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Forum Review

Glutaredoxins: Glutathione-Dependent Redox Enzymes with Functions Far Beyond a Simple Thioredoxin Backup System

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ABSTRACT

Most cells contain high levels of glutathione and multiple glutaredoxins, which utilize the reducing power of glutathione to catalyze disulfide reductions in the presence of NADPH and glutathione reductase (the glutaredoxin system). Glutaredoxins, like thioredoxins, may operate as dithiol reductants and are involved as alternative pathways in cellular functions such as formation of deoxyribonucleotides for DNA synthesis (by reducing the essential enzyme ribonucleotide reductase), the generation of reduced sulfur (via 3′-phosphoadenylylsulfate reductase), signal transduction, and the defense against oxidative stress. The three dithiol glutaredoxins of *E. coli* with the active-site sequence CPYC and a glutathione binding site in a thioredoxin/glutaredoxin fold display surprisingly different properties. These include the inducible OxyR-regulated 10-kDa Grx1 or the highly abundant 24-kDa glutathione *S*-transferase-like Grx2 (with Grx3 it accounts for 1% of total protein). Glutaredoxins uniquely reduce mixed disulfides with glutathione via a monothiol mechansim where only an N-terminal low pK_a Cys residue is required, by using their glutathione binding site. Glutaredoxins also catalyze formation of mixed disulfides (glutathionylation), which is an important redox regulatory mechanism, particularly in mammalian cells under oxidative stress conditions, to sense cellular redox potential. *Antioxid. Redox Signal.* 6, 63–74.

INTRODUCTION

REVERSIBLE REDUCTIONS OF DISULFIDE BONDS can be mediated by a variety of thiol-redox enzymes, which contain an active site with the sequence motif CXXC. These proteins may perform fast and reversible thiol–disulfide exchange reactions between their active–site cysteine residue and half-cystines of their disulfide substrates. The pathways of the thioredoxin and glutaredoxin systems are responsible for the reduction of intracellular disulfides *in vivo* (39, 85, 90). Thioredoxins and glutaredoxins are abundant proteins with a number of isoforms in different species, which operate in essential biosynthetic reactions and regulate many biological functions.

Glutaredoxins are now known to exist in most living organisms, including prokaryotes (*e.g., Escherichia coli*) (36), plants (*e.g.,* rice, spinach, poplar, *A. thaliana*) (17, 68, 71, 95), viruses (*e.g.,* bacteriophage T4, vaccinia, human immunodeficiency virus) (1, 22, 23, 25), and eukaryotes (*e.g.,* yeast, *P. falciparum*, rabbit, calf, pig, and human) (30, 45, 62, 63, 80, 86, 118). The active sites of thioredoxin and glutaredoxin (the CXXC motif) have been found in a growing number of redox-active enzymes. These include, *e.g.,* T4 glutaredoxin (101), protein disulfide isomerases (24), DsbA (7, 90), and NrdH redoxin (48).

The glutaredoxin system was first discovered in 1976 as a dithiol hydrogen donor system for ribonucleotide reductase, in a mutant lacking thioredoxin 1 (Trx1) in *E. coli* (36). In the glutaredoxin system, electrons are transferred from NADPH, to glutathione reductase (GR), then to glutathione (GSH), and finally to one of the three today known glutaredoxins (Grx1, Grx2, and Grx3) (Fig. 1) (41). Glutaredoxins were later shown to be general thiol–disulfide oxidoreductases (37, 38) that can reduce protein disulfides (by a dithiol mechanism) or

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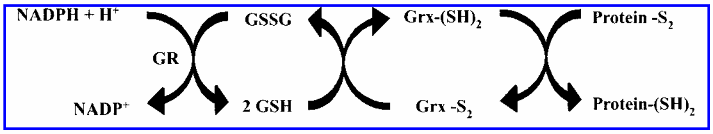

FIG. 1. General mechanism of the glutaredoxin system. In the glutaredoxin system, electrons are transferred from NADPH to glutathione reductase (GR), glutathione (GSH), and finally to the glutaredoxins. Glutaredoxins will in turn reduce disulfides in target proteins like ribonucleotide reductase.

mixed disulfides forming between GSH and proteins or low-molecular-weight thiols (by a dithiol and/or monothiol mechanism) (11).

Glutaredoxin isoforms

The glutaredoxin family has grown during the last years, and there are today numerous isoforms known in different organisms with quite different structures and catalytic activities. In terms of their structure and catalytic properties, glutaredoxins can today be classified in three categories (110).

The first is exemplified by the classical glutaredoxins, which are 10-kDa proteins with the CXXC motif (usually CPYC) as their active site (Fig. 2) and with the thioredoxin/glutaredoxin fold (Fig. 3). Grx1 and Grx3 of *E. coli* belong to this first classical category. Both are ~10-kDa proteins with similar structure (the thioredoxin/glutaredoxin fold), and they have 33% sequence identity (4, 12, 66). These enzymes are electron donors for reductive enzymes like ribonucleotide reductase.

The second category is structurally related to the glutathione *S*-transferases (GSTs), but with glutaredoxin oxidoreductase activity. Common structural characteristics are a two-domain structure, the first domain having a thioredoxin/glutaredoxin fold containing the active-site residues and the second domain having an α-helical structure. This class of glutaredoxins is defined by *E. coli* Grx2, which has a three-dimensional structure (Fig. 3), highly similar to GSTs (116). It mainly differs from the GSTs in that it contains the dithiol active-site sequence CPYC in the glutaredoxin domain, and thus has glutaredoxin activity. Other proteins that are structurally related to this category, even though they have no significant amino acid homology and only one active-site cysteine, are the human θ class GST, the human GST ω 1 (GSTO1), the mouse GST θ-like stress response protein (p28), and the human chloride intracellular channel 1 (CLIC1) (9, 34, 56, 94). All these proteins are detoxifying or stress response proteins.

The third category of glutaredoxins is defined by having a monothiol active site (normally CGFS). Monothiol glutaredoxins have so far been identified in yeast (yGrx3, yGrx4, and yGrx5) and man [protein kinase C-interacting cousin of thioredoxin (PICOT)] (92, 115). The yeast monothiol glutaredoxins have a protective role against oxidative stress, with the mutant lacking Grx5 being very sensitive to both menandione and hydrogen peroxide and containing high amounts of carbonylated proteins compared with the parental strain. The mutant also showed increased sensitivity (>10-fold) to high concentrations of KCl. A yeast null mutant for the three-monothiol glutaredoxins is not viable, suggesting that monothiol glutaredoxins are very specific for their substrates and their functions cannot be replaced by their dithiol counterparts (92). Moreover, yeast Grx5 has been shown to be part of the mitochondrial machinery involved in the synthesis and assembly of iron–sulfur clusters (93). The human monothiol, PICOT, is expressed in various tissues, and overexpression in T cells inhibits the activation of c-Jun N-terminal kinase (JNK) and the transcription factors activator protein 1 (AP-1) and nuclear factor-κB (NF-κB) (115). Monothiol glutaredox-

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E. coli Grx1      MQTVIFGRSGCPYCVRAKDLAEKLSNERDDFQYQYVDIRAEGITKEDLQQKAGKPVETVP
E. coli Grx2      --MKLYIYDHCPYCLKARMIFGLKN-----IPVELHVLLNDDAETP--TRMVGQ--KQVP
E. coli Grx3      ANVEIYTKETCPYCHRAKALLSSKG-----VSFQELPIDGNAAKREEMIKRSGR--TTVP
                      ::  . **** :*: :    .     .  :   :  :        :  *:    **

E. coli Grx1      QIFVD-QQHIGGYTDFAAWVKEN-LDA---------------------------------
E. coli Grx2      ILQKDDSRYMPESMDIVHYVDKLDGKPLLTGKRSPAIEEWLRKVNGYANKLLLPRFAKSA
E. coli Grx3      QIFID-AQHIGGCDDLYALDARGGLDPLLK------------------------------
                   :  *  :::    *:     .   ..

E. coli Grx1      ------------------------------------------------------------
E. coli Grx2      FDEFSTPAARKYFVDKKEASAGNFADLLAHSDGLIKNISDDLRALDKLIVKPNAVNGELS
E. coli Grx3      ------------------------------------------------------------

E. coli Grx1      ----------------------------------------------
E. coli Grx2      EDDIQLFPLLRNLTLVAGINWPSRVADYRDNMAKQTQINLLSSMAI
E. coli Grx3      ----------------------------------------------
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FIG. 2. Sequence alignment of the *E. coli* glutaredoxins. The active-site sequence is shown as gray boxes, as is the consensus proline residue. Residues involved in the binding of GSH in *E. coli* Grx1 and Grx3 are marked with black boxes (74, 117).

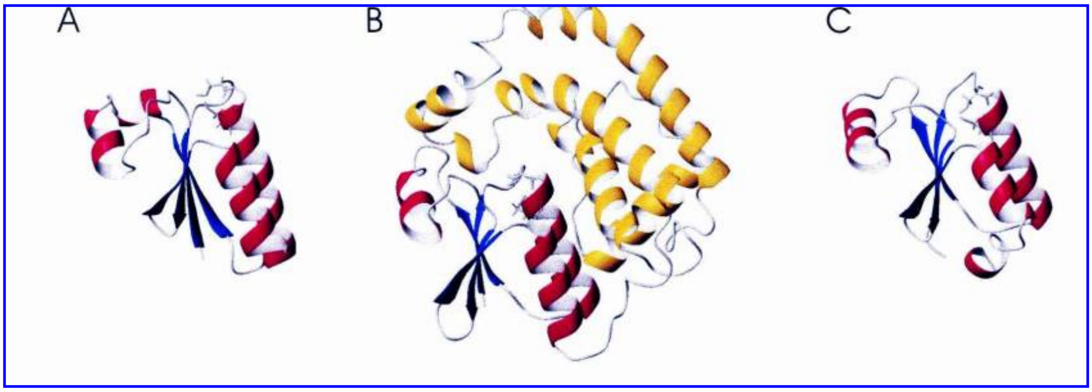


FIG. 3. Three-dimensional structures of the *E. coli* glutaredoxins. (A) Oxidized *E. coli* Grx1 (1EGO) (117). **(B)** Reduced *E. coli* Grx2 (1G7O) (116). **(C)** Oxidized *E. coli* Grx3 (1FOV) (75). The active-site cysteines are displayed as sticks. The structures are from the protein Data Bank, and the figures were generated using the program MOLMOL (57). β-sheets are displayed in blue, α-helices belonging to the thioredoxin/glutaredoxin fold in red, and the α-helices of the C-terminal domain of Grx2 in yellow.

ins have been identified in many different species, through genome databank searches (29, 47).

The glutaredoxin fold

The thioredoxin/glutaredoxin fold was first identified in 1975 (42) from the crystal structure of oxidized *E. coli* Trx1, and is characterized by a central core of a four to five stranded mixed β-sheet, flanked by three to four α-helices. In glutaredoxins, the fold consists of a four stranded mixed β-sheet surrounded by three α-helices (Fig. 3) (25, 66, 101). In addition, several other proteins apart from the thioredoxins and glutaredoxins share the common structural fold, and thus belong to the thioredoxin superfamily, despite the low sequence identity (18). Proteins belonging to the thioredoxin superfamily of enzymes include DsbA, NrdH redoxin, protein disulfide isomerases, chaperones, GSTs, and glutathione peroxidases (18, 25, 26, 51, 67, 88, 102, 104). In contrast to the relatively low homologies among different thioredoxins, glutaredoxins exhibit rather high amino acid sequence homology, particularly in the area of the active site. The three-dimensional structures of a number of glutaredoxins from different species, including bacteriophage T4, vaccinia Grx1, *E. coli* Grx1, Grx2, and Grx3, pig Grx1, and human Grx1, have been determined (25, 49, 50, 102, 106, 116). The three-dimensional structures of *E. coli* Grx1 (12, 102, 117) and Grx3 (28, 74, 75) have been obtained by NMR (Fig. 3), in the oxidized, reduced, and mixed-disulfide forms. Structural studies have revealed three characteristic regions within the dithiol glutaredoxins. First is the active-site CXXC motif (usually CPYC), second a solvent-accessible hydrophobic area, and finally a well defined binding site for GSH. The latter involves two intermolecular backbone–backbone hydrogen bonds forming an antiparallel intermolecular β-bridge between the protein and GSH (12, 74). In *E. coli* Grx3, these interactions involve residue Lys8, Tyr13, Arg16, Arg40, Arg49, Asp66, and Asp67. The binding of GSH to *E. coli* Grx1 and Grx3 is overall very similar. The conformation of the active site of oxidized glutaredoxins is also conserved. Moreover, local interactions and small, but significant, conformational changes in the active site modulate the redox potential by affecting the stability of each of the reduced, oxidized, and mixed disulfide forms (75). Comparison of the reduced and oxidized forms of *E. coli* Grx1 revealed that the solvent-accessible surface of the conserved hydrophobic area increases upon reduction. This should favor binding interactions with substrate proteins. After reduction of the substrate, the decrease of the hydrophobic interaction area of the now oxidized glutaredoxin could facilitate the release of the substrate (117). In contrast to *E. coli* Grx1 and Grx3 (both ~10 kDa), *E. coli* Grx2 is a much larger enzyme (24.3 kDa) with the N-terminal, residue 1–72, forming a glutaredoxin domain, connected by an 11-residue linker to the highly helical C-terminal domain, residue 84–215 (Fig. 3) (116). The structure of Grx2 is similar to that of GSTs, although they lack an obvious sequence homology. The structural similarity is interesting, because a relatively new class of mammalian GST-like protein, the single cysteine ω class, has glutathione oxidoreductase activity, rather than the GST activity (9).

