a subunit of the expected size (57 kDa), but the protein did not bind FAD and consequently lacked activity. Selenium in human thioredoxin reductase was discovered by Stadtman and co-workers (Tamura and Stadtman, 1996) using ^{35}S-labeled selenite in tissue culture experiments of carcinoma cells aimed at isolating a cytochrome P450 potentially containing selenium. This instead resulted in the isolation of a novel yellow protein that turned out to have thioredoxin reductase activity similar to the known rat liver enzyme (Tamura and Stadtman, 1996). The protein contained selenocysteine, and it was later shown that the TGA interpreted as a stop codon (Gasdaska *et al.*, 1995) encoded selenocysteine (Fig. 1) and the

true stop codon was the TAA downstream (Gladyshev *et al.*, 1996). In our own work, we had sequenced large parts of calf thymus thioredoxin reductase in 1996 and identified an unusual amino acid in the carboxy-terminal peptide and also found an active site sequence identical to that of glutathione reductase (Zhong *et al.*, 1998). On the basis of this, we cloned and sequenced the rat enzyme and found a high homology to GSH reductase, including a 16-residue elongation with the carboxy-terminal conserved sequence-Gly-Cys-SeCys-Gly. We also identified a typical selenocysteine insertion sequence (SECIS) element in the 3′-untranslated region required for selenocysteine synthesis (Zhong *et al.*, 1998). Alkylation of selenocysteine residue inactivating the enzyme was only possible after reduction by NADPH. Furthermore, treatment of this reduced enzyme with carboxypeptidase Y removed selenocysteine and also resulted in loss of enzyme activity in reduction of DTNB and thioredoxin (Zhong *et al.*, 1998). These results demonstrated that all the mammalian cytosolic enzymes contained selenocysteine, which was required for enzyme activity.

ESSENTIAL ROLE OF SELENOCYSTEINE AND RECOMBINANT EXPRESSION OF RAT THIOREDOXIN REDUCTASE

Because the SECIS element of the mRNA forms a complicated hairpin secondary structure not recognized by the *E. coli* selenocysteine synthesis machinery (Low and Berry, 1996), we decided to remove this element from the gene (Fig. 1) and introduce mutations at the selenocysteine residue (Zhong and Holmgren, 2000). Thus, we have expressed and purified to homogeneity recombinant enzymes with the selenocysteine replaced by cysteine or by serine. We also engineered the truncated protein expected in selenium deficiency by the UGA in the mRNA acting as a stop codon (Fig. 1). All three proteins were purified to homogeneity in high yields (Zhong and Holmgren, 2000). The truncated enzyme (Des-SeCys-Gly) and the Ser mutant lacked activity as reductants of thioredoxin. In contrast, the selenocystine to cysteine mutant enzyme had about 1.5% activity with a major loss in K_{cat} but also a lower K_m value for human thioredoxin compared to the wild-type rat liver enzyme (Zhong and Holmgren, 2000). Most important, the pH optimum for the cysteine mutant enzyme was 9 as supposed to 7 for the selenocysteine containing wild-type enzyme, strongly suggesting that a low pKa (5.2) selenol directly participates in the mechanism.

HYDROPEROXIDE REDUCTASE ACTIVITY OF MAMMALIAN THIOREDOXIN REDUCTASE

Hydroperoxides like hydrogen peroxide (H_2O_2) and different lipid hydroperoxides are generated in cells, e.g., from the electron transport chain, the metabolism involving cytochrome P450 or from arachidonic acid intermediates in the formation of prostaglandins and leukotrienes (Halliwell and Gutteridge, 1999). Previously, we discovered that mammalian thioredoxin reductases directly reduced HPETE by NADPH resulting in production of HETE (Bjornstedt *et al.*, 1995). This activity was strongly stimulated by the addition of free selenocystine and was reported before the subsequent discovery that the enzyme itself contained selenocysteine. Human thioredoxin reductase directly reduced H_2O_2 with initial an apparent K_m value of 2.8 m*M* and K_{cat} of 100 per min (Zhong and Holmgren, 2000). Analyzing the cysteine mutant enzyme demonstrated no detectable H_2O_2 reductase activity consistent with the selenocysteine residue being essential for this activity (Zhong and Holmgren, 2000).

STRUCTURE MODEL AND MECHANISMS OF MAMMALIAN THIOREDOXIN REDUCTASE

Today at least three different isoenzymes of mammalian thioredoxin reductase have been described. Apart from the classical cytosolic enzyme with potential splice variants (Rundlof *et al.*, 2000), there is a mitochondrial thioredoxin system involving a selenocysteine-containing enzyme (Rigobello *et al.*, 1998; Lee *et al.*, 1999; Miranda-Vizuete *et al.*, 1999). In addition, there

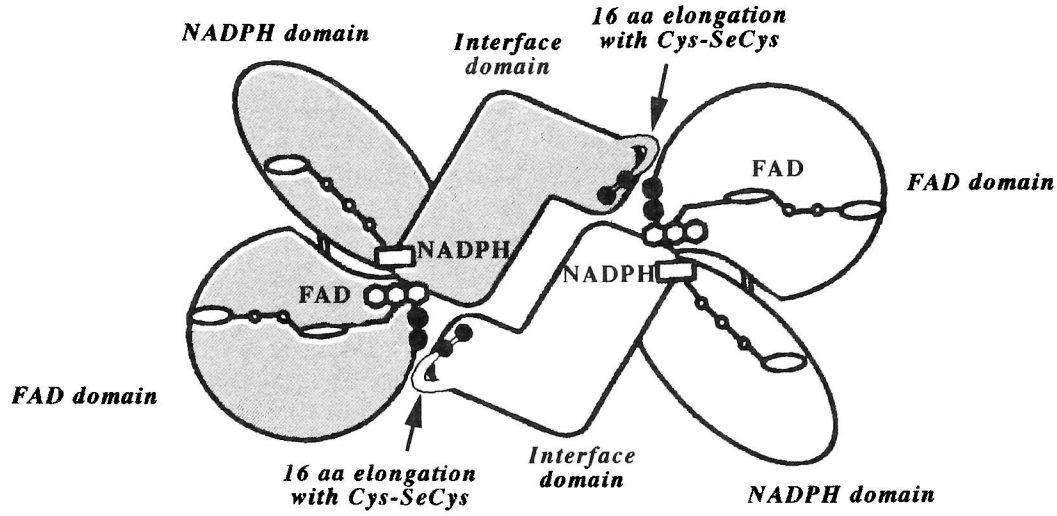

FIG. 2. Schematic structure of mammalian thioredoxin reductase based on homology to GSH reductase. The enzyme contains two identical subunits that from a functional perspective are arranged in a head-to-tail fashion. The NADPH, FAD, and interface domains are shown. The redox active disulfides in the FAD domains are represented as black circles. The selenenylsulfides in the interface domains are also shown. Electrons are transferred from NADPH to FAD and to the redox active disulfide in one subunit and across to the other subunit where the resulting selenolthiol is the active site (Zhong *et al.*, 2000).

is a third form reported, which appears to be testis specific and is elongated at the amino terminus (Sun *et al.*, 1999). However, all of these enzymes have the classical glutathione reductase structure active site (CVNVGC, Fig. 1) and the carboxy-terminal sequence -Gly-Cys-Se-Cys-Gly absolutely conserved.

All three mutant rat enzymes described above (Fig. 1), including the truncated version lacking the SeCys-Gly dipeptide, contained one mole of FAD per monomeric subunit and were enzymatically active proteins (Zhong and Holmgren, 2000). This was shown by titrations under anaerobic conditions with NADPH. The long wave-length spectral changes characteristic of the thiolate-flavin charge transfer complex (Arscott *et al.*, 1997) were observed, demonstrating that the reductive half-reaction characteristic of glutathione reductase operated also in the truncated enzyme (Zhong and Holmgren, 2000). This involves transfer of electrons from NADPH to the FAD and then to the redox active disulfide located in the amino-terminal part of the enzyme (Fig. 1). From the native oxidized enzyme we isolated the carboxy-terminal peptide, which contained a bridge joining the neighboring cysteine and selenocysteine residues (Zhong *et al.*, 2000). This unique selenenylsulfide is the state of the selenium in the oxidized form of the enzyme, which will be present as a selenolthiol in the NADPH-reduced enzyme (Zhong *et al.*, 2000). The active site of the enzyme (Fig. 2) is directly reducing thioredoxin or the other substrates, including hydroperoxides. The enzyme is thus a head-to-tail structure with transfer of electrons across the subunits (Zhong *et al.*, 2000).