Catalytic mechanism of glutaredoxin

Thiol redox control predicts that thiols that are oxidized to disulfides may affect protein structure and activity (39). Generally, disulfide bonds stabilize protein structure (*e.g.,* bovine serum albumin), while biological activity of proteins may also be affected (*e.g.,* OxyR). In some oxidoreductases, formation and reduction of disulfides are essential for enzymatic activity as part of a catalytic mechanism [e.g., ribonucleotide reductase and 3′-phosphoadenylylsulfate (PAPS) reductase].

Glutaredoxins catalyze GSH-disulfide oxidoreductions usually via the two redox-active cysteines separated by two other amino acids (typically CPYC) (39, 41). The oxidoreductions are either dithiol reactions reducing protein disulfides or monothiol reductions of mixed disulfides with GSH. In comparison, the structurally and functionally related thioredoxins reduce a wide range of protein disulfides, but have low or no activity with mixed disulfides.

In the dithiol reduction, the solvent-exposed N-terminal cysteine of the active-site sequence of the glutaredoxin initiates a nucleophilic attack on one of the sulfur atoms of the disulfide target (Fig. 4A). This results in the formation of a

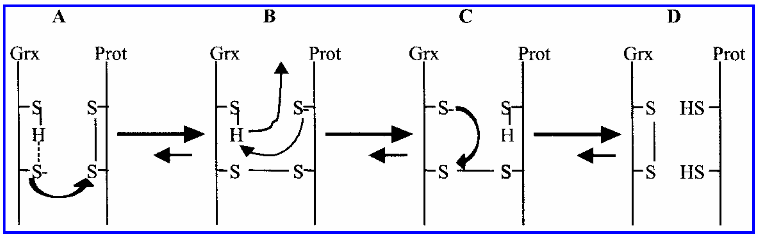


FIG. 4. The glutaredoxin dithiol oxidoreductase mechanism. Glutaredoxin-mediated oxidoreductions of disulfide bonds in target proteins are shown.

mixed disulfide between the glutaredoxin and the target protein (Fig. 4B). The free second C-terminal cysteine of the active site becomes deprotonated and attacks the N-terminal glutaredoxin sulfur atom participating in the mixed disulfide with the target protein (Fig. 4C). As a consequence, oxidized glutaredoxin (Grx-S_2) and reduced target [Prot-$(SH)_2$] are generated (Fig. 4D).

In the monothiol mechanism concerning the reduction of protein-SG mixed disulfides, glutaredoxins utilize only the N-terminal cysteine thiol (Fig. 5) (11). In this reaction, glutaredoxins specifically interact with the GSH moiety of the GSH-mixed disulfide target, and not the protein substrate, due to the glutaredoxin affinity for GSH (12, 74). This results in the formation of a covalent Grx-SG GSH mixed intermediate and release of the non-GSH moiety in its reduced form. The Grx-SG mixed intermediate is reduced by a second GSH molecule, generating glutathione disulfide (GSSG). Finally, GR regenerates GSH by reducing the GSSG.

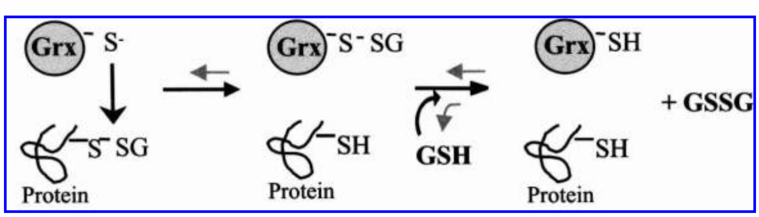
As the reduction of glutathionylated proteins seems to require the recognition of only the GSH moiety of the substrate, and not the substrate itself, the monothiol mechanism resulting in deglutathionylation can thus be seen as a more general function of the glutaredoxins. Contrary to what was originally believed, glutathionylation of proteins may not only occur due to increased GSSG levels as the formation of protein GSH conjugates has been reported without an increase of GSSG levels (64). Protein glutathionylation has been realized as an increasingly important regulatory mechanism in biochemical processes, by reversible modification of protein thiols (19). Several proteins have been detected to undergo glutathionylation due to changes in the intracellular redox environment. These include protein chaperones, cytoskeletal proteins, cell cycle regulators, and enzymes of the intermediate metabolism (61). Furthermore, these types of posttranslational modification are involved in the regulation of specific transcriptional events vital to the adaptation seen in cells during oxidative stress (53). For instance, glutathionylation of Cys62 of eukaryotic NF-κB subunit p50 and Cys269 of c-Jun result in loss of DNA binding activity (54, 81). Tyrosine hydroxylase, protein phosphatase 2A, tyrosine phosphatase 1B, and α-ketoglutarate dehydrogenase are all inhibited by reversible glutathionylation (8, 10, 76, 87). Recently, retinal pigment epithelium cells were shown to be glutathionylated and the reversible glutathionylation of these proteins was mediated by glutaredoxin (16). G-actin has also been reported to be glutathionylated at Cys374 and to undergo deglutathionylation by glutaredoxin. It has been further shown that human Grx1 knockdown cells affected G-actin in terms of polymerization, translocation, and reorganization near the cell periphery (113, 114).

Even though there are many reports about posttranscriptional regulation via *S*-glutathionylation in eukaryotic cells, only the transcription factor OxyR and PAPS reductase have so far been reported to be regulated in this manner in *E. coli* (52, 60). Recent studies showed that the OxyR protein can exist in an *S*-nitrosylated (S-NO), S-glutathionylated (S-SG), and hydroxylated (S-OH) state *in vivo*. The posttranslational modification of the protein's regulatory thiol (Cys199) is transcriptionally active, but differs in structure, cooperative properties, DNA binding affinity, and promoter activity, with glutathionylated OxyR having the highest transcriptional activity (52). Glutathionylated PAPS reductase is completely inactive, and was observed *in vivo* in poorly growing *gor⁻grxA⁻grxB⁻grxC⁻* expressing inactive Grx2-C9S/C12S. However, expression of monothiol Grx2-C12S or wild-type Grx2 (known not to be electron donors for PAPS reductase) in the *gor⁻grxA⁻grxB⁻grxC⁻* strain, the protein mixed disulfide species was absent. Glutaredoxins were further able to reduce glutathionylated PAPS reductase *in vitro*. Reversible glutathionylation may thus regulate the activity of PAPS reductase (60). Formation of protein-GSH mixed disulfides is of physiological relevance for *E. coli,* because up to 2% of the total GSH content (10—20 μ*M*) is in the form of protein-mixed disulfides in a wild-type cell and can be even higher, as for example in *trxAgrxA* null mutants (5—7%) (70).

THE GLUTAREDOXIN SYSTEM OF *ESCHERICHIA COLI*

Three glutaredoxins (Grx1, Grx2, and Grx3) have so far been described in *E. coli* (Fig. 2) (3, 36). The first (Grx1, en-

FIG. 5. The monothiol mechanism of the glutaredoxins. Reduction of protein GSH-mixed disulfides (black arrows) and the generation of glutathionylated protein (gray arrows) by the reversed reaction are shown.



coded by *grxA*) was discovered as a GSH-dependent electron donor for ribonucleotide reductase 1a, in a mutant lacking the first isolated electron donor, Trx1 (36). The other two glutaredoxins, Grx2 (encoded by *grxB*) and Grx3 (encoded by *grxC*), were purified from an *E. coli* null mutant for Grx1 and Trx1 (3). Because of the strong preference of glutaredoxins for GSH-mixed disulfides, they have been proposed to participate in enzyme regulation, particularly under oxidative conditions (31, 33).

In comparison with thioredoxins, little is still known about the actual function of these glutaredoxins (Table 1). However, apart from PAPS reductase and ribonucleotide reductase, glutaredoxins are required for the reduction of arsenate reductase (ArsC) and OxyR in *E. coli* (6, 32, 119). ArsC catalyzes the reduction of arsenate [As(V)] to arsenite [As(III)]. ArsC has a single catalytic cysteine residue, Cys12, that can form a covalent thiolate-As(V) intermediate (72). The reduction of the enzyme-bound As(V) intermediate to an enzyme-bound As(III) intermediate requires glutaredoxin. Glutaredoxin mutants lacking the N-terminal cysteine in the active site, leading to an inactive enzyme, could not catalyze the ArsC-As(V) reduction, whereas mutants lacking the C-terminal cysteine could still support the activity of ArsC (100). This finding led to the conclusion that the ArsC intermediate is not formed during the catalytic cycle, but instead an ArsC-S-SG complex, which subsequently is reduced by glutaredoxins via a monothiol mechanism. From the *E. coli* glutaredoxins, Grx2 has the highest catalytic activity (100-fold higher than Grx1) in reducing ArsC (100).

Oxidative stress occurs when cells are exposed to elevated levels of reactive oxygen species, such as superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and alkyl hydroperoxides (ROOH). Oxidative stress can lead to DNA damage and thus mutations, as well as lipid peroxidation, disassembly of iron–sulfur clusters, disulfide bond formation, protein carbonylation, and other potentially lethal effects. To protect cells against the oxidative damage, cells produce a number of antioxidant enzymes. Both thioredoxins and glutaredoxins have been shown to have a protective role against oxidative stress (for reviews, see 13, 40, 90). *E. coli* glutaredoxins contributed to the defense against hydrogen peroxide, with *gshA*$^-$ and *grxB*$^-$ cells being more sensitive to hydrogen peroxide as shown by increased carbonylation of intracellular proteins of the relevant mutants, particularly in the stationary phase (112). Furthermore, Grx1 (as well as Trx2 and GR) has been shown to be regulated by the transcription factor OxyR, which is known to activate the expression of several antioxidant defensive genes in response to elevated levels of hydrogen peroxide (13). Significant up-regulation of catalase activity has been observed in null mutants for Trx1 and the three glutaredoxins, whereas up-regulation of glutaredoxin activity was observed in catalase-deficient strains especially with additional defects in the thioredoxin pathway (112). In addition, elevation of all glutaredoxin species has been reported in catalase-deficient strains, particularly when combined with null mutants from the thioredoxin or glutaredoxin system (82). This shows an interconnection between the glutaredoxin and catalase antioxidant defenses.

It is generally believed that aging results from oxidative damage of macromolecules as a result of fluctuations in the balance between oxidants and antioxidants (65, 89). There is, for instance, an age-related decline in GSH levels that has been reported for a number of organisms. Overexpression of GSH in transgenic *Drosophila* results in an increased life span (103). Similar to eukaryotic cells, stationary phase *E. coli* becomes increasingly oxidized. This is despite their enhanced capacity to manage oxidative stress by the global regulator σ^s [*rpoS*-encoded sigma factor S (RpoS)], OxyR, and SoxRS (for more information, see reviews 77–79). The oxidative stress theory on aging thus opens the possibility of a pivotal potential function for the thioredoxin and the glutaredoxin systems.

Grx1

Grx1 was discovered and named as a small GSH-dependent donor for ribonucleotide reductase (36). Grx1 has close homologues in most living organisms (66). Trx1 is normally more abundant in the cell (10 µ*M*) compared with Grx1 (1 µ*M*), but Grx1 has a 10-fold lower K_m value for ribonucleotide reductase (38, 43). Measurements of thymidine incorporation in newly synthesized DNA further suggest that

TABLE 1. SUMMARY OF THE *E. COLI* GLUTAREDOXIN SYSTEM

					Substrate specificity	
Gene	*Protein*	*Molecular mass (kDa)*	*Regulation*	*Sensitivity*	*Protein disulfides*	*Mixed disulfides*
gor	Glutathione reductase (GR)		OxyR, ppGpp	H_2O_2, CHP, tBHP, diamide		GSH
grxA	Glutaredoxin 1 (Grx1)	9.7	OxyR	Diamide, H_2O_2	RR, OxyR, PAPS reductas, ArsC, (MSR)	ArsC, PAPS reductase
grxB	Glutaredoxin 2 (Grx2)	24.3	Acid stress, osmosis, RpoS, ppGpp, cyclic AMP	Diamide, H_2O_2	ArsC	ArsC, PAPS reductase
grxC	Glutaredoxin 3 (Grx3)	9		Menandione, CHP	(RR), ArsC	ArsC, PAPS reductase

CHP, Cumene hydroperoxide; MSR, methionine sulfoxide; RR, ribonucleotide reductase; tBHP, *tert*-butyl hydroperoxide.

mainly Grx1 and to a lesser extent Trx1 contribute to the reduction of ribonucleotides in *E. coli* (82). Grx1 is also an alternate electron donor to thioredoxin for the reduction of PAPS reductase (108, 109). When Grx1 was overexpressed to levels similar Trx1, Grx1 was able to rescue the growth defects of a *trxAmetE* null mutant, and could reduce methionine sulfoxide reductase (105).

Grx1 has 85 amino acid residues, including the active-site sequence CPYC (Fig. 2), and a molecular mass of 10 kDa. The protein level of Grx1 in the cell varies from ~600 ng/mg at the exponential phase to ~285 ng/mg at the stationary phase (82). Thermodynamic stability experiments showed that oxidized and reduced Grx1 are very similar in stability. In heat-induced denaturation, monitored by circular dichroism, the T_m was 55 and 57°C for the oxidized and reduced form, respectively. In guanidine hydrochloride solutions, the midpoint denaturation concentrations were 2 *M* for both the oxidized and reduced forms. This differs greatly from the thioredoxin in *E. coli*, where the oxidized form is far more stable than the reduced (98).

Grx1 is induced by hydrogen peroxide in an OxyR-dependent fashion (107). The transcriptional regulator OxyR is sensitive to oxidation and activates the expression of antioxidant genes (there among Grx1) in response to hydrogen peroxide. Grx1 catalyzes the reduction, and thus the inactivation, of OxyR *in vivo*, and as OxyR regulates Grx1, the response is autoregulated (6, 119). However, the role of Grx1 as a reductant of disulfide bonds can be reversed to that of an oxidant in very oxidizing environments (112).