ROLE OF SELENIUM IN ANTIOXIDANT DEFENSE

The essential role of selenium in thioredoxin reductase provides a new mechanism for coupling decreased antioxidant defense and loss of cell growth with selenium deficiency. As previously shown, the immunomodulating electrophile 1-chloro-2,4-dinitrobenzene (DNCB) is a strong irreversible inhibitor of thioredoxin reductase, inactivating the enzyme only in the

presence of NADPH (Arner *et al.*, 1995). We showed that the carboxy-terminal adjacent cysteine and selenocysteine residues were both alkylated by DNCB (Nordberg *et al.*, 1998). However, the modified enzyme is still active and has a more than 30-fold increase in activity as an NADPH oxidase activity producing superoxide from NADPH and oxygen (Arner *et al.*, 1995). This ROS may account for some of the immunomodulating properties of DNCB (Arner, 1999). It has been reported that the selenium content of thioredoxin reductase varies with the selenium status (Hill *et al.*, 1997) and that more active enzyme is particularly produced when selenium is supplemented (Berggren *et al.*, 1997; Gallegos *et al.*, 1997; Fujiwara *et al.*, 1999). Thus, if the truncated version of the enzyme is made, our results show that this may well produce more superoxide from FAD and account for an increased production of reactive species resulting in a higher mutation frequency in cells. This hypothesis would be consistent with known protective roles of selenium in carcinogenesis (Ganther, 1999) and should be tested experimentally.

In electron paramagnetic resonance (EPR) spin trap experiments, we have observed that the pure rat thioredoxin reductase incubated with NADPH in a closed system with initial containing atmospheric oxygen will consume NADPH corresponding to dissolved oxygen (~240 μM) and then give rise to a burst of hydroxyl radicals (S. Kuprin, T. Kerimov, and A. Holmgren, unpublished). The selenium-containing enzyme showed a small burst, whereas *E. coli* thioredoxin reductase and the selenocysteine-to-cysteine mutant rat enzyme produced more of this free radical also inactivating the enzyme. This may be one reason why the mammalian enzyme contains selenium to remove H_2O_2 to avoid toxic production of free radicals.

GLUTAREDOXINS AS ANTIOXIDANTS

Glutaredoxins catalyze the reduction of protein as well as of low-molecular-weight mixed disulfides with GSH and are themselves reduced by glutathione via a specific binding site (Reactions 4–8):

$$\text{Grx-S}_2 + 2\text{GSH} \rightleftarrows \text{Grx-(SH)}_2 + \text{GSSG} \quad (4)$$

$$\text{Grx-(SH)}_2 + \text{Protein-S-SG} \rightleftarrows \text{Grx-S-SG} + \text{Protein-(SH)}_2 \quad (5)$$

$$\text{Grx-S-SG} + \text{GSH} \rightleftarrows \text{Grx-(SH)}_2 + \text{GSSG} \quad (6)$$

$$\text{Grx-(SH)}_2 + \text{Protein-S}_2 \rightleftarrows \text{Grx-S}_2 + \text{Protein-(SH)}_2 \quad (7)$$

$$\text{GSSG} + \text{NADPH} + \text{H}^+ \xrightarrow{\text{GR}} 2\text{GSH} + \text{NADP}^+ \quad (8)$$

As a dithiol protein disulfide reductase (Reactions 4 and 7), glutaredoxin is known to work with ribonucleotide reductase and other proteins (Holmgren and Aslund, 1995). The reaction of glutaredoxin is coupled to GSH reductase and NADPH (Reaction 8) or *de novo* synthesis of GSH. Under oxidative stress, glutaredoxin may catalyze formation of mixed disulfides from GSSG (reversal of Reaction 5 and 6), which may be of a protective function to avoid oxidation of a thiol to higher oxidation states. Regulating the activity of phosphotyrosine phosphatases, which contain a low pKa catalytically active SH-group, is one such example (Lee *et al.*, 1998; Barrett *et al.*, 1999). Under conditions, when oxidative stress is relieved, glutaredoxins are the major catalysts to remove glutathione mixed disulfides, which generally lead to inactivation of protein function (Chai *et al.*, 1991).

In the context of GSH peroxidase, it was shown that the extracellular plasma enzyme could utilize glutaredoxin as well as thioredoxin or mammalian thioredoxin reductase as an electron donor. Because plasma lacks free GSH, this may explain how GSH peroxidase can operate in the extracellular space via glutaredoxins (Bjornstedt *et al.*, 1994). How this is related to intracellular functions is not known. However, it was observed that glutaredoxin also functions as an electron donor for

the cytosolic GSH peroxidase (Bjornstedt *et al.*, 1994).

Because glutaredoxin and GSH reductase have no requirement for selenium, this system will be operative under conditions of low selenium and may then partly compensate for the loss of thioredoxin reductase activity. However, all functions of thioredoxin cannot be performed by glutaredoxins.

REACTIONS OF EBSELEN WITH MAMMALIAN THIOREDOXIN REDUCTASE

Ebselen is a selenazol drug with GSH peroxidase-like properties and has extensive effects on cells (Sies, 1995). Because of its antioxidant properties, it has been used in clinical trials against stroke and other forms of ischemic disease (Ogawa *et al.*, 1999). We have found that ebselen promotes the activity of thioredoxin reductase as a hydroperoxide reductase. With H_2O_2 as a substrate, ebselen at 2 μM will stimulate reductase activity 15-fold (M.H. Amiri, H. Masayasu, and A. Holmgren, unpublished). These results suggest that major effects of ebselen are via thioredoxin reductase.

CONCLUSIONS

Because the number of thioredoxin reductases, thioredoxins, and glutaredoxins is still growing, the complexity of redox reactions involved in defense against oxidative stress requires analysis of the enzymatic mechanisms and expression of each enzyme. As with ribonucleotide reductase, the relative contribution and functions of thiols and selenol groups from the thioredoxin systems and thiols from the glutaredoxin systems in a cellular context of defense against oxidative stress and other stresses is yet unknown.

ACKNOWLEDGMENTS

The excellent secretarial assistance of Ms Lena Ringdén is gratefully acknowledged. Research was supported by grants from the Swedish Medical Research Council, The Swedish Cancer Society, the K.A. Wallenberg Foundation, and the I.-B. and A. Lundberg Foundation.

ABBREVIATIONS

DTNB, 5,5′-Dithiobis(2-nitrobenzoic acid); DNCB, 1-chloro-2,4-dinitrobenzene; ebselen, 2-phenyl-1,2-benzisoselenazol-3(2H)-one; Grx, glutaredoxin; HPETE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid; SECIS, selenocysteine insertion sequence; SeCys, selenocysteine; Trx, thioredoxin; TrxR, thioredoxin reductase.

REFERENCES

ARNER, E.S., BJORNSTEDT, M., and HOLMGREN, A. (1995). 1-Chloro-2,4-dinitrobenzene is an irreversible inhibitor of human thioredoxin reductase. Loss of thioredoxin disulfide reductase activity is accompanied by a large increase in NADPH oxidase activity. J. Biol. Chem. **270,** 3479–3482.

ARNER, E.S.J. (1999). Superoxide production by dinitrophenyl-derivatized thioredoxin reductase—a model for the mechanism and correlation to immunostimulation by dinitrohalobenzenes. BioFactors **10,** 219–226.

ARSCOTT, L.D., GROMER, S., SCHIRMER, R.H., BECKER, K., and WILLIAMS, C.H.J. (1997). The mechanism of thioredoxin reductase from human placenta is similar to the mechanisms of lipoamide dehydrogenase and glutathione reductase and is distinct from the mechanism of thioredoxin reductase from Escherichia coli. Proc. Natl. Acad. Sci. USA **94,** 3621–3626.

BARRETT, W.C., DEGNORE, J.P., KONIG, S., FALES, H.M., KENG, Y.F., ZHANG, Z.Y., YIM, M.B., and CHOCK, P.B. (1999). Regulation of PTP1B via glutathionylation of the active site cysteine 215. Biochemistry **38,** 6699–6705.

BERGGREN, M., GALLEGOS, A., GASDASKA, J., and POWIS, G. (1997). Cellular thioredoxin reductase activity is regulated by selenium. Anticancer Res. **17,** 3377–3380.