The first null mutant for Grx1 was constructed in 1988, and showed no significant phenotype (96). The combined null mutant for *trxAgrxA* was viable in rich media, but showed no viability in minimal media unless supplemented with reduced cysteine. This finding led to the conclusion that either Trx1 or Grx1 is essential for the reduction of PAPS reductase. However, the null mutant for *trxAgrxA* maintained deoxyribonucleotide synthesis, with an increase of ribonucleotide reductase activity of up to 23-fold, implying that a third hydrogen donor must exist in the cell (later found to be Trx2 and Grx3) (69, 97). Lack of Trx1 or Grx1 leads to an increased level of the other enzyme (as determined by enzyme-linked immunosorbent assay), most probably in order to maintain a balanced supply of deoxyribonucleotides. Grx1 is 10-fold induced in the absence of thioredoxin reductase, and the effect is even more pronounced in null mutants for *trxA-trxC* and *trxAtrxBtrxC* (20–30-fold) (44, 82). An extremely high (70-fold) increase has also been observed for Grx1 in null mutants for *gshAtrxA* (70).

Grx2

Grx2 was purified from an *E. coli* null mutant lacking Trx1 and Grx1 (3). Characterization of Grx2 shows that it is highly different from the other known glutaredoxins in terms of molecular mass (24.3 kDa), amino acid sequence, and catalytic activity (111). Grx2 cannot reduce ribonucleotide reductase or PAPS reductase, but has the highest catalytic activity using the mixed disulfide between GSH and β-hydroxyethyl disulfide (HED) as substrate with a turnover of 554 s^{-1} (HED assay) (3, 59, 111). *E. coli* Grx2 has close homologues in *Actinobacillus actinomycetemcomitans* (87% amino acid identity), *Neisseria meningitidis* (58%), and *Vibrio cholerae* (42%), all known pathogens, but it is not a ubiquitous protein.

Grx2 was found to contribute to 80% of the total glutaredoxin activity measured by the HED assay. Null mutants for *grxB* and all three glutaredoxin genes (*grxA*$^-$*grxB*$^-$*grxC*$^-$) are viable in rich and minimal media. However, the null mutant for *grxB* has been prone to lysis under starvation conditions and exhibits a distorted morphology (83).

The levels of Grx2 are growth phase-dependent, and are elevated at stationary phase of growth (up to 10 μg/mg of protein) (82). Guanosine-3′,5′-tetraphosphate (ppGpp) and σ^s (RpoS) are two major factors controlling the transcription of genes in the stationary phase of growth, as well as genes involved in the antioxidant response (15, 35). Both ppGpp and RpoS dramatically affect the expression of Grx2. ppGpp and RpoS are thus necessary for the high up-regulation of Grx2 at stationary phase, whereas cyclic AMP inhibits Grx2 at exponential phase. Grx2 levels are also positively affected by osmotic upshock and acidic stress (2, 83).

Grx2 contributes to the defense against hydrogen peroxide, with the *grxB*$^-$ cells being more sensitive to hydrogen peroxide as shown by increased carbonylation of intracellular proteins of the relevant mutant, particularly in the stationary phase (112). Despite this, the transcription factor OxyR did not affect the levels of Grx2 (83), and these were instead shown to be elevated in an *oxyR* null mutant. Additionally, the levels of Grx2 decrease after treatment with hydrogen peroxide (82). Recombinant *E. coli* Grx2 is also a potent antioxidant *in vitro* against dopamine-induced oxidative stress and cell death in rat cerebral granule neurons, preventing their apoptosis by activating the binding activity of NF-κB (20). *E. coli* Grx2 was able to penetrate into the granule neurons and exert its activity by activating NF-κB. Addition of Grx2 resulted in promotion of the phosphorylation and degradation of I-κBα, thus causing translocation of NF-κB from the cytoplasm to the nucleus. In addition, the DNA binding activity of preexisting nucleus NF-κB was enhanced. The effect was mediated by up-regulation of Ref-1, which in turn activated NF-κB. Moreover, Grx2 could activate both the Ras/phosphoinositide 3-kinase/Akt/NF-κB and the JNK1/2/AP-1 cascades (21).

Grx3

Grx3 was identified and purified at the same time as Grx2 in the null mutant lacking Trx1 and Grx1 (3). It was given its name from being eluted after Grx2 on size-separating gel chromatography. Grx3 has 5% of the catalytic activity of Grx1 for ribonucleotide reductase, but lacks activity for PAPS reductase (3, 59). Even though Grx3 can act as an electron donor for ribonucleotide reductase 1a *in vitro,* it most probably cannot reduce ribonucleotide reductase 1a *in vivo.* Triple mutants lacking Trx1, Trx2, and Grx1 are nonviable and can grow when only cotransfected with a plasmid overexpressing any one of these three proteins (105). Grx3 consists of 82 amino acid residues (10-kDa protein), with 33% sequence identity to *E. coli* Grx1 (4). The active site of Grx3 is CPYC as in the other glutaredoxins (Fig. 2), and the three-dimensional structure is similar to that of Grx1 (Fig. 3). The activity of Grx3 is reduced in a Grx3-H15V mutant, indicating electrostatic contributions for the stabilization of C11 (73). Denaturation of Grx3 with guanidine hydrochloride showed no difference in stability between the reduced and oxidized forms (5). The levels of Grx3 are relatively high (~3.5 µg/mg) and remain the same during all stages of growth. The null mutant for grxC shows increased sensitivity to menandione and cumene hydroperoxide (112). The mechanism(s) that regulates grxC expression remains unknown, but it is considered not to be affected by global regulators like RpoS, ppGpp, cyclic AMP, and OxyR.

GENETIC STUDIES ON THE THIOREDOXIN AND GLUTAREDOXIN SYSTEMS

In *E. coli*, neither glutaredoxin nor thioredoxin single mutation results in a lethal phenotype (105, 112). This is likely due to redundancy, because double mutants lacking both thioredoxin reductase (*trxB*) and GR (*gor*) are nonviable unless supplemented with a reductant like dithiothreitol, which chemically will reduce the redoxins (36, 39). Recently, Beckwith and co-workers isolated a viable mutant from the *trxB⁻gor⁻ E. coli* strain, which had a trinucleotide insertion in the gene for the oxidative stress defense enzyme alkylhydroperoxide reductase (AhpC) (91). The mutation results in conversion of AhpC from a peroxidase to an intradisulfide reductase, which in turn enables it to reduce Grx1 (91).

The role of the glutaredoxins and thioredoxins in *E. coli*, the best characterized bacterial cell, can be viewed in relation to studies of other minimal gene sets in bacteria to sustain a living cell. Such studies to specify a minimum bacterial cell have been done with *Bacillus subtilis* and *Mycoplasma genitalium* (46, 55). The latter contains only 480 genes (46) out of which maybe 260 genes are essential. Recently, essential *Bacillus subtilis* genes were studied by single inactivation of a gene (55). The genome size of *Bacillus subtilis*, a gram-positive organism without GSH (27), is similar to that of *E. coli,* with 4,100 genes. In *Bacillus subtilis*, there are ~10 known thioredoxin genes and four genes for thioredoxin reductase. The single gene inactivation study showed that a total of three genes (one for thioredoxin and two for thioredoxin reductase) were essential (58, 99). Obviously, the essential but redundant thioredoxin genes in *Bacillus subtilis* code for protein functions, which cannot be replaced by other gene products. This is in all likelihood due to the requirement of an electron donor for ribonucleotide reductase, which is needed for the synthesis of the deoxyribonucleotides for DNA (55). In view of the results for gram-positive organisms lacking GSH and some other organisms not having GSH (27), the role of the glutaredoxin system can be seen as a paralogue allowing the cell to respond to changing environmental conditions and provide means of regulation and defense. The role of the glutaredoxin and thioredoxin set of genes under conditions of oxidative stress (84) or on minimal medium would probably encompass more functions. For instance, sulfate assimilation with PAPS reductase requires either Trx1 or Grx1 when grown on minimal medium (97), whereas ribonucleotide reductase requires Trx1, Trx2, or Grx1 (105). Growth in arsenite requires arsenite reductase, which in turn most likely requires GSH and Grx2 (100).

Concluding remarks

Today the glutaredoxin and thioredoxin systems are considered to be parallel redox systems. In fact, the absence of cross-reactivity between the redoxins and the respective NADPH-dependent reductases may have a special importance in regulation because the systems can operate independently. The more robust system, in terms of keeping a reduced environment in the cell by reducing protein disulfides even under severe oxidative stress, is obviously the thioredoxin system. This is probably also the more evolutionary old system (27). In comparison, the glutaredoxins may be viewed as the more sophisticated system, being able to reduce both protein disulfides and GSH-mixed disulfides. This enables the glutaredoxins to compensate for the thioredoxin system to a large extent, and at the same time have its own unique function. Oxidative stress conditions or energy lack may lead to oxidized glutaredoxin due to lack of GSH and accumulation of GSSG. In mammalian cells, there seems to be cross talk between the thioredoxin system and the glutaredoxins. Human thioredoxin can be glutathionylated on Cys73 with inactivation probably catalyzed by glutaredoxin (14).

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ABBREVIATIONS

AhpC, alkylhydroperoxide reductase; AP-1, activator protein 1; ArsC, arsenate reductase; As(III), arsenite; As(V), arsenate; GR, glutathione reductase; Grx1, Grx2, and Grx3, glutaredoxins 1, 2, and 3; GSH, glutathione; GSSG, glutathione disulfide; GST, glutathione *S*-transferase; HED, β-hydroxyethyl disulfide; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; PAPS, 3′-phosphoadenylylsulfate; PICOT, protein kinase C-interacting cousin of thioredoxin; ppGpp, guanosine-3′,5′-tetraphosphate; RpoS, or σ^S, *rpoS*-encoded sigma factor S; Trx1 and Trx2, thioredoxins 1 and 2.

REFERENCES

1. Ahn BY and Moss B. Glutaredoxin homolog encoded by vaccinia virus is a virion-associated enzyme with thioltransferase and dehydroascorbate reductase activities. *Proc Natl Acad Sci U S A* 89: 7060–7064, 1992.
2. Arnold CN, McElhanon J, Lee A, Leonhart R, and Siegele DA. Global analysis of *Escherichia coli* gene expression during the acetate-induced acid tolerance response. *J Bacteriol* 183: 2178–2186, 2001.

3. Åslund F, Ehn B, Miranda-Vizuete A, Pueyo C, and Holmgren A. Two additional glutaredoxins exist in *Escherichia coli:* glutaredoxin 3 is a hydrogen donor for ribonucleotide reductase in a thioredoxin/glutaredoxin 1 double mutant. *Proc Natl Acad Sci U S A* 91: 9813–9817, 1994.
4. Åslund F, Nordstrand K, Berndt KD, Nikkola M, Bergman T, Ponstingl H, Jörnvall H, Otting G, and Holmgren A. Glutaredoxin-3 from *Escherichia coli.* Amino acid sequence, ^{1}H AND ^{15}N NMR assignments, and structural analysis. *J Biol Chem* 271: 6736–6745, 1996.
5. Åslund F, Berndt KD, and Holmgren A. Redox potentials of glutaredoxins and other thiol-disulfide oxidoreductases of the thioredoxin superfamily determined by direct protein–protein redox equilibria. *J Biol Chem* 272: 30780–30786, 1997.
6. Åslund F, Zheng M, Beckwith J, and Storz G. Regulation of the OxyR transcription factor by hydrogen peroxide and the cellular thiol-disulfide status. *Proc Natl Acad Sci U S A* 96: 6161–6165, 1999.
7. Bardwell JC, McGovern K, and Beckwith J. Identification of a protein required for disulfide bond formation in vivo. *Cell* 67: 581–589, 1991.
8. Barrett WC, DeGnore JP, Konig S, Fales HM, Keng YF, Zhang ZY, Yim MB, and Chock PB. Regulation of PTP1B via glutathionylation of the active site cysteine 215. *Biochemistry* 38: 6699–6705, 1999.
9. Board PG, Coggan M, Chelvanayagam G, Easteal S, Jermiin LS, Schulte GK, Danley DE, Hoth LR, Griffor MC, Kamath AV, Rosner MH, Chrunyk BA, Perregaux DE, Gabel CA, Geoghegan KF, and Pandit J. Identification, characterization, and crystal structure of the Omega class glutathione transferases. *J Biol Chem* 275: 24798–24806, 2000.
10. Borges CR, Geddes TJ, Watson JT, and Kuhn DM. Dopamine biosynthesis is regulated by *S*-glutathionylation. Potential mechanism of tyrosine hydroxylase inhibition during oxidative stress. *J Biol Chem* 277: 48295–48302, 2002.
11. Bushweller JH, Åslund F, Wuthrich K, and Holmgren A. Structural and functional characterization of the mutant *Escherichia coli* glutaredoxin (C14→rr;S) and its mixed disulfide with glutathione. *Biochemistry* 31: 9288–9293, 1992.
12. Bushweller JH, Billeter M, Holmgren A, and Wuthrich K. The nuclear magnetic resonance solution structure of the mixed disulfide between *Escherichia coli* glutaredoxin (C14S) and glutathione. *J Mol Biol* 235: 1585–1597, 1994.
13. Carmel-Harel O and Storz G. Roles of the glutathione- and thioredoxin-dependent reduction systems in the *Escherichia coli* and *Saccharomyces cerevisiae* responses to oxidative stress. *Annu Rev Microbiol* 54: 439–461, 2000.
14. Casagrande S, Bonetto V, Fratelli M, Gianazza E, Eberini I, Massignan T, Salmona M, Chang G, Holmgren A, and Ghezzi P. Glutathionylation of human thioredoxin: a possible crosstalk between the glutathione and thioredoxin systems. *Proc Natl Acad Sci U S A* 99: 9745–9749, 2002.
15. Cashel M, Gentry DR, Hernandez VJ, and Vinella D. The stringent response. In: *Eschericha coli and Salmonella: Cellular and Molecular Biology,* 2nd edit., edited by Neidhardt FC, Curtiss R III, Ingraham JL, Lin ECC, Low KB, Magasanik B, Reznikoff WS, Riley M, Schaechter M, and Umbarger HE. Washington, DC: ASM Press, 1996, pp. 1458–1483.
16. Chai YC, Hoppe G, and Sears J. Reversal of protein *S*-glutathiolation by glutaredoxin in the retinal pigment epithelium. *Exp Eye Res* 76: 155–159, 2003.
17. Cho YW, Kim JC, Jin CD, Han TJ, and Lim CJ. Thioltransferase from *Arabidopsis thaliana* seed: purification to homogeneity and characterization. *Mol Cells* 8: 550–555, 1998.
18. Clissold PM and Bicknell R. The thioredoxin-like fold: hidden domains in protein disulfide isomerases and other chaperone proteins. *Bioessays* 25: 603–611, 2003.
19. Cotgreave IA and Gerdes RG. Recent trends in glutathione biochemistry—glutathione–protein interactions: a molecular link between oxidative stress and cell proliferation? *Biochem Biophys Res Commun* 242: 1–9, 1998.
20. Daily D, Vlamis-Gardikas A, Offen D, Mittelman L, Melamed E, Holmgren A, and Barzilai A. Glutaredoxin protects cerebellar granule neurons from dopamine-induced apoptosis by activating NF-kappa B via Ref-1. *J Biol Chem* 276: 1335–1344, 2001.
21. Daily D, Vlamis-Gardikas A, Offen D, Mittelman L, Melamed E, Holmgren A, and Barzilai A. Glutaredoxin protects cerebellar granule neurons from dopamine-induced apoptosis by dual activation of the ras-phosphoinositide 3-kinase and jun N-terminal kinase pathways. *J Biol Chem* 276: 21618–21626, 2001.
22. Davis DA, Dorsey K, Wingfield PT, Stahl SJ, Kaufman J, Fales HM, and Levine RL. Regulation of HIV-1 protease activity through cysteine modification. *Biochemistry* 35: 2482–2488, 1996.
23. Davis DA, Newcomb FM, Starke DW, Ott DE, Mieyal JJ, and Yarchoan R. Thioltransferase (glutaredoxin) is detected within HIV-1 and can regulate the activity of glutathionylated HIV-1 protease in vitro. *J Biol Chem* 272: 25935–25940, 1997.
24. Edman JC, Ellis L, Blacher RW, Roth RA, and Rutter WJ. Sequence of protein disulphide isomerase and implications of its relationship to thioredoxin. *Nature* 317: 267–270, 1985.
25. Eklund H, Ingelman M, Soderberg BO, Uhlin T, Nordlund P, Nikkola M, Sonnerstam U, Joelson T, and Petratos K. Structure of oxidized bacteriophage T4 glutaredoxin (thioredoxin). Refinement of native and mutant proteins. *J Mol Biol* 228: 596–618, 1992.
26. Epp O, Ladenstein R, and Wendel A. The refined structure of the selenoenzyme glutathione peroxidase at 0.2-nm resolution. *Eur J Biochem* 133: 51–69, 1983.
27. Fahey RC. Novel thiols of prokaryotes. *Annu Rev Microbiol* 55: 333–356, 2001.
28. Foloppe N, Sagemark J, Nordstrand K, Berndt KD, and Nilsson L. Structure, dynamics and electrostatics of the active site of glutaredoxin 3 from *Escherichia coli*: comparison with functionally related proteins. *J Mol Biol* 310: 449–470, 2001.
29. Fomenko DE and Gladyshev VN. CxxS: fold-independent redox motif revealed by genome-wide searches for

thiol/disulfide oxidoreductase function. *Protein Sci* 11: 2285–2296, 2002.

30. Gan ZR, Polokoff MA, Jacobs JW, and Sardana MK. Complete amino acid sequence of yeast thioltransferase (glutaredoxin). *Biochem Biophys Res Commun* 168: 944–951, 1990.
31. Gilbert HF. Redox control of enzyme activities by thiol/disulfide exchange. *Methods Enzymol* 107: 330–351, 1984.
32. Gladysheva TB, Oden KL, and Rosen BP. Properties of the arsenate reductase of plasmid R773. *Biochemistry* 33: 7288–7293, 1994.
33. Gravina SA and Mieyal JJ. Thioltransferase is a specific glutathionyl mixed disulfide oxidoreductase. *Biochemistry* 32: 3368–3376, 1993.
34. Harrop SJ, DeMaere MZ, Fairlie WD, Reztsova T, Valenzuela SM, Mazzanti M, Tonini R, Qiu MR, Jankova L, Warton K, Bauskin AR, Wu WM, Pankhurst S, Campbell TJ, Breit SN, and Curmi PM. Crystal structure of a soluble form of the intracellular chloride ion channel CLIC1 (NCC27) at 1.4-A resolution. *J Biol Chem* 276: 44993–45000, 2001.
35. Hengge-Aronis R. Regulation of gene expression during entry into stationary phase. In: *Escherichia coli and Salmonella: Cellular and Molecular Biology,* 2nd edit., edited by Neidhardt FC, Curtiss R III, Ingraham JL, Lin ECC, Low KB, Magasanik B, Reznikoff WS, Riley M, Schaechter M, and Umbarger HE. Washington, DC: ASM Press, 1996, pp. 1497–1512.
36. Holmgren A. Hydrogen donor system for *Escherichia coli* ribonucleoside-diphosphate reductase dependent upon glutathione. *Proc Natl Acad Sci U S A* 73: 2275–2279, 1976.
37. Holmgren A. Glutathione-dependent synthesis of deoxyribonucleotides. Characterization of the enzymatic mechanism of *Escherichia coli* glutaredoxin. *J Biol Chem* 254: 3672–3678, 1979.
38. Holmgren A. Glutathione-dependent synthesis of deoxyribonucleotides. Purification and characterization of glutaredoxin from *Escherichia coli. J Biol Chem* 254: 3664–3671, 1979.
39. Holmgren A. Thioredoxin and glutaredoxin systems. *J Biol Chem* 264: 13963–13966, 1989.
40. Holmgren A. Antioxidant function of thioredoxin and glutaredoxin systems. *Antioxid Redox Signal* 2: 811–820, 2000.
41. Holmgren A and Åslund F. Glutaredoxin. *Methods Enzymol* 252: 283–292, 1995.
42. Holmgren A, Söderberg BO, Eklund H, and Bränden CI. Three-dimensional structure of *Escherichia coli* thioredoxin-S2 to 2.8 A resolution. *Proc Natl Acad Sci U S A* 72: 2305–2309, 1975.
43. Holmgren A, Ohlsson I, and Grankvist ML. Thioredoxin from *Escherichia coli.* Radioimmunological and enzymatic determinations in wild type cells and mutants defective in phage T7 DNA replication. *J Biol Chem* 253: 430–436, 1978.
44. Hoog JO, Jornvall H, Holmgren A, Carlquist M, and Persson M. The primary structure of *Escherichia coli* glutaredoxin. Distant homology with thioredoxins in a superfamily of small proteins with a redox-active cystine disulfide/cysteine dithiol. *Eur J Biochem* 136: 223–232, 1983.
45. Hopper S, Johnson RS, Vath JE, and Biemann K. Glutaredoxin from rabbit bone marrow. Purification, characterization, and amino acid sequence determined by tandem mass spectrometry. *J Biol Chem* 264: 20438–20447, 1989.
46. Hutchison CA, Peterson SN, Gill SR, Cline RT, White O, Fraser CM, Smith HO, and Venter JC. Global transposon mutagenesis and a minimal *Mycoplasma* genome. *Science* 286: 2165–2169, 1999.
47. Isakov N, Witte S, and Altman A. PICOT-HD: a highly conserved protein domain that is often associated with thioredoxin and glutaredoxin modules. *Trends Biochem Sci* 25: 537–539, 2000.
48. Jordan A, Aslund F, Pontis E, Reichard P, and Holmgren A. Characterization of *Escherichia coli* NrdH. A glutaredoxin-like protein with a thioredoxin-like activity profile. *J Biol Chem* 272: 18044–18050, 1997.
49. Katti SK, Robbins AH, Yang Y, and Wells WW. Crystal structure of thioltransferase at 2.2 A resolution. *Protein Sci* 4: 1998–2005, 1995.
50. Kelley JJ 3rd and Bushweller JH. ^{1}H, ^{13}C and ^{15}N NMR resonance assignments of vaccinia glutaredoxin-1 in the fully reduced form. *J Biomol NMR* 12: 353–355, 1998.
51. Kemmink J, Darby NJ, Dijkstra K, Nilges M, and Creighton TE. Structure determination of the N-terminal thioredoxin-like domain of protein disulfide isomerase using multidimensional heteronuclear ^{13}C/^{15}N NMR spectroscopy. *Biochemistry* 35: 7684–7691, 1996.
52. Kim SO, Merchant K, Nudelman R, Beyer WF Jr, Keng T, DeAngelo J, Hausladen A, and Stamler JS. OxyR: a molecular code for redox-related signaling. *Cell* 109: 383–396, 2002.
53. Klatt P and Lamas S. Regulation of protein function by S-glutathiolation in response to oxidative and nitrosative stress. *Eur J Biochem* 267: 4928–4944, 2000.
54. Klatt P, Molina EP, and Lamas S. Nitric oxide inhibits c-Jun DNA binding by specifically targeted *S*-glutathionylation. *J Biol Chem* 274: 15857–15864, 1999.
55. Kobayashi K, Ehrlich SD, Albertini A, Amati G, Andersen KK, Arnaud M, Asai K, Ashikaga S, Aymerich S, Bessieres P, Boland F, Brignell SC, Bron S, Bunai K, Chapuis J, Christiansen LC, Danchin A, Debarbouille M, Dervyn E, Deuerling E, Devine K, Devine SK, Dreesen O, Errington J, Fillinger S, Foster SJ, Fujita Y, Galizzi A, Gardan R, Eschevins C, Fukushima T, Haga K, Harwood CR, Hecker M, Hosoya D, Hullo MF, Kakeshita H, Karamata D, Kasahara Y, Kawamura F, Koga K, Koski P, Kuwana R, Imamura D, Ishimaru M, Ishikawa S, Ishio I, Le Coq D, Masson A, Mauel C, Meima R, Mellado RP, Moir A, Moriya S, Nagakawa E, Nanamiya H, Nakai S, Nygaard P, Ogura M, Ohanan T, O'Reilly M, O'Rourke M, Pragai Z, Pooley HM, Rapoport G, Rawlins JP, Rivas LA, Rivolta C, Sadaie A, Sadaie Y, Sarvas M, Sato T, Saxild HH, Scanlan E, Schumann W, Seegers JF, Sekiguchi J, Sekowska A, Seror SJ, Simon M, Stragier P, Studer R, Takamatsu H, Tanaka T, Takeuchi M, Thomaides HB, Vagner V, van Dijl JM, Watabe K, Wipat

A, Yamamoto H, Yamamoto M, Yamamoto Y, Yamane K, Yata K, Yoshida K, Yoshikawa H, Zuber U, and Ogasawara N. Essential *Bacillus subtilis* genes. *Proc Natl Acad Sci U S A* 100: 4678–4683, 2003.