BJORNSTEDT, M., KUMAR, S., and HOLMGREN, A. (1992). Selenodiglutathione is a highly efficient oxidant of reduced thioredoxin and a substrate for mammalian thioredoxin reductase. J. Biol. Chem. **267,** 8030–8034.

BJORNSTEDT, M., XUE, J., HUANG, W., AKESSON, B., and HOLMGREN, A. (1994). The thioredoxin and glutaredoxin systems are efficient electron donors to human plasma glutathione peroxidase. J. Biol. Chem. **269,** 29382–29384.

BJORNSTEDT, M., HAMBERG, M., KUMAR, S., XUE, J., and HOLMGREN, A. (1995). Human thioredoxin re-

ductase directly reduces lipid hydroperoxides by NADPH and selenocystine strongly stimulates the reaction via catalytically generated selenols. J. Biol. Chem. **270,** 11761–11764.

BJÖRNSTEDT, M., KUMAR, S., BJORKHEM, L., SPYROU, G., and HOLMGREN, A. (1997). Selenium and the thioredoxin and glutaredoxin systems. Biomed. Environmental Sci. **10,** 271–279.

BÖCK, A., FORCHHAMMER, K., HEIDER, L., LEINFELDER, W., SAWERS, G., VEPREK, B., and ZINONI, F. (1991). Selenocysteine: the 21st amino acid. Mol. Microbiol. **5,** 515–520.

CHAE, H.Z., KANG, S.W., and RHEE, S.G. (1999). Isoforms of mammalian peroxiredoxin that reduce peroxides in presence of thioredoxin. Methods Enzymol. **300,** 219–226.

CHAI, Y.C., JUNG, C.H., LII, C.K., ASHRAF, S.S., HENDRICH, S., WOLF, B., SIES, H., and THOMAS, J.A. (1991). Identification of an abundant S-thiolated rat liver protein as carbonic anhydrase III; characterization of S-thiolation and dethiolation reactions. Arch. Biochem. Biophys. **284,** 270–280.

ENGSTROM, N.E., HOLMGREN, A., LARSSON, A., and SODERHALL, S. (1974). Isolation and characterization of calf liver thioredoxin. J. Biol. Chem. **249,** 205–210.

FERRARI, D.M., and SÖLING, H.-D. (1999). The protein disulphide-isomerase family: unravelling a string of folds. Biochem. J. **339,** 1–10.

FUJIWARA, N., FUJII, T., FUJII, J., and TANIGUCHI, N. (1999). Functional expression of rat thioredoxin reductase: selenocysteine insertion sequence element is essential for the active enzyme. Biochem. J. **340,** 439–444.

GALLEGOS, A., BERGGREN, M., GASDASKA, J.R., and POWIS, G. (1997). Mechanisms of the regulation of thioredoxin reductase activity in cancer cells by the chemopreventive agent selenium. Cancer Res. **57,** 4965–4970.

GANTHER, H.E. (1999). Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogenesis **20,** 1657–1666.

GASDASKA, P.Y., GASDASKA, J.R., COCHRAN, S., and POWIS, G. (1995). Cloning and sequencing of a human thioredoxin reductase. FEBS Lett. **373,** 5–9.

GLADYSHEV, V.N., JEANG, K.-T., and STADTMAN, T.C. (1996). Selenocysteine, identified as the penultimate C-terminal residue in human T-cell thioredoxin reductase, corresponds to TGA in the human placental gene. Proc. Natl. Acad. Sci. USA **93,** 6146–6151.

GROMER, S., ARSCOTT, L.D., WILLIAMS, C.H.J., SCHIRMER, R.H., and BECKER, K. (1998). Human placenta thioredoxin reductase: isolation of the selenoenzyme, steady state kinetics, and inhibition by therapeutic gold compounds. J. Biol. Chem. **273,** 20096–20101.

HALLIWELL, B., and GUTTERIGDE, J.M. (1999). *Free Radicals in Biology and Medicine,* 3rd ed. (Oxford University Press, New York) pp. 1–936.

HILL, K.E., MCCOLLUM, G.W., BOEGLIN, M.E., and BURK, R.F. (1997). Thioredoxin reductase activity is decreased by selenium deficiency. Biochem. Biophys. Res. Commun. **234,** 293–295.

HOLMGREN, A. (1977). Bovine thioredoxin system. Purification of thioredoxin reductase from calf liver and thymus and studies of its function in disulfide reduction. J. Biol. Chem. **252,** 4600–4606.

HOLMGREN, A. (1979a). Reduction of disulfides by thioredoxin. Exceptional reactivity of insulin and suggested functions of thioredoxin in mechanism of hormone action. J. Biol. Chem. **254,** 9113–9119.

HOLMGREN, A. (1979b). Thioredoxin catalyzes the reduction of insulin disulfides by dithiothreitol and dihydrolipoamide. J. Biol. Chem. **254,** 9627–9632.

HOLMGREN, A. (1985). Thioredoxin. Annu. Rev. Biochem. **54,** 237–271.

HOLMGREN, A. (1989). Thioredoxin and glutaredoxin systems. J. Biol. Chem. **264,** 13963–13966.

HOLMGREN, A., and ASLUND, F. (1995). Glutaredoxin. Methods Enzymol. **252,** 283–292.

HOLMGREN, A., and BJORNSTEDT, M. (1995). Thioredoxin and thioredoxin reductase. Methods Enzymol. **252,** 199–208.

HOLMGREN, A., and KUMAR, S. (1989). Reactions of the thioredoxin system with selenium. In *Proceedings of the 4th International Symposium on Selenium in Biology and Medicine.* A. Wendel, ed. Heidelberg: Springer Verlag, pp. 47–51.

HOLMGREN, A., and LYCKEBORG, C. (1980). Enzymatic reduction of alloxan by thioredoxin and NADPH-thioredoxin reductase. Proc. Natl. Acad. Sci. USA **77,** 5149–5152.

IP, C. (1998). Lessons from basic research in selenium and cancer prevention. J. Nutr. **128,** 1845–1854.

KUMAR, S., BJORNSTEDT, M., and HOLMGREN, A. (1992). Selenite is a substrate for calf thymus thioredoxin reductase and thioredoxin and elicits a large nonstoichiometric oxidation of NADPH in the presence of oxygen. Eur. J. Biochem. **207,** 435–439.

LEE, S.R., KWON, K.S., KIM, S.R., and RHEE, S.G. (1998). Reversible inactivation of protein-tyrosine phosphatase 1B in A431 cells stimulated with epidermal growth factor. J. Biol. Chem. **273,** 15366–15372.

LEE, S.R., KIM, J.R., KWON, K.S., YOON, H.W., LEVINE, R.L., GINSBURG, A., and RHEE, S.G. (1999). Molecular cloning and characterization of a mitochondrial selenocysteine-containing thioredoxin reductase from rat liver. J. Biol. Chem. **274,** 4722–4734.

LOW, S.C., and BERRY, M.J. (1996). Knowing when not to stop: selenocysteine incorporation in eukaryotes. Trends Biochem. Sci. **21,** 203–208.

LUNDSTROM, J., and HOLMGREN, A. (1990). Protein disulfide-isomerase is a substrate for thioredoxin reductase and has thioredoxin-like activity. J. Biol. Chem. **265,** 9114–9120.

LUNDSTROM, J., BIRNBACH, U., RUPP, K., SOLING, H.-D., and HOLMGREN, A. (1995). Two resident ER proteins CaBP1 and CaBP2 with thioredoxin domains, are substrates for thioredoxin reductase. Comparison with protein disulfide isomerase. FEBS Lett. **357,** 305–308.

LUTHMAN, M., and HOLMGREN, A. (1982). Rat liver thioredoxin and thioredoxin reductase: purification and characterization. Biochemistry **21,** 6628–6633.

MARTIN, J.L. (1995). Thioredoxin—a fold for all reasons. Structure **3,** 245–250.

MIRANDA-VIZUETE, A., DAMDIMOPOULOS, A.E., PEDRAJAS, J.R., GUSTAFSSON, J.A., and SPYROU, G. (1999). Human mitochondrial thioredoxin reductase cDNA cloning, expression and genomic organization. Eur. J. Biochem. **261,** 405–412.

MORAD, M., and SUZUKI, Y.J. (2000). Redox regulation of cardiac muscle calcium signaling. Antiox. Redox Signal. **2,** 65–71.