56. Kodym R, Calkins P, and Story M. The cloning and characterization of a new stress response protein. A mammalian member of a family of theta class glutathione *S*-transferase-like proteins. *J Biol Chem* 274: 5131–5137, 1999.
57. Koradi R, Billeter M, and Wuthrich K. MOLMOL: a program for display and analysis of macromolecular structures. *J Mol Graph* 14: 51–55, 29–32, 1996.
58. Kunst F, Ogasawara N, Moszer I, Albertini AM, Alloni G, Azevedo V, Bertero MG, Bessieres P, Bolotin A, Borchert S, Borriss R, Boursier L, Brans A, Braun M, Brignell SC, Bron S, Brouillet S, Bruschi CV, Caldwell B, Capuano V, Carter NM, Choi SK, Codani JJ, Connerton IF, Danchin A, *et al.* The complete genome sequence of the gram-positive bacterium *Bacillus subtilis*. *Nature* 390: 249–256, 1997.
59. Lillig CH, Prior A, Schwenn JD, Åslund F, Ritz D, Vlamis-Gardikas A, and Holmgren A. New thioredoxins and glutaredoxins as electron donors of 3′-phosphoadenylylsulfate reductase. *J Biol Chem* 274: 7695–7698, 1999.
60. Lillig CH, Potamitou A, Schwenn JD, Vlamis-Gardikas A, and Holmgren A. Redox regulation of 3′-phosphoadenylylsulfate reductase from *Escherichia coli* by glutathione and glutaredoxins. *J Biol Chem* 278: 22325–22330, 2003.
61. Lind C, Gerdes R, Hamnell Y, Schuppe-Koistinen I, von Lowenhielm HB, Holmgren A, and Cotgreave I. Identification of *S*-glutathionylated cellular proteins during oxidative stress and constitutive metabolism by affinity purification and proteomic analysis. *Arch Biochem Biophys* 406: 229–240, 2002.
62. Lundberg M, Johansson C, Chandra J, Enoksson M, Jacobsson G, Ljung J, Johansson M, and Holmgren A. Cloning and expression of a novel human glutaredoxin (Grx2) with mitochondrial and nuclear isoforms. *J Biol Chem* 276: 26269–26275, 2001.
63. Luthman M, Eriksson S, Holmgren A, and Thelander L. Glutathione-dependent hydrogen donor system for calf thymus ribonucleoside-diphosphate reductase. *Proc Natl Acad Sci U S A* 76: 2158–2162, 1979.
64. Maples KR, Kennedy CH, Jordan SJ, and Mason RP. In vivo thiyl free radical formation from hemoglobin following administration of hydroperoxides. *Arch Biochem Biophys* 277: 402–409, 1990.
65. Martin GM, Austad SN, and Johnson TE. Genetic analysis of ageing: role of oxidative damage and environmental stresses. *Nat Genet* 13: 25–34, 1996.
66. Martin JL. Thioredoxin—a fold for all reasons. *Structure* 3: 245–250, 1995.
67. Martin JL, Waksman G, Bardwell JC, Beckwith J, and Kuriyan J. Crystallization of DsbA, an *Escherichia coli* protein required for disulphide bond formation in vivo. *J Mol Biol* 230: 1097–1100, 1993.
68. Minakuchi K, Yabushita T, Masumura T, Ichihara K, and Tanaka K. Cloning and sequence analysis of a cDNA encoding rice glutaredoxin. *FEBS Lett* 337: 157–160, 1994.
69. Miranda-Vizuete A, Martinez-Galisteo E, Åslund F, Lopez-Barea J, Pueyo C, and Holmgren A. Null thioredoxin and glutaredoxin *Escherichia coli* K-12 mutants have no enhanced sensitivity to mutagens due to a new GSH-dependent hydrogen donor and high increases in ribonucleotide reductase activity. *J Biol Chem* 269: 16631–16637, 1994.
70. Miranda-Vizuete A, Rodriguez-Ariza A, Toribio F, Holmgren A, Lopez-Barea J, and Pueyo C. The levels of ribonucleotide reductase, thioredoxin, glutaredoxin 1, and GSH are balanced in *Escherichia coli* K12. *J Biol Chem* 271: 19099–19103, 1996.
71. Morell S, Follmann H, and Haberlein I. Identification and localization of the first glutaredoxin in leaves of a higher plant. *FEBS Lett* 369: 149–152, 1995.
72. Mukhopadhyay R and Rosen BP. Arsenate reductases in prokaryotes and eukaryotes. *Environ Health Perspect* 110 (Suppl 5): 745–748, 2002.
73. Nordstrand K, Aslund F, Meunier S, Holmgren A, Otting G, and Berndt KD. Direct NMR observation of the Cys-14 thiol proton of reduced *Escherichia coli* glutaredoxin-3 supports the presence of an active site thiol-thiolate hydrogen bond. *FEBS Lett* 449: 196–200, 1999.
74. Nordstrand K, Aslund F, Holmgren A, Otting G, and Berndt KD. NMR structure of *Escherichia coli* glutaredoxin 3–glutathione mixed disulfide complex: implications for the enzymatic mechanism. *J Mol Biol* 286: 541–552, 1999.
75. Nordstrand K, Sandstrom A, Aslund F, Holmgren A, Otting G, and Berndt KD. NMR structure of oxidized glutaredoxin 3 from *Escherichia coli*. *J Mol Biol* 303: 423–432, 2000.
76. Nulton-Persson AC, Starke DW, Mieyal JJ, and Szweda LI. Reversible inactivation of alpha-ketoglutarate dehydrogenase in response to alterations in the mitochondrial glutathione status. *Biochemistry* 42: 4235–4242, 2003.
77. Nystrom T. Aging in bacteria. *Curr Opin Microbiol* 5: 596–601, 2002.
78. Nystrom T. Translational fidelity, protein oxidation, and senescence: lessons from bacteria. *Ageing Res Rev* 1: 693–703, 2002.
79. Nystrom T. Nonculturable bacteria: programmed survival forms or cells at death's door? *Bioessays* 25: 204–211, 2003.
80. Padilla CA, Martinez-Galisteo E, Barcena JA, Spyrou G, and Holmgren A. Purification from placenta, amino acid sequence, structure comparisons and cDNA cloning of human glutaredoxin. *Eur J Biochem* 227: 27–34, 1995.
81. Pineda-Molina E, Klatt P, Vazquez J, Marina A, Garcia de Lacoba M, Perez-Sala D, and Lamas S. Glutathionylation of the p50 subunit of NF-kappaB: a mechanism for redox-induced inhibition of DNA binding. *Biochemistry* 40: 14134–14142, 2001.
82. Potamitou A, Holmgren A, and Vlamis-Gardikas A. Protein levels of *Escherichia coli* thioredoxins and glutaredoxins and their relation to null mutants, growth phase, and function. *J Biol Chem* 277: 18561–18567, 2002.
83. Potamitou A, Neubauer P, Holmgren A, and Vlamis-Gardikas A. Expression of *Escherichia coli* glutaredoxin 2 is mainly regulated by ppGpp and sigmaS. *J Biol Chem* 277: 17775–17780, 2002.

84. Prieto-Alamo MJ, Jurado J, Gallardo-Madueno R, Monje-Casas F, Holmgren A, and Pueyo C. Transcriptional regulation of glutaredoxin and thioredoxin pathways and related enzymes in response to oxidative stress. *J Biol Chem* 275: 13398–13405, 2000.
85. Prinz WA, Åslund F, Holmgren A, and Beckwith J. The role of the thioredoxin and glutaredoxin pathways in reducing protein disulfide bonds in the *Escherichia coli* cytoplasm. *J Biol Chem* 272: 15661–15667, 1997.
86. Rahlfs S, Fischer M, and Becker K. *Plasmodium falciparum* possesses a classical glutaredoxin and a second, glutaredoxin-like protein with a PICOT homology domain. *J Biol Chem* 276: 37133–37140, 2001.
87. Rao RK and Clayton LW. Regulation of protein phosphatase 2A by hydrogen peroxide and glutathionylation. *Biochem Biophys Res Commun* 293: 610–616, 2002.
88. Reinemer P, Dirr HW, Ladenstein R, Schaffer J, Gallay O, and Huber R. The three-dimensional structure of class pi glutathione *S*-transferase in complex with glutathione sulfonate at 2.3 A resolution. *EMBO J* 10: 1997–2005, 1991.
89. Rikans LE and Hornbrook KR. Lipid peroxidation, antioxidant protection and aging. *Biochim Biophys Acta* 1362: 116–127, 1997.
90. Ritz D and Beckwith J. Roles of thiol-redox pathways in bacteria. *Annu Rev Microbiol* 55: 21–48, 2001.
91. Ritz D, Lim J, Reynolds CM, Poole LB, and Beckwith J. Conversion of a peroxiredoxin into a disulfide reductase by a triplet repeat expansion. *Science* 294: 158–160, 2001.
92. Rodriguez-Manzaneque MT, Ros J, Cabiscol E, Sorribas A, and Herrero E. Grx5 glutaredoxin plays a central role in protection against protein oxidative damage in *Saccharomyces cerevisiae. Mol Cell Biol* 19: 8180–8190, 1999.
93. Rodriguez-Manzaneque MT, Tamarit J, Belli G, Ros J, and Herrero E. Grx5 is a mitochondrial glutaredoxin required for the activity of iron/sulfur enzymes. *Mol Biol Cell* 13: 1109–1121, 2002.
94. Rossjohn J, McKinstry WJ, Oakley AJ, Verger D, Flanagan J, Chelvanayagam G, Tan KL, Board PG, and Parker MW. Human theta class glutathione transferase: the crystal structure reveals a sulfate-binding pocket within a buried active site. *Structure* 6: 309–322, 1998.
95. Rouhier N, Gelhaye E, Sautiere PE, and Jacquot JP. Enhancement of poplar glutaredoxin expression by optimization of the cDNA sequence. *Protein Expr Purif* 24: 234–241, 2002.
96. Russel M and Holmgren A. Construction and characterization of glutaredoxin-negative mutants of *Escherichia coli. Proc Natl Acad Sci U S A* 85: 990–994, 1988.
97. Russel M, Model P, and Holmgren A. Thioredoxin or glutaredoxin in *Escherichia coli* is essential for sulfate reduction but not for deoxyribonucleotide synthesis. *J Bacteriol* 172: 1923–1929, 1990.
98. Sandberg VA, Kren B, Fuchs JA, and Woodward C. *Escherichia coli* glutaredoxin: cloning and overexpression, thermodynamic stability of the oxidized and reduced forms, and report of an N-terminal extended species. *Biochemistry* 30: 5475–5484, 1991.
99. Scharf C, Riethdorf S, Ernst H, Engelmann S, Volker U, and Hecker M. Thioredoxin is an essential protein induced by multiple stresses in *Bacillus subtilis. J Bacteriol* 180: 1869–1877, 1998.
100. Shi J, Vlamis-Gardikas A, Åslund F, Holmgren A, and Rosen BP. Reactivity of glutaredoxins 1, 2, and 3 from *Escherichia coli* shows that glutaredoxin 2 is the primary hydrogen donor to ArsC-catalyzed arsenate reduction. *J Biol Chem* 274: 36039–36042, 1999.
101. Sjoberg BM and Holmgren A. Studies on the structure of T4 thioredoxin. II. Amino acid sequence of the protein and comparison with thioredoxin from *Escherichia coli. J Biol Chem* 247: 8063–8068, 1972.
102. Sodano P, Xia TH, Bushweller JH, Bjornberg O, Holmgren A, Billeter M, and Wuthrich K. Sequence-specific ^{1}H n.m.r. assignments and determination of the three-dimensional structure of reduced *Escherichia coli* glutaredoxin. *J Mol Biol* 221: 1311–1324, 1991.
103. Sohal RS and Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 273: 59–63, 1996.
104. Stehr M, Schneider G, Aslund F, Holmgren A, and Lindqvist Y. Structural basis for the thioredoxin-like activity profile of the glutaredoxin-like NrdH-redoxin from *Escherichia coli. J Biol Chem* 276: 35836–35841, 2001.
105. Stewart EJ, Åslund F, and Beckwith J. Disulfide bond formation in the *Escherichia coli* cytoplasm: an in vivo role reversal for the thioredoxins. *EMBO J* 17: 5543–5550, 1998.
106. Sun C, Berardi MJ, and Bushweller JH. The NMR solution structure of human glutaredoxin in the fully reduced form. *J Mol Biol* 280: 687–701, 1998.
107. Tao K. oxyR-dependent induction of *Escherichia coli* grx gene expression by peroxide stress. *J Bacteriol* 179: 5967–5970, 1997.
108. Tsang ML. Assimilatory sulfate reduction in *Escherichia coli*: identification of the alternate cofactor for adenosine 3′-phosphate 5′-phosphosulfate reductase as glutaredoxin. *J Bacteriol* 146: 1059–1066, 1981.
109. Tsang ML and Schiff JA. Assimilatory sulfate reduction in an *Escherichia coli* mutant lacking thioredoxin activity. *J Bacteriol* 134: 131–138, 1978.
110. Vlamis-Gardikas A and Holmgren A. Thioredoxin and glutaredoxin isoforms. *Methods Enzymol* 347: 286–296, 2002.
111. Vlamis-Gardikas A, Åslund F, Spyrou G, Bergman T, and Holmgren A. Cloning, overexpression, and characterization of glutaredoxin 2, an atypical glutaredoxin from *Escherichia coli. J Biol Chem* 272: 11236–11243, 1997.
112. Vlamis-Gardikas A, Potamitou A, Zarivach R, Hochman A, and Holmgren A. Characterization of *Escherichia coli* null mutants for glutaredoxin 2. *J Biol Chem* 277: 10861–10868, 2002.
113. Wang J, Boja ES, Tan W, Tekle E, Fales HM, English S, Mieyal JJ, and Chock PB. Reversible glutathionylation regulates actin polymerization in A431 cells. *J Biol Chem* 276: 47763–47766, 2001.
114. Wang J, Tekle E, Oubrahim H, Mieyal JJ, Stadtman ER, and Chock PB. Stable and controllable RNA interference: investigating the physiological function of glutathionylated actin. *Proc Natl Acad Sci U S A* 100: 5103–5106, 2003.
115. Witte S, Villalba M, Bi K, Liu Y, Isakov N, and Altman A. Inhibition of the c-Jun N-terminal kinase/AP-1 and NF-kappaB pathways by PICOT, a novel protein kinase

C-interacting protein with a thioredoxin homology domain. *J Biol Chem* 275: 1902–1909, 2000.
116. Xia B, Vlamis-Gardikas A, Holmgren A, Wright PE, and Dyson HJ. Solution structure of *Escherichia coli* glutaredoxin-2 shows similarity to mammalian glutathione-*S*-transferases. *J Mol Biol* 310: 907–918, 2001.
117. Xia TH, Bushweller JH, Sodano P, Billeter M, Bjornberg O, Holmgren A, and Wuthrich K. NMR structure of oxidized *Escherichia coli* glutaredoxin: comparison with reduced *E. coli* glutaredoxin and functionally related proteins. *Protein Sci* 1: 310–321, 1992.
118. Yang YF and Wells WW. Identification and characterization of the functional amino acids at the active center of pig liver thioltransferase by site-directed mutagenesis. *J Biol Chem* 266: 12759–12765, 1991.
119. Zheng M, Åslund F, and Storz G. Activation of the OxyR transcription factor by reversible disulfide bond formation. *Science* 279: 1718–1721, 1998.

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1. Yves Meyer , Christophe Belin , Valérie Delorme-Hinoux , Jean-Philippe Reichheld , Christophe Riondet . 2012. Thioredoxin and Glutaredoxin Systems in Plants: Molecular Mechanisms, Crosstalks, and Functional Significance. *Antioxidants & Redox Signaling* **17**:8, 1124-1160. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
2. David L. Williams , Mariana Bonilla , Vadim N. Gladyshev , Gustavo Salinas . Thioredoxin Glutathione Reductase-Dependent Redox Networks in Platyhelminth Parasites. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
3. Jos H. M. Schippers, Hung M. Nguyen, Dandan Lu, Romy Schmidt, Bernd Mueller-Roeber. 2012. ROS homeostasis during development: an evolutionary conserved strategy. *Cellular and Molecular Life Sciences* **69**:19, 3245-3257. [CrossRef]
4. Haike Antelmann, Chris J. Hamilton. 2012. Bacterial mechanisms of reversible protein S -thiolation: structural and mechanistic insights into mycoredoxins. *Molecular Microbiology* n/a-n/a. [CrossRef]
5. Koen Van Laer, Lieven Buts, Nicolas Foloppe, Didier Vertommen, Karolien Van Belle, Khadija Wahni, Goedele Roos, Lennart Nilsson, Luis M. Mateos, Mamta Rawat, Nico A. J. van Nuland, Joris Messens. 2012. Mycoredoxin-1 is one of the missing links in the oxidative stress defence mechanism of Mycobacteria. *Molecular Microbiology* n/a-n/a. [CrossRef]
6. Magdalena L. Circu, Tak Yee Aw. 2012. Intestinal redox biology and oxidative stress. *Seminars in Cell & Developmental Biology* **23**:7, 729-737. [CrossRef]
7. Ivan Dimauro, Timothy Pearson, Daniela Caporossi, Malcolm J. Jackson. 2012. In vitro susceptibility of thioredoxins and glutathione to redox modification and ageing-related changes in skeletal muscle. *Free Radical Biology and Medicine* . [CrossRef]
8. Catherine Putonti, Bryan Quach, Rachel A. Kooistra, Stefan M. Kanzok. 2012. The evolution and putative function of phosducin-like proteins in the malaria parasite Plasmodium. *Infection, Genetics and Evolution* . [CrossRef]
9. Samantha D. Bouldin, Maxwell A. Darch, P. John Hart, Caryn E. Outten. 2012. Redox properties of the disulfide bond of human Cu,Zn superoxide dismutase and the effects of human glutaredoxin 1. *Biochemical Journal* **446**:1, 59-67. [CrossRef]
10. X.-W. Chi, C.-T. Lin, Y.-C. Jiang, L. Wen, C.-T. Lin. 2012. A dithiol glutaredoxin cDNA from sweet potato (Ipomoea batatas [L.] Lam): enzyme properties and kinetic studies. *Plant Biology* **14**:4, 659-665. [CrossRef]
11. Z. S. Zhou, J. B. Song, Z. M. Yang. 2012. Genome-wide identification of Brassica napus microRNAs and their targets in response to cadmium. *Journal of Experimental Botany* **63**:12, 4597-4613. [CrossRef]
12. Kenneth D. Tew , Danyelle M. Townsend . Glutathione-S-Transferases As Determinants of Cell Survival and Death. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
13. Haoran Li, Caryn E. Outten. 2012. Monothiol CGFS Glutaredoxins and BolA-like Proteins: [2Fe-2S] Binding Partners in Iron Homeostasis. *Biochemistry* **51**:22, 4377-4389. [CrossRef]
14. Young-Mee Oh, Seung-Keun Hong, Jeong-Tae Yeon, Mee-Kyung Cha, Il-Han Kim. 2012. Interaction between Saccharomyces cerevisiae glutaredoxin 5 and SPT10 and their in vivo functions. *Free Radical Biology and Medicine* **52**:9, 1519-1530. [CrossRef]
15. Yuan-Chun Lin, Guan-Da Huang, Chia-Wen Hsieh, Being-Sun Wung. 2012. The glutathionylation of p65 modulates NF-#B activity in 15-deoxy-#12,14-prostaglandin J2-treated endothelial cells. *Free Radical Biology and Medicine* **52**:9, 1844-1853. [CrossRef]
16. Vikas Anathy , Elle C. Roberson , Amy S. Guala , Karolyn E. Godburn , Ralph C. Budd , Yvonne M.W. Janssen-Heininger . 2012. Redox-Based Regulation of Apoptosis: S-Glutathionylation As a Regulatory Mechanism to Control Cell Death. *Antioxidants & Redox Signaling* **16**:6, 496-505. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

17. Mirko Zaffagnini , Mariette Bedhomme , Christophe H. Marchand , Samuel Morisse , Paolo Trost , Stéphane D. Lemaire . 2012. Redox Regulation in Photosynthetic Organisms: Focus on Glutathionylation. *Antioxidants & Redox Signaling* **16**:6, 567-586. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
18. David Pimentel , Dagmar Johanna Haeussler , Reiko Matsui , Joseph Robert Burgoyne , Richard Alan Cohen , Markus Michael Bachschmid . 2012. Regulation of Cell Physiology and Pathology by Protein S-Glutathionylation: Lessons Learned from the Cardiovascular System. *Antioxidants & Redox Signaling* **16**:6, 524-542. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
19. Mirko Zaffagnini , Mariette Bedhomme , Christophe H. Marchand , Jérémy Couturier , Xing-Huang Gao , Nicolas Rouhier , Paolo Trost , Stéphane D. Lemaire . 2012. Glutaredoxin S12: Unique Properties for Redox Signaling. *Antioxidants & Redox Signaling* **16**:1, 17-32. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
20. Millie M. GeorgiadisApurinic/Apyrimindinic Endonuclease in Redox Regulation and Oxidative Stress 235-255. [CrossRef]
21. Changkao Mu, Qing Wang, Zeyi Yuan, Zhendong Zhang, Chunlin Wang. 2011. Identification of glutaredoxin 1 and glutaredoxin 2 genes from Venerupis philippinarum and their responses to benzo[a]pyrene and bacterial challenge. *Fish & Shellfish Immunology* . [CrossRef]
22. Emma L. Bastow, Campbell W. Gourlay, Mick F. Tuite. 2011. Using yeast models to probe the molecular basis of amyotrophic lateral sclerosis. *Biochemical Society Transactions* **39**:5, 1482-1487. [CrossRef]
23. 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]
24. Magdalena L. Circu, Tak Yee Aw. 2011. Redox biology of the intestine. *Free Radical Research* 1-22. [CrossRef]
25. Elias S.J. Arnér . 2011. Redox Pioneer: Professor Arne Holmgren. *Antioxidants & Redox Signaling* **15**:3, 845-851. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
26. Xiang Ming Xu , Simon Geir Møller . 2011. Iron–Sulfur Clusters: Biogenesis, Molecular Mechanisms, and Their Functional Significance. *Antioxidants & Redox Signaling* **15**:1, 271-307. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
27. Moêz Smiri, Abdelilah Chaoui, Nicolas Rouhier, Eric Gelhaye, Jean-Pierre Jacquot, Ezzedine Ferjani. 2011. Cadmium Affects the Glutathione/Glutaredoxin System in Germinating Pea Seeds. *Biological Trace Element Research* **142**:1, 93-105. [CrossRef]
28. Kenneth D. Tew, Yefim Manevich, Christina Grek, Ying Xiong, Joachim Uys, Danyelle M. Townsend. 2011. The role of glutathione S-transferase P in signaling pathways and S-glutathionylation in cancer. *Free Radical Biology and Medicine* **51**:2, 299-313. [CrossRef]
29. Stefanie Prast-Nielsen, Hsin-Hung Huang, David L. Williams. 2011. Thioredoxin glutathione reductase: Its role in redox biology and potential as a target for drugs against neglected diseases. *Biochimica et Biophysica Acta (BBA) - General Subjects* . [CrossRef]
30. Ning-Hui Cheng, Wei Zhang, Wei-Qin Chen, Jianping Jin, Xiaojiang Cui, Nancy F. Butte, Lawrence Chan, Kendal D. Hirschi. 2011. A mammalian monothiol glutaredoxin, Grx3, is critical for cell cycle progression during embryogenesis. *FEBS Journal* no-no. [CrossRef]
31. Lissbeth Leon-Bollotte, Selvakumar Subramaniam, Olivier Cauvard, Stéphanie Plenchette–Colas, Catherine Paul, Cindy Godard, Antonio Martinez–Ruiz, Patrick Legembre, Jean–François Jeannin, Ali Bettaieb. 2011. S-Nitrosylation of the Death Receptor Fas Promotes Fas Ligand–Mediated Apoptosis in Cancer Cells. *Gastroenterology* **140**:7, 2009-2018.e4. [CrossRef]

32. Tiffany Vinckx, Qing Wei, Sandra Matthijs, Jean-Paul Noben, Ruth Daniels, Pierre Cornelis. 2011. A proteome analysis of the response of a Pseudomonas aeruginosa oxyR mutant to iron limitation. *BioMetals* **24**:3, 523-532. [CrossRef]

33. Stacy L. Gelhaus, Ian A. BlairMass Spectrometry in the Analysis of DNA, Protein, Peptide, and Lipid Biomarkers of Oxidative Stress 645-683. [CrossRef]

34. B. McDonagh, R. Requejo, C.A. Fuentes-Almagro, S. Ogueta, J.A. Bárcena, C.A. Padilla. 2011. Thiol redox proteomics identifies differential targets of cytosolic and mitochondrial glutaredoxin-2 isoforms in Saccharomyces cerevisiae. Reversible S-glutathionylation of DHBP synthase (RIB3). *Journal of Proteomics* . [CrossRef]

35. Kang Tang , Xun Li , Ming-Qi Zheng , George J. Rozanski . 2011. Role of Apoptosis Signal-Regulating Kinase-1-c-Jun NH2-Terminal Kinase-p38 Signaling in Voltage-Gated K+ Channel Remodeling of the Failing Heart: Regulation by Thioredoxin. *Antioxidants & Redox Signaling* **14**:1, 25-35. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

36. José Rodrigo Godoy, Maria Funke, Waltraud Ackermann, Petra Haunhorst, Sabrina Oesteritz, Francisco Capani, Hans-Peter Elsässer, Christopher Horst Lillig. 2011. Redox atlas of the mouse. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1810**:1, 2-92. [CrossRef]

37. Wenbin Qi, J. A. Cowan. 2011. Mechanism of glutaredoxin—ISU [2Fe–2S] cluster exchange. *Chemical Communications* **47**:17, 4989. [CrossRef]

38. Kondethimmanahalli H Chandramouli, Flora SY Mok, Hao Wang, Pei-Yuan Qian. 2011. Phosphoproteome analysis during larval development and metamorphosis in the spionid polychaete Pseudopolydora vexillosa. *BMC Developmental Biology* **11**:1, 31. [CrossRef]

39. Pascal Dammeyer, Elias S.J. Arnér. 2011. Human Protein Atlas of redox systems — What can be learnt?. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1810**:1, 111-138. [CrossRef]

40. Byung Cheon Lee, Vadim N. Gladyshev. 2011. The biological significance of methionine sulfoxide stereochemistry. *Free Radical Biology and Medicine* **50**:2, 221-227. [CrossRef]

41. Jeremy Michael Van Raamsdonk , Siegfried Hekimi . 2010. Reactive Oxygen Species and Aging in Caenorhabditis elegans: Causal or Casual Relationship?. *Antioxidants & Redox Signaling* **13**:12, 1911-1953. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

42. 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]

43. Emilia Pedone, Danila Limauro, Katia D'Ambrosio, Giuseppina Simone, Simonetta Bartolucci. 2010. Multiple catalytically active thioredoxin folds: a winning strategy for many functions. *Cellular and Molecular Life Sciences* **67**:22, 3797-3814. [CrossRef]

44. Eun-Hae Cho, Phil-Ok Koh. 2010. Proteomic identification of proteins differentially expressed by melatonin in hepatic ischemia-reperfusion injury. *Journal of Pineal Research* **49**:4, 349-355. [CrossRef]

45. Yushuang Guo, Changjun Huang, Yan Xie, Fengming Song, Xueping Zhou. 2010. A tomato glutaredoxin gene SlGRX1 regulates plant responses to oxidative, drought and salt stresses. *Planta* **232**:6, 1499-1509. [CrossRef]

46. Amy L. Turnbull, Michael G. Surette. 2010. Cysteine biosynthesis, oxidative stress and antibiotic resistance in Salmonella typhimurium. *Research in Microbiology* **161**:8, 643-650. [CrossRef]

47. Tobias H. Elgán, Anne#Gaëlle Planson, Jon Beckwith, Peter Güntert, Kurt D. Berndt. 2010. Determinants of activity in glutaredoxins: an in vitro evolved Grx1-like variant of Escherichia coli Grx3. *Biochemical Journal* **430**:3, 487-495. [CrossRef]

48. Andreas J. Meyer , Tobias P. Dick . 2010. Fluorescent Protein-Based Redox Probes. *Antioxidants & Redox Signaling* **13**:5, 621-650. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

49. U. Eichenlaub-Ritter, M. Wieczorek, S. Lüke, T. Seidel. 2010. Age related changes in mitochondrial function and new approaches to study redox regulation in mammalian oocytes in response to age or maturation conditions. *Mitochondrion* . [CrossRef]

50. V. I. Kulinsky, L. S. Kolesnichenko. 2010. The nuclear glutathione and its functions. *Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry* **4**:3, 224-227. [CrossRef]

51. 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]

52. Yvonne M.W. Janssen-Heininger, Scott W. Aesif, Jos Van Der Velden, Amy S. Guala, Jessica N. Reiss, Elle C. Roberson, Ralph C. Budd, Niki L. Reynaert, Vikas Anathy. 2010. Regulation of apoptosis through cysteine oxidation: implications for fibrotic lung disease. *Annals of the New York Academy of Sciences* **1203**:1, 23-28. [CrossRef]

53. Marita Wallenberg, Eric Olm, Christina Hebert, Mikael Björnstedt, Aristi P. Fernandes. 2010. Selenium compounds are substrates for glutaredoxins: a novel pathway for selenium metabolism and a potential mechanism for selenium-mediated cytotoxicity. *Biochemical Journal* **429**:1, 85-93. [CrossRef]