MOSKOVITZ, J., BERLETT, B.S., POSTON, J.M., and STADTMAN, E.R. (1999). Methionine sulfoxide reductase in antioxidant defense. Methods Enzymol. **300,** 239–244.

NIKITOVIC, D., and HOLMGREN, A. (1996). S-nitrosoglutathione is cleaved by the thioredoxin system with liberation of glutathione and redox regulating nitric oxide. J. Biol. Chem. **271,** 19180–19185.

NORDBERG, J., ZHONG, L., HOLMGREN, A., and ARNER, E.S.J. (1998). Mammalian thioredoxin reductase is irreversibly inhibited by dinitrohalobenzenes by alkylation of both the redox active selenocysteine and its neighboring cysteine residue. J. Biol. Chem. **273,** 10835–10842.

OGAWA, A., YOSIMOTO, T., KIKUCHI, H., SANO, K., SAITO, I., YAMAGUCHI, T., and YASUHARA, H. (1999). Ebselen in acute middle cerebral artery occlusion: A placebo-controlled, double-blind clinical trial. Cerebrovasc. Dis. **9,** 112–118.

REN, X., BJORNSTEDT, M., SHEN, B., ERICSON, M.L., and HOLMGREN, A. (1993). Mutagenesis of structural half-cystine residues in human thioredoxin and effects on the regulation of activity by selenodiglutathione. Biochemistry **32,** 9701–9708.

RIGOBELLO, M.P., CALLEGARO, M.T., BARZON, E., BENETTI, M., and BINDOLI, A. (1998). Purification of mitochondrial thioredoxin reductase and its involvement in the redox regulation of membrane permeability. Free Radic. Biol. Med. **24,** 370–376.

RUNDOLF, A.K., CARLSTEN, M., GIACOBINI, M.M., and ARNER, E.S. (2000). Prominent expression of the selenoprotein thioredoxin reductase in the medullary rays of the rat kidney and thioredoxin reductase mRNA variants differing at the 5′ untranslated region. Biochem. J. **347,** 661–668.

SEKO, Y., and IMURA, N. (1997). Active oxygen generation as a possible mechanism of selenium toxicity. Biomed. Environmental Sci. **10,** 333–339.

SIES, H. (1995). Ebselen. Methods Enzymol. **252,** 341–348.

SUN, Q.-A., WU, Y., ZAPPACOSTA, F., JEANG, K.-T., LEE, B.J., HATFIELD, D.L., and GLADYSHEV, V.N. (1999). Redox regulation of cell signaling by selenocysteine in mammalian thioredoxin reductases. J. Biol. Chem. **274,** 24522–24530.

TAMURA, T., and STADTMAN, T.C. (1996). A new selenoprotein from human lung adenocarcinoma cells: Purification, properties, and thioredoxin reductase activity. Proc. Natl. Acad. Sci. USA **93,** 1006–1011.

WEICHSEL, A., GASDASKA, J.R., POWIS, G., and MONTFORT, W.R. (1996). Crystal structures of reduced, oxidized and mutated human thioredoxins: evidence for a regulatory homodimer. Structure **4,** 735–751.

WHITING, R.F., WEI, L., and STICH, H.F. (1980). Unscheduled DNA synthesis and chromosome aberrations induced by inorganic and organic selenium compounds in the presence of glutathione. Mutat. Res. **78,** 159–169.

ZHONG, L., and HOLMGREN, A. (2000). Essential role of selenium in the catalytic activities of mammalian thioredoxin reductase revealed by characterization of recombinant enzymes with selenocysteine mutations. J. Biol. Chem. **97,** 5854–5859.

ZHONG, L., ARNER, E., LJUNG, J., ASLUND F., and HOLMGREN, A. (1998). Rat and calf thioredoxin reductases are homologous to glutathione reductase with a carboxyterminal elongation containing a conserved catalytically active penultimate selenocysteine residue. J. Biol. Chem. **273,** 8581–8591.

ZHONG, L., ARNÉR, E.S.J., and HOLMGREN, A. (2000). Structure and mechanism of mammalian thioredoxin reductase: The active site is a redox-active selenolthiol/selenenylsulfide formed from the conserved cysteine-selenocysteine sequence. Proc. Natl. Acad. Sci USA **275,** 18121–18128.

Address reprint requests to:
Dr. Arne Holmgren
Medical Nobel Institute for Biochemistry
Department of Medical Biochemistry
and Biophysics
Karolinska Institutet
S-171 77 Stockholm, Sweden

E-mail: arne.holmgren@mbb.ki.se

Received for publication April 23, 2000; accepted June 29, 2000.

This article has been cited by:

1. Tim-Christian Zschauer , Shouji Matsushima , Joachim Altschmied , Dan Shao , Junichi Sadoshima , Judith Haendeler . Interacting with Thioredoxin-1—Disease or No Disease?. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
2. Irfan Rahman, Vuokko L Kinnula. 2012. Strategies to decrease ongoing oxidant burden in chronic obstructive pulmonary disease. *Expert Review of Clinical Pharmacology* **5**:3, 293-309. [CrossRef]
3. Zhi Huang , Aaron H. Rose , Peter R. Hoffmann . 2012. The Role of Selenium in Inflammation and Immunity: From Molecular Mechanisms to Therapeutic Opportunities. *Antioxidants & Redox Signaling* **16**:7, 705-743. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
4. Dmitri E. Fomenko , Vadim N. Gladyshev . 2012. Comparative Genomics of Thiol Oxidoreductases Reveals Widespread and Essential Functions of Thiol-based Redox Control of Cellular Processes. *Antioxidants & Redox Signaling* **16**:3, 193-201. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
5. Jenny K. Ngo, Kelvin J. A. DaviesProtein Degradation in Aging Cells and Mitochondria: Relevance to the Neuromuscular System 89-96. [CrossRef]
6. Esra Birben, Umit Murat Sahiner, Cansin Sackesen, Serpil Erzurum, Omer Kalayci. 2012. Oxidative Stress and Antioxidant Defense. *World Allergy Organization Journal* **5**:1, 9-19. [CrossRef]
7. Claudia Piccoli, Annamaria D'Aprile, Rosella Scrima, Luigi Ambrosi, Roberto Zefferino, Nazzareno Capitanio. 2012. Subcytotoxic mercury chloride inhibits gap junction intercellular communication by a redox- and phosphorylation-mediated mechanism. *Free Radical Biology and Medicine* . [CrossRef]
8. Justin R. Prigge, Sofi Eriksson, Sonya V. Iverson, Tesia A. Meade, Mario R. Capecchi, Elias S.J. Arnér, Edward E. Schmidt. 2011. Hepatocyte DNA replication in growing liver requires either glutathione or a single allele of txnrd1. *Free Radical Biology and Medicine* . [CrossRef]
9. Christian H. Eggers, Melissa J. Caimano, Robert A. Malizia, Toru Kariu, Brian Cusack, Daniel C. Desrosiers, Karsten R. O. Hazlett, Al Claiborne, Utpal Pal, Justin D. Radolf. 2011. The coenzyme A disulphide reductase of Borrelia burgdorferi is important for rapid growth throughout the enzootic cycle and essential for infection of the mammalian host. *Molecular Microbiology* no-no. [CrossRef]
10. Laura Mateos, Torbjörn Persson, Shirin Kathozi, Francisco Javier Gil-Bea, Angel Cedazo-Minguez. 2011. Estrogen protects against amyloid-# toxicity by estrogen receptor #-mediated inhibition of Daxx translocation. *Neuroscience Letters* . [CrossRef]
11. Elena Shumilina, Alice Soldà, Maxim Gerashchenko, Vadim N. Gladyshev, Alexander Dikiy. 2011. 1H, 13C, and 15N NMR resonance assignments of reduced full length and shortened forms of the Grx domain of Mus musculus TGR. *Biomolecular NMR Assignments* . [CrossRef]
12. Pål A. Olsvik, Heidi Amlund, Bente E. Torstensen. 2011. Dietary lipids modulates methylmercury toxicity in Atlantic salmon. *Food and Chemical Toxicology* . [CrossRef]
13. Bradley A. Carlson, Min-Hyuk Yoo, Marcus Conrad, Vadim N. Gladyshev, Dolph L. Hatfield, Jin Mo Park. 2011. Protein kinase-regulated expression and immune function of thioredoxin reductase 1 in mouse macrophages. *Molecular Immunology* . [CrossRef]
14. A. Degrossoli, W. W. Arrais-Silva, M. C. Colhone, F. R. Gadelha, P. P. Joazeiro, S. Giorgio. 2011. The Influence of Low Oxygen on Macrophage Response to Leishmania Infection. *Scandinavian Journal of Immunology* **74**:2, 165-175. [CrossRef]
15. Yu-Lan Niu, Chong Li, Guang-Yi Zhang. 2011. Blocking Daxx trafficking attenuates neuronal cell death following ischemia/reperfusion in rat hippocampus CA1 region. *Archives of Biochemistry and Biophysics* . [CrossRef]
16. Ryan J. Mailloux, Mary-Ellen Harper. 2011. Uncoupling proteins and the control of mitochondrial reactive oxygen species production. *Free Radical Biology and Medicine* . [CrossRef]
17. Athar Alam, Manish Goyal, Mohd. Shameel Iqbal, Samik Bindu, Sumanta Dey, Chinmay Pal, Pallab Maity, Nahren Manuel Mascarenhas, Nanda Ghoshal, Uday Bandyopadhyay. 2011. Cysteine-3 and cysteine-4 are essential for the thioredoxin-like oxidoreductase and antioxidant activities of Plasmodium falciparum macrophage migration inhibitory factor. *Free Radical Biology and Medicine* **50**:11, 1659-1668. [CrossRef]