54. B.-C. Liao, C.-W. Hsieh, Y.-C. Lin, B.-S. Wung. 2010. The Glutaredoxin/Glutathione System Modulates NF- B Activity by Glutathionylation of p65 in Cinnamaldehyde-Treated Endothelial Cells. *Toxicological Sciences* **116**:1, 151-163. [CrossRef]

55. Wei-Fang Li, Jiang Yu, Xiao-Xiao Ma, Yan-Bin Teng, Ming Luo, Ya-Jun Tang, Cong-Zhao Zhou. 2010. Structural basis for the different activities of yeast Grx1 and Grx2. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1804**:7, 1542-1547. [CrossRef]

56. Montserrat Marí , Anna Colell , Albert Morales , Claudia von Montfort , Carmen Garcia-Ruiz , José C. Fernández-Checa . 2010. Redox Control of Liver Function in Health and Disease. *Antioxidants & Redox Signaling* **12**:11, 1295-1331. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

57. Meihua Luo , Hongzhen He , Mark R. Kelley , Millie M. Georgiadis . 2010. Redox Regulation of DNA Repair: Implications for Human Health and Cancer Therapeutic Development. *Antioxidants & Redox Signaling* **12**:11, 1247-1269. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

58. Ming Luo, Yong-Liang Jiang, Xiao-Xiao Ma, Ya-Jun Tang, Yong-Xing He, Jiang Yu, Rong-Guang Zhang, Yuxing Chen, Cong-Zhao Zhou. 2010. Structural and Biochemical Characterization of Yeast Monothiol Glutaredoxin Grx6. *Journal of Molecular Biology* **398**:4, 614-622. [CrossRef]

59. Pablo Porras, Brian McDonagh, Jose Rafael Pedrajas, J. Antonio Bárcena, C. Alicia Padilla. 2010. Structure and function of yeast glutaredoxin 2 depend on postranslational processing and are related to subcellular distribution. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1804**:4, 839-845. [CrossRef]

60. Ariel Ohayon, Yael Babichev, Ronit Pasvolsky, Guangyu Dong, Ignacio Sztarkier, Daniel Benharroch, Amnon Altman, Noah Isakov. 2010. Hodgkin's lymphoma cells exhibit high expression levels of the PICOT protein. *Journal of Immunotoxicology* **7**:1, 8-14. [CrossRef]

61. 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]

62. Margit Schraders, Kwanghyuk Lee, Jaap Oostrik, Patrick L.M. Huygen, Ghazanfar Ali, Lies H. Hoefsloot, Joris A. Veltman, Frans P.M. Cremers, Sulman Basit, Muhammad Ansar, Cor W.R.J. Cremers, Henricus P.M. Kunst, Wasim Ahmad, Ronald J.C. Admiraal, Suzanne M. Leal, Hannie Kremer. 2010. Homozygosity Mapping Reveals Mutations of GRXCR1 as a Cause of Autosomal-Recessive Nonsyndromic Hearing Impairment. *The American Journal of Human Genetics* **86**:2, 138-147. [CrossRef]

63. Suzy A.A. Comhair , Serpil C. Erzurum . 2010. Redox Control of Asthma: Molecular Mechanisms and Therapeutic Opportunities. *Antioxidants & Redox Signaling* **12**:1, 93-124. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
64. Nicolas Rouhier, Jérémy Couturier, Michael K. Johnson, Jean-Pierre Jacquot. 2010. Glutaredoxins: roles in iron homeostasis. *Trends in Biochemical Sciences* **35**:1, 43-52. [CrossRef]
65. Ehab H. Sarsour , Maneesh G. Kumar , Leena Chaudhuri , Amanda L. Kalen , Prabhat C. Goswami . 2009. Redox Control of the Cell Cycle in Health and Disease. *Antioxidants & Redox Signaling* **11**:12, 2985-3011. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
66. Gyorgy Szabadkai, Michael R. Duchen. 2009. Mitochondria mediated cell death in diabetes. *Apoptosis* **14**:12, 1405-1423. [CrossRef]
67. Margaret S. Lee, Mina Yaar, Mark S. Eller, Thomas M. Rünger, Ying Gao, Barbara A. Gilchrest. 2009. Telomeric DNA induces p53-dependent reactive oxygen species and protects against oxidative damage. *Journal of Dermatological Science* **56**:3, 154-162. [CrossRef]
68. Jun Lu , Arne Holmgren Glutaredoxin Catalysis and Function in Redox Regulation 3-6. [Abstract] [Summary] [Full Text PDF] [Full Text PDF with Links]
69. Md. Kaimul Ahsan , Istvan Lekli , Diptarka Ray , Junji Yodoi , Dipak K. Das . 2009. Redox Regulation of Cell Survival by the Thioredoxin Superfamily: An Implication of Redox Gene Therapy in the Heart. *Antioxidants & Redox Signaling* **11**:11, 2741-2758. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
70. Yusuke Iwasaki, Yusuke Saito, Yuki Nakano, Keisuke Mochizuki, Osamu Sakata, Rie Ito, Koichi Saito, Hiroyuki Nakazawa. 2009. Chromatographic and mass spectrometric analysis of glutathione in biological samples#. *Journal of Chromatography B* **877**:28, 3309-3317. [CrossRef]
71. Aristi P Fernandes, Arrigo Capitanio, Markus Selenius, Ola Brodin, Anna-Klara Rundlöf, Mikael Björnstedt. 2009. Expression profiles of thioredoxin family proteins in human lung cancer tissue: correlation with proliferation and differentiation. *Histopathology* **55**:3, 313-320. [CrossRef]
72. Eric Olm, Kerstin Jönsson-Videsäter, Inmaculada Ribera-Cortada, Aristi P. Fernandes, Lennart C. Eriksson, Sören Lehmann, Anna-Klara Rundlöf, Christer Paul, Mikael Björnstedt. 2009. Selenite is a potent cytotoxic agent for human primary AML cells. *Cancer Letters* **282**:1, 116-123. [CrossRef]
73. V. I. Kulinsky, L. S. Kolesnichenko. 2009. The glutathione system. II. Other enzymes, thiol-disulfide metabolism, inflammation, and immunity, functions. *Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry* **3**:3, 211-220. [CrossRef]
74. Scott W. Aesif, Vikas Anathy, Marije Havermans, Amy S. Guala, Karina Ckless, Douglas J. Taatjes, Yvonne M.W. Janssen-Heininger. 2009. In Situ Analysis of Protein S-Glutathionylation in Lung Tissue Using Glutaredoxin-1-Catalyzed Cysteine Derivatization. *The American Journal of Pathology* **175**:1, 36-45. [CrossRef]
75. E ARNER. 2009. Focus on mammalian thioredoxin reductases — Important selenoproteins with versatile functions. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1790**:6, 495-526. [CrossRef]
76. Joeri Auwerx, Ola Isacsson, Johan Söderlund, Jan Balzarini, Magnus Johansson, Mathias Lundberg. 2009. Human glutaredoxin-1 catalyzes the reduction of HIV-1 gp120 and CD4 disulfides and its inhibition reduces HIV-1 replication. *The International Journal of Biochemistry & Cell Biology* **41**:6, 1269-1275. [CrossRef]
77. Molly M. Gallogly , David W. Starke , John J. Mieyal . 2009. Mechanistic and Kinetic Details of Catalysis of Thiol-Disulfide Exchange by Glutaredoxins and Potential Mechanisms of Regulation. *Antioxidants & Redox Signaling* **11**:5, 1059-1081. [Abstract] [Full Text PDF] [Full Text PDF with Links]
78. Alexandra T. P. Carvalho, Pedro A. Fernandes, Marcel Swart, Joost N. P. Van Stralen, F. Matthias Bickelhaupt, Maria J. Ramos. 2009. Role of the variable active site residues in the function of thioredoxin family oxidoreductases. *Journal of Computational Chemistry* **30**:5, 710-724. [CrossRef]

79. Irene M. Sotirchos, Amanda L. Hudson, John Ellis, Mary W. Davey. 2009. A unique thioredoxin of the parasitic nematode Haemonchus contortus with glutaredoxin activity. *Free Radical Biology and Medicine* **46**:5, 579-585. [CrossRef]
80. V. Anathy, S. W. Aesif, A. S. Guala, M. Havermans, N. L. Reynaert, Y.-S. Ho, R. C. Budd, Y. M.W. Janssen-Heininger. 2009. Redox amplification of apoptosis by caspase-dependent cleavage of glutaredoxin 1 and S-glutathionylation of Fas. *The Journal of Cell Biology* **184**:2, 241-252. [CrossRef]
81. Xing-Huang Gao, Mariette Bedhomme, Laure Michelet, Mirko Zaffagnini, Stéphane D. LemaireChapter 12 Glutathionylation in Photosynthetic Organisms **52**, 363-403. [CrossRef]
82. Yuki Ogasawara, Masayo Funakoshi, Kazuyuki Ishii. 2009. Determination of Reduced Nicotinamide Adenine Dinucleotide Phosphate Concentration Using High-Performance Liquid Chromatography with Fluorescence Detection: Ratio of the Reduced Form as a Biomarker of Oxidative Stress. *Biological & Pharmaceutical Bulletin* **32**:11, 1819-1823. [CrossRef]
83. Masahiko MINAMI, Kazumi SUZUKI, Akifumi SHIMIZU, Tomohiro HONGO, Takaiku SAKAMOTO, Naoki OHYAMA, Hironori KITAURA, Akiho KUSAKA, Kenji IWAMA, Toshikazu IRIE. 2009. Changes in the Gene Expression of the White Rot Fungus Phanerochaete chrysosporium Due to the Addition of Atropine. *Bioscience, Biotechnology, and Biochemistry* **73**:8, 1722-1731. [CrossRef]
84. Karen Fulan Discola, Marcos Antonio de Oliveira, José Renato Rosa Cussiol, Gisele Monteiro, José Antonio Bárcena, Pablo Porras, C. Alicia Padilla, Beatriz Gomes Guimarães, Luis Eduardo Soares Netto. 2009. Structural Aspects of the Distinct Biochemical Properties of Glutaredoxin 1 and Glutaredoxin 2 from Saccharomyces cerevisiae. *Journal of Molecular Biology* **385**:3, 889-901. [CrossRef]
85. Benoit Marteyn, Francis Domain, Pierre Legrain, Franck Chauvat, Corinne Cassier-Chauvat. 2009. The thioredoxin reductase-glutaredoxins-ferredoxin crossroad pathway for selenate tolerance in Synechocystis PCC6803. *Molecular Microbiology* **71**:2, 520-532. [CrossRef]
86. Benjamin Selles, Nicolas Rouhier, Kamel Chibani, Jeremy Couturier, Filipe Gama, Jean-Pierre JacquotChapter 13 Glutaredoxin **52**, 405-436. [CrossRef]
87. Laure Michelet, Mirko Zaffagnini, D. LemaireThioredoxins and Related Proteins 401-443. [CrossRef]
88. Yu-Jin Kim, Ju-Sun Shim, Pulla Rama Krishna, Se-Young Kim, Jun-Gyo In, Myung-Kyum Kim, Deok-Chun Yang. 2008. Isolation and Characterization of a Glutaredoxin Gene from Panax ginseng C. A. Meyer. *Plant Molecular Biology Reporter* **26**:4, 335-349. [CrossRef]
89. 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]
90. E HERRERO, J ROS, G BELLI, E CABISCOL. 2008. Redox control and oxidative stress in yeast cells. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1217-1235. [CrossRef]
91. R KRAUTHSIEGEL, M COMINI. 2008. Redox control in trypanosomatids, parasitic protozoa with trypanothione-based thiol metabolism. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1236-1248. [CrossRef]
92. C LILLIG, C BERNDT, A HOLMGREN. 2008. Glutaredoxin systems. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1304-1317. [CrossRef]
93. Jiang Yu, Nan-Nan Zhang, Pei-Dong Yin, Pei-Xin Cui, Cong-Zhao Zhou. 2008. Glutathionylation-triggered conformational changes of glutaredoxin Grx1 from the yeast Saccharomyces cerevisiae. *Proteins: Structure, Function, and Bioinformatics* **72**:3, 1077-1083. [CrossRef]
94. Z. Wang, S. Xing, R. P. Birkenbihl, S. Zachgo. 2008. Conserved Functions of Arabidopsis and Rice CC-Type Glutaredoxins in Flower Development and Pathogen Response. *Molecular Plant* **2**:2, 323-335. [CrossRef]
95. Cecilia Hidalgo , Paulina Donoso . 2008. Crosstalk Between Calcium and Redox Signaling: From Molecular Mechanisms to Health Implications. *Antioxidants & Redox Signaling* **10**:7, 1275-1312. [Abstract] [Full Text PDF] [Full Text PDF with Links]