18. Niv Bachnoff, Michael Trus, Daphne Atlas. 2011. Alleviation of oxidative stress by potent and selective thioredoxin-mimetic peptides. *Free Radical Biology and Medicine* **50**:10, 1355-1367. [CrossRef]
19. Gil Leibowitz, Nurit Kaiser, Erol Cerasi. 2011. #-Cell failure in type 2 diabetes. *Journal of Diabetes Investigation* **2**:2, 82-91. [CrossRef]
20. G. Kapoor, H.S. Banyal. 2011. Purification and Characterization of Plasmodium berghei Thioredoxin Reductase. *Asian Journal of Animal Sciences* **5**:2, 145-152. [CrossRef]
21. Ying Qu, Jinhua Wang, Partha S. Ray, Hua Guo, Jian Huang, Miyung Shin-Sim, Bolanle A. Bukoye, Bingya Liu, Adrian V. Lee, Xin Lin, Peng Huang, John W. Martens, Armando E. Giuliano, Ning Zhang, Ning-Hui Cheng, Xiaojiang Cui. 2011. Thioredoxin-like 2 regulates human cancer cell growth and metastasis via redox homeostasis and NF-#B signaling. *Journal of Clinical Investigation* **121**:1, 212-225. [CrossRef]
22. Michael J Morgan, Zheng-gang Liu. 2011. Crosstalk of reactive oxygen species and NF-#B signaling. *Cell Research* **21**:1, 103-115. [CrossRef]
23. Huihui Zhang, Dong Cao, Wei Cui, Mingjuan Ji, Xiaohong Qian, Liangwei Zhong. 2010. Molecular bases of thioredoxin and thioredoxin reductase-mediated prooxidant actions of (-)-epigallocatechin-3-gallate. *Free Radical Biology and Medicine* **49**:12, 2010-2018. [CrossRef]
24. K. L. Morgan, A. O. Estevez, C. L. Mueller, B. Cacho-Valadez, A. Miranda-Vizuete, N. J. Szewczyk, M. Estevez. 2010. The Glutaredoxin GLRX-21 Functions to Prevent Selenium-Induced Oxidative Stress in Caenorhabditis elegans. *Toxicological Sciences* **118**:2, 530-543. [CrossRef]
25. Thorsten Brenner, Stefan Hofer, Claudia Rosenhagen, Jochen Steppan, Christoph Lichtenstern, Jürgen Weitz, Thomas Bruckner, Ivan K. Lukic, Eike Martin, Angelika Bierhaus. 2010. Macrophage Migration Inhibitory Factor (MIF) and Manganese Superoxide Dismutase (MnSOD) as Early Predictors for Survival in Patients with Severe Sepsis or Septic Shock. *Journal of Surgical Research* **164**:1, e163-e171. [CrossRef]
26. G. Leibowitz, E. Bachar, M. Shaked, A. Sinai, M. Ketzinel-Gilad, E. Cerasi, N. Kaiser. 2010. Glucose regulation of #-cell stress in type 2 diabetes. *Diabetes, Obesity and Metabolism* **12**, 66-75. [CrossRef]
27. Y. Ioannou, J.-Y. Zhang, F. H. Passam, S. Rahgozar, J. C. Qi, B. Giannakopoulos, M. Qi, P. Yu, D. M. Yu, P. J. Hogg, S. A. Krilis. 2010. Naturally occurring free thiols within 2-glycoprotein I in vivo: nitrosylation, redox modification by endothelial cells, and regulation of oxidative stress-induced cell injury. *Blood* **116**:11, 1961-1970. [CrossRef]
28. Nicolas Ugarte , Isabelle Petropoulos , Bertrand Friguet . 2010. Oxidized Mitochondrial Protein Degradation and Repair in Aging and Oxidative Stress. *Antioxidants & Redox Signaling* **13**:4, 539-549. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
29. Young-Mi Go , Dean P. Jones . 2010. Redox Control Systems in the Nucleus: Mechanisms and Functions. *Antioxidants & Redox Signaling* **13**:4, 489-509. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
30. Yan Xu , Leslie R. Morse , Raquel Assed Bezerra da Silva , Paul R. Odgren , Hajime Sasaki , Philip Stashenko , Ricardo A. Battaglino . 2010. PAMM: A Redox Regulatory Protein That Modulates Osteoclast Differentiation. *Antioxidants & Redox Signaling* **13**:1, 27-37. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
31. Michael J. Morgan, Zheng-gang Liu. 2010. Reactive oxygen species in TNF#-induced signaling and cell death. *Molecules and Cells* **30**:1, 1-12. [CrossRef]
32. Vanisree Mulabagal, Angela I. Calderón. 2010. Development of binding assays to screen ligands for Plasmodium falciparum thioredoxin and glutathione reductases by ultrafiltration and liquid chromatography/mass spectrometry. *Journal of Chromatography B* **878**:13-14, 987-993. [CrossRef]
33. Mohammad Ali Esmaeili, Ali Sonboli. 2010. Antioxidant, free radical scavenging activities of Salvia brachyantha and its protective effect against oxidative cardiac cell injury. *Food and Chemical Toxicology* **48**:3, 846-853. [CrossRef]
34. Hana Odeh, Kristina L. Hunker, Inna A. Belyantseva, Hela Azaiez, Matthew R. Avenarius, Lili Zheng, Linda M. Peters, Leona H. Gagnon, Nobuko Hagiwara, Michael J. Skynner, Murray H. Brilliant, Nicholas D. Allen, Saima Riazuddin, Kenneth R. Johnson, Yehoash Raphael, Hossein Najmabadi, Thomas B. Friedman, James R. Bartles,

Richard J.H. Smith, David C. Kohrman. 2010. Mutations in Grxcr1 Are The Basis for Inner Ear Dysfunction in the Pirouette Mouse. *The American Journal of Human Genetics* **86**:2, 148-160. [CrossRef]

35. Woojin Jeong, Yuyeon Jung, Hojin Kim, Sun Joo Park, Sue Goo Rhee. 2009. Thioredoxin-related protein 14, a new member of the thioredoxin family with disulfide reductase activity: Implication in the redox regulation of TNF-# signaling. *Free Radical Biology and Medicine* **47**:9, 1294-1303. [CrossRef]
36. Rodgoun Attarian, Chelsea Bennie, Horacio Bach, Yossef Av-Gay. 2009. Glutathione disulfide and S-nitrosoglutathione detoxification by Mycobacterium tuberculosis thioredoxin system. *FEBS Letters* **583**:19, 3215-3220. [CrossRef]
37. Alicia J. Kowaltowski, Nadja C. de Souza-Pinto, Roger F. Castilho, Anibal E. Vercesi. 2009. Mitochondria and reactive oxygen species. *Free Radical Biology and Medicine* **47**:4, 333-343. [CrossRef]
38. Joachim Altschmied , Judith Haendeler . 2009. Thioredoxin-1 and Endothelial Cell Aging: Role in Cardiovascular Diseases. *Antioxidants & Redox Signaling* **11**:7, 1733-1740. [Abstract] [Full Text PDF] [Full Text PDF with Links]
39. Stefan Hofer, Claudia Rosenhagen, Hajime Nakamura, Junji Yodoi, Christian Bopp, Johannes B. Zimmermann, Meike Goebel, Peter Schemmer, Kartrin Hoffmann, Klaus Schulze-Osthoff, Raoul Breitkreutz, Markus A. Weigand. 2009. Thioredoxin in human and experimental sepsis*. *Critical Care Medicine* **37**:7, 2155-2159. [CrossRef]
40. Jean-Pierre Jacquot, Hans Eklund, Nicolas Rouhier, Peter Schürmann. 2009. Structural and evolutionary aspects of thioredoxin reductases in photosynthetic organisms. *Trends in Plant Science* **14**:6, 336-343. [CrossRef]
41. D LEE, N AHSAN, S LEE, J LEE, J BAHK, K KANG, B LEE. 2009. Chilling stress-induced proteomic changes in rice roots. *Journal of Plant Physiology* **166**:1, 1-11. [CrossRef]
42. Laure Michelet, Mirko Zaffagnini, D. LemaireThioredoxins and Related Proteins 401-443. [CrossRef]
43. E. V. Kalinina, N. N. Chernov, A. N. Saprin. 2008. Involvement of thio-, peroxi-, and glutaredoxins in cellular redox-dependent processes. *Biochemistry (Moscow)* **73**:13, 1493-1510. [CrossRef]
44. Y GO, D JONES. 2008. Redox compartmentalization in eukaryotic cells. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1273-1290. [CrossRef]
45. M. E. Perez-Perez, E. Martin-Figueroa, F. J. Florencio. 2008. Photosynthetic Regulation of the Cyanobacterium Synechocystis sp. PCC 6803 Thioredoxin System and Functional Analysis of TrxB (Trx x) and TrxQ (Trx y) Thioredoxins. *Molecular Plant* **2**:2, 270-283. [CrossRef]
46. John M. Wood, Karin U. Schallreuter. 2008. A plaidoyer for cutaneous enzymology: our view of some important unanswered questions on the contributions of selected key enzymes to epidermal homeostasis. *Experimental Dermatology* **17**:7, 569-578. [CrossRef]
47. Talin Ebrahimian , Rhian M. Touyz . 2008. Thioredoxin in Vascular Biology: Role in Hypertension. *Antioxidants & Redox Signaling* **10**:6, 1127-1136. [Abstract] [Full Text PDF] [Full Text PDF with Links]
48. Nicolas Rouhier, Stéphane D. Lemaire, Jean-Pierre Jacquot. 2008. The Role of Glutathione in Photosynthetic Organisms: Emerging Functions for Glutaredoxins and Glutathionylation. *Annual Review of Plant Biology* **59**:1, 143-166. [CrossRef]
49. Bertrand Friguet, Anne-Laure Bulteau, Isabelle Petropoulos. 2008. Mitochondrial protein quality control: Implications in ageing. *Biotechnology Journal* **3**:6, 757-764. [CrossRef]
50. Jolanta Sroka, Agata Antosik, Jaros#aw Czy#, Ivan Nalvarte, Jerker M. Olsson, Giannis Spyrou, Zbigniew Madeja. 2007. Overexpression of thioredoxin reductase 1 inhibits migration of HEK-293 cells. *Biology of the Cell* **99**:12, 677. [CrossRef]
51. Isabella Dalle-Donne, Ranieri Rossi, Daniela Giustarini, Roberto Colombo, Aldo Milzani. 2007. S-glutathionylation in protein redox regulation. *Free Radical Biology and Medicine* **43**:6, 883-898. [CrossRef]
52. Alla A. Bondareva, Mario R. Capecchi, Sonya V. Iverson, Yan Li, Nathan I. Lopez, Olivier Lucas, Gary F. Merrill, Justin R. Prigge, Ashley M. Siders, Maki Wakamiya, Stephanie L. Wallin, Edward E. Schmidt. 2007. Effects of thioredoxin reductase-1 deletion on embryogenesis and transcriptome. *Free Radical Biology and Medicine* **43**:6, 911-923. [CrossRef]
53. Yosuke Funato , Hiroaki Miki . 2007. Nucleoredoxin, a Novel Thioredoxin Family Member Involved in Cell Growth and Differentiation. *Antioxidants & Redox Signaling* **9**:8, 1035-1058. [Abstract] [Full Text PDF] [Full Text PDF with Links]

54. Sun Yee Kim, Su Min Lee, Jean Kyoung Tak, Kyeong Sook Choi, Taeg Kyu Kwon, Jeen-Woo Park. 2007. Regulation of singlet oxygen-induced apoptosis by cytosolic NADP+-dependent isocitrate dehydrogenase. *Molecular and Cellular Biochemistry* **302**:1-2, 27-34. [CrossRef]
55. Marianne Ilbert, Janina Horst, Sebastian Ahrens, Jeannette Winter, Paul C F Graf, Hauke Lilie, Ursula Jakob. 2007. The redox-switch domain of Hsp33 functions as dual stress sensor. *Nature Structural & Molecular Biology* **14**:6, 556-563. [CrossRef]
56. Alberto Jiménez, Laura Mateos, José R. Pedrajas, Antonio Miranda-Vizuete, José L. Revuelta. 2007. The txl1 + gene from Schizosaccharomyces pombe encodes a new thioredoxin-like 1 protein that participates in the antioxidant defence against tert -butyl hydroperoxide. *Yeast* **24**:6, 481-490. [CrossRef]
57. Stéphane D. Lemaire, Laure Michelet, Mirko Zaffagnini, Vincent Massot, Emmanuelle Issakidis-Bourguet. 2007. Thioredoxins in chloroplasts. *Current Genetics* **51**:6, 343-365. [CrossRef]
58. Maria L. Mansego , Sebastian Blesa , Veronica Gonzalez-Albert , Maria C. Tormos , Guillermo Saez , Josep Redon , Felipe J. Chaves . 2007. Discordant Response of Glutathione and Thioredoxin Systems in Human Hypertension?. *Antioxidants & Redox Signaling* **9**:4, 507-514. [Abstract] [Full Text PDF] [Full Text PDF with Links]
59. Masashi Takizawa, Kumiko Komori, Yoshiko Tampo, Masanori Yonaha. 2007. Paraquat-induced oxidative stress and dysfunction of cellular redox systems including antioxidative defense enzymes glutathione peroxidase and thioredoxin reductase. *Toxicology in Vitro* **21**:3, 355-363. [CrossRef]
60. Haifeng Zhang, Yan Luo, Wei Zhang, Yun He, Shengchuan Dai, Rong Zhang, Yan Huang, Pascal Bernatchez, Frank J. Giordano, Gerald Shadel, William C. Sessa, Wang Min. 2007. Endothelial-Specific Expression of Mitochondrial Thioredoxin Improves Endothelial Cell Function and Reduces Atherosclerotic Lesions. *The American Journal of Pathology* **170**:3, 1108-1120. [CrossRef]
61. Ying Hu, Stefan Rahlfs, Volker Mersch-Sundermann, Katja Becker. 2007. Resveratrol modulates mRNA transcripts of genes related to redox metabolism and cell proliferation in non-small-cell lung carcinoma cells. *Biological Chemistry* **388**:2, 207-219. [CrossRef]
62. C.G. Clark, U.C.M. Alsmark, M. Tazreiter, Y. Saito#Nakano, V. Ali, S. Marion, C. Weber, C. Mukherjee, I. Bruchhaus, E. Tannich, M. Leippe, T. Sicheritz#Ponten, P.G. Foster, J. Samuelson, C.J. Noël, R.P. Hirt, T.M. Embley, C.A. Gilchrist, B.J. Mann, U. Singh, J.P. Ackers, S. Bhattacharya, A. Bhattacharya, A. Lohia, N. Guillén, M. Duchêne, T. Nozaki, N. HallStructure and Content of the Entamoeba histolytica Genome **65**, 51-190. [CrossRef]
63. Laure Michelet, Mirko Zaffagnini, Vincent Massot, Eliane Keryer, Hélène Vanacker, Myroslawa Miginiac-Maslow, Emmanuelle Issakidis-Bourguet, Stéphane D. Lemaire. 2006. Thioredoxins, glutaredoxins, and glutathionylation: new crosstalks to explore. *Photosynthesis Research* **89**:2-3, 225-245. [CrossRef]
64. Jonathan L. Pan, James C.A. Bardwell. 2006. The origami of thioredoxin-like folds. *Protein Science* **15**:10, 2217-2227. [CrossRef]
65. Judith Haendeler . 2006. Thioredoxin-1 and Posttranslational Modifications. *Antioxidants & Redox Signaling* **8**:9-10, 1723-1728. [Abstract] [Full Text PDF] [Full Text PDF with Links]
66. S Akterin, R F Cowburn, A Miranda-Vizuete, A Jiménez, N Bogdanovic, B Winblad, A Cedazo-Minguez. 2006. Involvement of glutaredoxin-1 and thioredoxin-1 in #-amyloid toxicity and Alzheimer's disease. *Cell Death and Differentiation* **13**:9, 1454-1465. [CrossRef]
67. Bernard J. Scallon, Linda A. Snyder, G. Mark Anderson, Qiming Chen, Li Yan, Louis M. Weiner, Marian T. Nakada. 2006. A Review of Antibody Therapeutics and Antibody-Related Technologies for Oncology. *Journal of Immunotherapy* **29**:4, 351-364. [CrossRef]
68. Marianne Ilbert , Paul C.F. Graf , Ursula Jakob . 2006. Zinc Center as Redox Switch—New Function for an Old Motif. *Antioxidants & Redox Signaling* **8**:5-6, 835-846. [Abstract] [Full Text PDF] [Full Text PDF with Links]
69. Kirk T. Kitchin, Kathleen Wallace. 2006. Arsenite binding to synthetic peptides: The effect of increasing length between two cysteines. *Journal of Biochemical and Molecular Toxicology* **20**:1, 35-38. [CrossRef]
70. Judith Haendeler. 2006. Nitric oxide and endothelial cell aging. *European Journal of Clinical Pharmacology* **62**:S1, 137-140. [CrossRef]
71. Petra Štefanková, Dušan Pere#ko, Imrich Barák, Marta Kollárová. 2006. The thioredoxin system fromStreptomyces coelicolor. *Journal of Basic Microbiology* **46**:1, 47-55. [CrossRef]

72. Alberto Jiménez, Markku Pelto-Huikko, Jan-Åke Gustafsson, Antonio Miranda-Vizuete. 2006. Characterization of human thioredoxin-like-1: Potential involvement in the cellular response against glucose deprivation. *FEBS Letters* **580**:3, 960-967. [CrossRef]

73. Luc Farout , Bertrand Friguet . 2006. Proteasome Function in Aging and Oxidative Stress: Implications in Protein Maintenance Failure. *Antioxidants & Redox Signaling* **8**:1-2, 205-216. [Abstract] [Full Text PDF] [Full Text PDF with Links]

74. Alexander V. Peskin, Christine C. Winterbourn. 2006. Taurine chloramine is more selective than hypochlorous acid at targeting critical cysteines and inactivating creatine kinase and glyceraldehyde-3-phosphate dehydrogenase. *Free Radical Biology and Medicine* **40**:1, 45-53. [CrossRef]

75. Jaanus Kruusma, Adam M. Benham, J. A. Gareth Williams, Ritu Kataky. 2006. An introduction to thiol redox proteins in the endoplasmic reticulum and a review of current electrochemical methods of detection of thiols. *The Analyst* **131**:4, 459. [CrossRef]

76. In Sup Kil, Tae Lin Huh, Young Sup Lee, You Mie Lee, Jeen-Woo Park. 2006. Regulation of replicative senescence by NADP+-dependent isocitrate dehydrogenase. *Free Radical Biology and Medicine* **40**:1, 110-119. [CrossRef]

77. J. Pallauf, A.S. MüllerChapter 6 Inorganic feed additives **4**, 179-249. [CrossRef]

78. Paul A Marks, Milos Dokmanovic. 2005. Histone deacetylase inhibitors: discovery and development as anticancer agents. *Expert Opinion on Investigational Drugs* **14**:12, 1497-1511. [CrossRef]

79. Judith Haendeler. 2005. Protective role of thioredoxin-1 in cardiovascular systems. *Signal Transduction* **5**:6, 314-321. [CrossRef]

80. Kumuda C. Das . 2005. Thioredoxin and Its Role in Premature Newborn Biology. *Antioxidants & Redox Signaling* **7**:11-12, 1740-1743. [Abstract] [Full Text PDF] [Full Text PDF with Links]

81. Mark D. Temple, Gabriel G. Perrone, Ian W. Dawes. 2005. Complex cellular responses to reactive oxygen species. *Trends in Cell Biology* **15**:6, 319-326. [CrossRef]

82. Luis Moroder. 2005. Isosteric replacement of sulfur with other chalcogens in peptides and proteins. *Journal of Peptide Science* **11**:4, 187-214. [CrossRef]

83. Alicia J. Kowaltowski , Gary Fiskum . 2005. Redox Mechanisms of Cytoprotection by Bcl-2. *Antioxidants & Redox Signaling* **7**:3-4, 508-514. [Abstract] [Full Text PDF] [Full Text PDF with Links]

84. Andreas Barthel, Lars-Oliver Klotz. 2005. Phosphoinositide 3-kinase signaling in the cellular response to oxidative stress. *Biological Chemistry* **386**:3, 207-216. [CrossRef]

85. Hideaki Kamata, Shi-ichi Honda, Shin Maeda, Lufen Chang, Hajime Hirata, Michael Karin. 2005. Reactive Oxygen Species Promote TNF#-Induced Death and Sustained JNK Activation by Inhibiting MAP Kinase Phosphatases. *Cell* **120**:5, 649-661. [CrossRef]

86. T ASIKAINEN, C WHITE. 2005. Antioxidant defenses in the preterm lung: role for hypoxia-inducible factors in BPD?. *Toxicology and Applied Pharmacology* **203**:2, 177-188. [CrossRef]

87. Bernd Sido, Thomas Giese, Frank Autschbach, Felix Lasitschka, Jutta Braunstein, Stefan?C. Meuer. 2005. Potential role of thioredoxin in immune responses in intestinal lamina propria T?lymphocytes. *European Journal of Immunology* **35**:2, 408-417. [CrossRef]

88. Markus C. Wahl, Angelika Irmler, Beate Hecker, R. Heiner Schirmer, Katja Becker. 2005. Comparative Structural Analysis of Oxidized and Reduced Thioredoxin from Drosophila melanogaster. *Journal of Molecular Biology* **345**:5, 1119-1130. [CrossRef]

89. Isabelle Petropoulos, Bertrand Friguet. 2005. Protein maintenance in aging and replicative senescence: a role for the peptide methionine sulfoxide reductases. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1703**:2, 261-266. [CrossRef]

90. Cathy J Aitken, Jason M Hodge, Yumiko Nishinaka, Tanya Vaughan, Junji Yodoi, Christopher J Day, Nigel A Morrison, Geoffrey C Nicholson. 2004. Regulation of Human Osteoclast Differentiation by Thioredoxin Binding Protein-2 and Redox-Sensitive Signaling. *Journal of Bone and Mineral Research* **19**:12, 2057-2064. [CrossRef]

91. Judith Haendeler, Verena Tischler, Jörg Hoffmann, Andreas M. Zeiher, Stefanie Dimmeler. 2004. Low doses of reactive oxygen species protect endothelial cells from apoptosis by increasing thioredoxin-1 expression. *FEBS Letters* **577**:3, 427-433. [CrossRef]

92. Sylke Müller. 2004. Redox and antioxidant systems of the malaria parasite Plasmodium falciparum. *Molecular Microbiology* **53**:5, 1291-1305. [CrossRef]
93. J MARY, S VOUGIER, C PICOT, M PERICHON, I PETROPOULOS, B FRIGUET. 2004. Enzymatic reactions involved in the repair of oxidized proteins. *Experimental Gerontology* **39**:8, 1117-1123. [CrossRef]
94. Vuokko L Kinnula, Paavo Pääkkö, Ylermi Soini. 2004. Antioxidant enzymes and redox regulating thiol proteins in malignancies of human lung. *FEBS Letters* **569**:1-3, 1-6. [CrossRef]
95. Helene Pelicano, Dennis Carney, Peng Huang. 2004. ROS stress in cancer cells and therapeutic implications. *Drug Resistance Updates* **7**:2, 97-110. [CrossRef]
96. Vuokko L Kinnula, James D Crapo. 2004. Superoxide dismutases in malignant cells and human tumors. *Free Radical Biology and Medicine* **36**:6, 718-744. [CrossRef]
97. Aristi Potamitou Fernandes , Arne Holmgren . 2004. Glutaredoxins: Glutathione-Dependent Redox Enzymes with Functions Far Beyond a Simple Thioredoxin Backup System. *Antioxidants & Redox Signaling* **6**:1, 63-74. [Abstract] [Full Text PDF] [Full Text PDF with Links]
98. Kumuda C. Das . 2004. Thioredoxin System in Premature and Newborn Biology. *Antioxidants & Redox Signaling* **6**:1, 177-184. [Abstract] [Full Text PDF] [Full Text PDF with Links]
99. Tiina M. Asikainen , Carl W. White . 2004. Pulmonary Antioxidant Defenses in the Preterm Newborn with Respiratory Distress and Bronchopulmonary Dysplasia in Evolution: Implications for Antioxidant Therapy. *Antioxidants & Redox Signaling* **6**:1, 155-167. [Abstract] [Full Text PDF] [Full Text PDF with Links]
100. Katja Becker, Leann Tilley, Jonathan L. Vennerstrom, David Roberts, Stephen Rogerson, Hagai Ginsburg. 2004. Oxidative stress in malaria parasite-infected erythrocytes: host–parasite interactions. *International Journal for Parasitology* **34**:2, 163-189. [CrossRef]
101. Stephan Gromer, Sabine Urig, Katja Becker. 2004. The thioredoxin system?From science to clinic. *Medicinal Research Reviews* **24**:1, 40-89. [CrossRef]
102. Leena Tiitto, Riitta Kaarteenaho-Wiik, Raija Sormunen, Arne Holmgren, Paavo P##kk#, Ylermi Soini, Vuokko L Kinnula. 2003. Expression of the thioredoxin system in interstitial lung disease. *The Journal of Pathology* **201**:3, 363-370. [CrossRef]
103. Sylke Müller. 2003. Thioredoxin reductase and glutathione synthesis in <I>Plasmodium falciparum</I>. *Redox Report* **8**:5, 251-255. [CrossRef]
104. Jörg Hoffmann, Stefanie Dimmeler, Judith Haendeler. 2003. Shear stress increases the amount of S-nitrosylated molecules in endothelial cells: important role for signal transduction. *FEBS Letters* **551**:1-3, 153-158. [CrossRef]
105. S Akerman. 2003. 2-Cys peroxiredoxin PfTrx-Px1 is involved in the antioxidant defence of Plasmodium falciparum. *Molecular and Biochemical Parasitology* **130**:2, 75-81. [CrossRef]
106. Dmitri E. Fomenko , Vadim N. Gladyshev . 2003. Genomics Perspective on Disulfide Bond Formation. *Antioxidants & Redox Signaling* **5**:4, 397-402. [Abstract] [Full Text PDF] [Full Text PDF with Links]
107. H. I. Alanen , K. E. H. Salo , M. Pekkala , H. M. Siekkinen , A. Pirneskoski , L. W. Ruddock . 2003. Defining the Domain Boundaries of the Human Protein Disulfide Isomerases. *Antioxidants & Redox Signaling* **5**:4, 367-374. [Abstract] [Full Text PDF] [Full Text PDF with Links]
108. George Hoppe, Yuh Cherng Chai, Jonathan Sears. 2003. Endogenous oxidoreductase expression is induced by aminoglycosides. *Archives of Biochemistry and Biophysics* **414**:1, 19-23. [CrossRef]
109. Brian Speake, Nick Sparks, Peter SuraiComparative Aspects of Lipid Peroxidation and Antioxidant Protection in Avian Semen . [CrossRef]
110. Walter H. Watson, Dean P. Jones. 2003. Oxidation of nuclear thioredoxin during oxidative stress. *FEBS Letters* **543**:1-3, 144-147. [CrossRef]
111. K. Becker, S. Rahlfs, C. Nickel, R. H. Schirmer. 2003. Glutathione – Functions and Metabolism in the Malarial Parasite Plasmodium falciparum. *Biological Chemistry* **384**:4, 551-566. [CrossRef]
112. Jeffrey A. Klein, Susan L. Ackerman. 2003. Oxidative stress, cell cycle, and neurodegeneration. *Journal of Clinical Investigation* **111**:6, 785-793. [CrossRef]
113. R Watkin. 2003. Mechanisms regulating the cadmium-mediated suppression of Sp1 transcription factor activity in alveolar epithelial cells. *Toxicology* **184**:2-3, 157-178. [CrossRef]

114. Katja Becker, Stefan M. Kanzok, Rimma Iozef, Marina Fischer, R. Heiner Schirmer, Stefan Rahlfs. 2003. Plasmoredoxin, a novel redox-active protein unique for malarial parasites. *European Journal of Biochemistry* **270**:6, 1057-1064. [CrossRef]

115. Nicolas Rouhier , Alexios Vlamis-Gardikas , Christopher Horst Lillig , Carsten Berndt , Jens-Dirk Schwenn , Arne Holmgren , Jean-Pierre Jacquot . 2003. Characterization of the Redox Properties of Poplar Glutaredoxin. *Antioxidants & Redox Signaling* **5**:1, 15-22. [Abstract] [Full Text PDF] [Full Text PDF with Links]

116. Y Bing. 2003. Effects of thioredoxin on the preimplantation development of bovine embryos. *Theriogenology* **59**:3-4, 863-873. [CrossRef]

117. Walter H. Watson, Yan Chen, Dean P. Jones. 2003. Redox state of glutathione and thioredoxin in differentiation and apoptosis. *BioFactors* **17**:1-4, 307-314. [CrossRef]

118. Risa Kurozumi, Sachiko Tokuzumi, Shuji Kojima. 2003. Does Peroxynitrite Involve in the Elevation of Cellular Glutathione Induced by Sodium Nitroprusside (SNP) in RAW 264.7 Cells?. *Biological & Pharmaceutical Bulletin* **26**:8, 1070-1075. [CrossRef]

119. Gary A. BannonUsing Plant Biotechnology to Reduce Allergens in Food 1-11. [CrossRef]

120. Dmitri E. Fomenko, Vadim N. Gladyshev. 2002. CxxS: Fold-independent redox motif revealed by genome-wide searches for thiol/disulfide oxidoreductase function. *Protein Science* **11**:10, 2285-2296. [CrossRef]

121. C Jung. 2002. Ebselen Has Dehydroascorbate Reductase and Thioltransferase-like Activities,. *Biochemical and Biophysical Research Communications* **291**:3, 550-553. [CrossRef]

122. Vuokko L. Kinnula , Ylermi Soini , Kirsi Kvist-Mäkelä , Eeva-Riitta Savolainen , Pirjo Koistinen . 2002. Antioxidant Defense Mechanisms in Human Neutrophils. *Antioxidants & Redox Signaling* **4**:1, 27-34. [Abstract] [Full Text PDF] [Full Text PDF with Links]

123. Nicolas Rouhier, Eric Gelhaye, Jean-Pierre Jacquot. 2002. Exploring the active site of plant glutaredoxin by site-directed mutagenesis. *FEBS Letters* **511**:1-3, 145-149. [CrossRef]

124. Linna Makmura , Michael Hamann , Arcel Areopagita , Saori Furuta , Amparo Muñoz , Jamil Momand . 2001. Development of a Sensitive Assay to Detect Reversibly Oxidized Protein Cysteine Sulfhydryl Groups. *Antioxidants & Redox Signaling* **3**:6, 1105-1118. [Abstract] [Full Text PDF] [Full Text PDF with Links]

125. Jonas Nordberg, Elias S.J. Arnér. 2001. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system1 1This review is based on the licentiate thesis “Thioredoxin reductase—interactions with the redox active compounds 1-chloro-2,4-dinitrobenzene and lipoic acid” by Jonas Nordberg, 2001, Karolinska Institute, Stockholm, ISBN 91-631-1064-4. *Free Radical Biology and Medicine* **31**:11, 1287-1312. [CrossRef]

126. John F. Engelhardt , Chandan K. Sen , Larry Oberley . 2001. Redox-Modulating Gene Therapies for Human Diseases. *Antioxidants & Redox Signaling* **3**:3, 341-346. [Abstract] [Full Text PDF] [Full Text PDF with Links]