96. Yvonne M.W. Janssen-Heininger, Brooke T. Mossman, Nicholas H. Heintz, Henry J. Forman, Balaraman Kalyanaraman, Toren Finkel, Jonathan S. Stamler, Sue Goo Rhee, Albert van der Vliet. 2008. Redox-based regulation of signal transduction: Principles, pitfalls, and promises. *Free Radical Biology and Medicine* **45**:1, 1-17. [CrossRef]
97. Gustavo M. Silva, Luis E.S. Netto, Karen F. Discola, Gilberto M. Piassa-Filho, Daniel C. Pimenta, José A. Bárcena, Marilene Demasi. 2008. Role of glutaredoxin 2 and cytosolic thioredoxins in cysteinyl-based redox modification of the 20S proteasome. *FEBS Journal* **275**:11, 2942-2955. [CrossRef]
98. Ehab H. Sarsour, Sujatha Venkataraman, Amanda L. Kalen, Larry W. Oberley, Prabhat C. Goswami. 2008. Manganese superoxide dismutase activity regulates transitions between quiescent and proliferative growth. *Aging Cell* **7**:3, 405-417. [CrossRef]
99. Marcus Gutscher, Anne-Laure Pauleau, Laurent Marty, Thorsten Brach, Guido H Wabnitz, Yvonne Samstag, Andreas J Meyer, Tobias P Dick. 2008. Real-time imaging of the intracellular glutathione redox potential. *Nature Methods* **5**:6, 553-559. [CrossRef]
100. Timir Tripathi, Stefan Rahlfs, Katja Becker, Vinod Bhakuni. 2008. Structural and stability characteristics of a monothiol glutaredoxin: Glutaredoxin-like protein 1 from Plasmodium falciparum. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1784**:6, 946-952. [CrossRef]
101. C.-n. Chen, H. M. Brown-Borg, S. G. Rakoczy, L. V. Thompson. 2008. Muscle Disuse: Adaptation of Antioxidant Systems Is Age Dependent. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **63**:5, 461-466. [CrossRef]
102. Efthimios Prinarakis, Eleni Chantzoura, Dimitris Thanos, Giannis Spyrou. 2008. S-glutathionylation of IRF3 regulates IRF3–CBP interaction and activation of the IFN# pathway. *The EMBO Journal* **27**:6, 865-875. [CrossRef]
103. N CHENG. 2008. AtGRX4, an Arabidopsis chloroplastic monothiol glutaredoxin, is able to suppress yeast grx5 mutant phenotypes and respond to oxidative stress. *FEBS Letters* **582**:6, 848-854. [CrossRef]
104. Carmen Alicia Padilla, Pablo Porras, Raquel Requejo, José Rafael Pedrajas, Emilia Martínez-Galisteo, José Antonio Bárcena, José PeinadoRedoxin Connection of Lipoic Acid **20080652**, . [CrossRef]
105. Isabella Dalle–Donne , Aldo Milzani , Nicoletta Gagliano , Roberto Colombo , Daniela Giustarini , Ranieri Rossi . 2008. Molecular Mechanisms and Potential Clinical Significance of S-Glutathionylation. *Antioxidants & Redox Signaling* **10**:3, 445-474. [Abstract] [Full Text PDF] [Full Text PDF with Links]
106. Marilene Demasi, Gilberto M. Piassa Filho, Leandro M. Castro, Juliana C. Ferreira, Vanessa Rioli, Emer S. Ferro. 2008. Oligomerization of the cysteinyl-rich oligopeptidase EP24.15 is triggered by S-glutathionylation. *Free Radical Biology and Medicine* **44**:6, 1180-1190. [CrossRef]
107. Albert W. Girotti. 2008. Translocation as a means of disseminating lipid hydroperoxide-induced oxidative damage and effector action. *Free Radical Biology and Medicine* **44**:6, 956-968. [CrossRef]
108. Shuping Xing, Sabine Zachgo. 2008. ROXY1 and ROXY2, two Arabidopsis glutaredoxin genes, are required for anther development. *The Plant Journal* **53**:5, 790-801. [CrossRef]
109. Débora Silva Gomes, Marcos Dias Pereira, Anita Dolly Panek, Leonardo Rodrigues Andrade, Elis Cristina Araújo Eleutherio. 2008. Apoptosis as a mechanism for removal of mutated cells of Saccharomyces cerevisiae: The role of Grx2 under cadmium exposure. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:2, 160-166. [CrossRef]
110. Won-Jin Kang, Hyun-Soon Kim, Youn-Il Park, Hyouk Joung, Jae-Heung Jeon. 2007. Differential Expression in Response to Biotic and Abiotic Stress from Three Potato Glutaredoxins Induced during Suberization. *Journal of Plant Biology* **50**:6, 663-670. [CrossRef]
111. M RAWAT, C JOHNSON, V CADIZ, Y AVGAY. 2007. Comparative analysis of mutants in the mycothiol biosynthesis pathway in Mycobacterium smegmatis. *Biochemical and Biophysical Research Communications* **363**:1, 71-76. [CrossRef]
112. Harish V. Pai , David W. Starke , Edward J. Lesnefsky , Charles L. Hoppel , John J. Mieyal . 2007. What is the Functional Significance of the Unique Location of Glutaredoxin 1 (GRx1) in the Intermembrane

Space of Mitochondria?. *Antioxidants & Redox Signaling* **9**:11, 2027-2034. [Abstract] [Full Text PDF] [Full Text PDF with Links]

113. A RUBARTELLI, M LOTZE. 2007. Inside, outside, upside down: damage-associated molecular-pattern molecules (DAMPs) and redox. *Trends in Immunology* **28**:10, 429-436. [CrossRef]
114. Ying Hu, Sabine Urig, Sasa Koncarevic, Xinjiang Wu, Marina Fischer, Stefan Rahlfs, Volker Mersch-Sundermann, Katja Becker. 2007. Glutathione- and thioredoxin-related enzymes are modulated by sulfur-containing chemopreventive agents. *Biological Chemistry* **388**:10, 1069-1081. [CrossRef]
115. 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]
116. Nicolas Foloppe, Lennart Nilsson. 2007. Stabilization of the Catalytic Thiolate in a Mammalian Glutaredoxin: Structure, Dynamics and Electrostatics of Reduced Pig Glutaredoxin and its Mutants. *Journal of Molecular Biology* **372**:3, 798-816. [CrossRef]
117. Johan Sagemark, Tobias H. Elgán, Thomas R. Bürglin, Catrine Johansson, Arne Holmgren, Kurt D. Berndt. 2007. Redox properties and evolution of human glutaredoxins. *Proteins: Structure, Function, and Bioinformatics* **68**:4, 879-892. [CrossRef]
118. Luis Eduardo Soares Netto, Marcos Antonio de Oliveira, Gisele Monteiro, Ana Paula Dias Demasi, José Renato Rosa Cussiol, Karen Fulan Discola, Marilene Demasi, Gustavo Monteiro Silva, Simone Vidigal Alves, Victor Genu Faria. 2007. Reactive cysteine in proteins: Protein folding, antioxidant defense, redox signaling and more#. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* **146**:1-2, 180-193. [CrossRef]
119. V. I. Kulinsky, L. S. Kolesnichenko. 2007. Mitochondrial glutathione. *Biochemistry (Moscow)* **72**:7, 698-701. [CrossRef]
120. Trevor Tyson, Wesley Reardon, John A. Browne, Ann M. Burnell. 2007. Gene induction by desiccation stress in the entomopathogenic nematode Steinernema carpocapsae reveals parallels with drought tolerance mechanisms in plants. *International Journal for Parasitology* **37**:7, 763-776. [CrossRef]
121. N. Rouhier, H. Unno, S. Bandyopadhyay, L. Masip, S.-K. Kim, M. Hirasawa, J. M. Gualberto, V. Lattard, M. Kusunoki, D. B. Knaff, G. Georgiou, T. Hase, M. K. Johnson, J.-P. Jacquot. 2007. Functional, structural, and spectroscopic characterization of a glutathione-ligated [2Fe-2S] cluster in poplar glutaredoxin C1. *Proceedings of the National Academy of Sciences* **104**:18, 7379-7384. [CrossRef]
122. Juan Diego Maya, Bruce K. Cassels, Patricio Iturriaga-Vásquez, Jorge Ferreira, Mario Faúndez, Norbel Galanti, Arturo Ferreira, Antonio Morello. 2007. Mode of action of natural and synthetic drugs against Trypanosoma cruzi and their interaction with the mammalian host. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology* **146**:4, 601-620. [CrossRef]
123. Min Li, Qing Yang, Yang Gao, Qingyu Wu. 2007. N-terminus deletion affecting the preparation of soluble cyanobacterial glutaredoxin in Escherichia coli. *Biochemistry (Moscow)* **72**:3, 313-319. [CrossRef]
124. S G Menon, P C Goswami. 2007. A redox cycle within the cell cycle: ring in the old with the new. *Oncogene* **26**:8, 1101-1109. [CrossRef]
125. John-Paul Bacik, Bart Hazes. 2007. Crystal Structures of a Poxviral Glutaredoxin in the Oxidized and Reduced States Show Redox-correlated Structural Changes. *Journal of Molecular Biology* **365**:5, 1545-1558. [CrossRef]
126. 2007. Irreversible Inactivation of Glutaredoxins 1 and 2 by Peroxynitrite. *Bulletin of the Korean Chemical Society* **28**:1, 125-128. [CrossRef]
127. Christopher Horst Lillig , Arne Holmgren . 2007. Thioredoxin and Related Molecules–From Biology to Health and Disease. *Antioxidants & Redox Signaling* **9**:1, 25-47. [Abstract] [Full Text PDF] [Full Text PDF with Links]

128. Mirko Zaffagnini, Laure Michelet, Christophe Marchand, Francesca Sparla, Paulette Decottignies, Pierre Le Maréchal, Myroslawa Miginiac-Maslow, Graham Noctor, Paolo Trost, Stéphane D. Lemaire. 2007. The thioredoxin-independent isoform of chloroplastic glyceraldehyde-3-phosphate dehydrogenase is selectively regulated by glutathionylation. *FEBS Journal* **274**:1, 212-226. [CrossRef]

129. Enrique Herrero, Joaquim Ros, Jordi Tamarit, Gemma Bellí. 2006. Glutaredoxins in fungi. *Photosynthesis Research* **89**:2-3, 127-140. [CrossRef]

130. 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]

131. Pamela Maher . 2006. Redox Control of Neural Function: Background, Mechanisms, and Significance. *Antioxidants & Redox Signaling* **8**:11-12, 1941-1970. [Abstract] [Full Text PDF] [Full Text PDF with Links]

132. Martin Ekman, Petter Tollbäck, Johan Klint, Birgitta Bergman. 2006. Protein Expression Profiles in an Endosymbiotic Cyanobacterium Revealed by a Proteomic Approach. *Molecular Plant-Microbe Interactions* **19**:11, 1251-1261. [CrossRef]

133. Kenji Maeda, Per Hägglund, Christine Finnie, Birte Svensson, Anette Henriksen. 2006. Structural Basis for Target Protein Recognition by the Protein Disulfide Reductase Thioredoxin. *Structure* **14**:11, 1701-1710. [CrossRef]

134. S YEGOROVA, O YEGOROV, M LOU. 2006. Thioredoxin induced antioxidant gene expressions in human lens epithelial cells#. *Experimental Eye Research* **83**:4, 783-792. [CrossRef]

135. C LIM, M CATER, J MERCER, S LAFONTAINE. 2006. Copper-dependent interaction of glutaredoxin with the N termini of the copper-ATPases (ATP7A and ATP7B) defective in Menkes and Wilson diseases#. *Biochemical and Biophysical Research Communications* **348**:2, 428-436. [CrossRef]

136. Cristen Pantano , Niki L. Reynaert , Albert Van Der Vliet , Yvonne M. W. Janssen–Heininger . 2006. Redox-Sensitive Kinases of the Nuclear Factor-#B Signaling Pathway. *Antioxidants & Redox Signaling* **8**:9-10, 1791-1806. [Abstract] [Full Text PDF] [Full Text PDF with Links]

137. Birgit Koch, Ole Nybroe. 2006. Initial characterization of a bolA homologue from Pseudomonas fluorescens indicates different roles for BolA-like proteins in P. fluorescens and Escherichia coli. *FEMS Microbiology Letters* **262**:1, 48-56. [CrossRef]

138. S. Xing, A. Lauri, S. Zachgo. 2006. Redox Regulation and Flower Development: A Novel Function for Glutaredoxins. *Plant Biology* **8**:5, 547-555. [CrossRef]

139. Christine Nickel , Stefan Rahlfs , Marcel Deponte , Sasa Koncarevic , Katja Becker . 2006. Thioredoxin Networks in the Malarial Parasite Plasmodium falciparum. *Antioxidants & Redox Signaling* **8**:7-8, 1227-1239. [Abstract] [Full Text PDF] [Full Text PDF with Links]

140. Alexandra P. Carvalho, Pedro A. Fernandes, Maria J. Ramos. 2006. Similarities and differences in the thioredoxin superfamily. *Progress in Biophysics and Molecular Biology* **91**:3, 229-248. [CrossRef]

141. Katherine L. Berry, Oliver Hobert. 2006. Mapping Functional Domains of Chloride Intracellular Channel (CLIC) Proteins in Vivo. *Journal of Molecular Biology* **359**:5, 1316-1333. [CrossRef]

142. Lars I. Leichert , Ursula Jakob . 2006. Global Methods to Monitor the Thiol–Disulfide State of Proteins In Vivo. *Antioxidants & Redox Signaling* **8**:5-6, 763-772. [Abstract] [Full Text PDF] [Full Text PDF with Links]

143. Maria Micaela Molina-Navarro, Celia Casas, Lidia Piedrafita, Gemma Bellí, Enrique Herrero. 2006. Prokaryotic and eukaryotic monothiol glutaredoxins are able to perform the functions of Grx5 in the biogenesis of Fe/S clusters in yeast mitochondria. *FEBS Letters* **580**:9, 2273-2280. [CrossRef]

144. Wanda Maria Almeida von Krüger, Leticia Miranda Santos Lery, Marcia Regina Soares, Fernanda Saloum de Neves-Manta, Celia Maria Batista e Silva, Ana Gisele da Costa Neves-Ferreira, Jonas Perales, Paulo Mascarello Bisch. 2006. The phosphate-starvation response inVibrio cholerae O1

andphoB mutant under proteomic analysis: Disclosing functions involved in adaptation, survival and virulence. *PROTEOMICS* **6**:5, 1495-1511. [CrossRef]

145. N REYNAERT, K CKLESS, A GUALA, E WOUTERS, A VANDERVLIET, Y JANSSENHEININGER. 2006. In situ detection of S-glutathionylated proteins following glutaredoxin-1 catalyzed cysteine derivatization. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1760**:3, 380-387. [CrossRef]
146. Holger Röhr, Christian Trieflinger, Knut Rurack, Jörg Daub. 2006. Proton- and Redox-Controlled Switching of Photo- and Electrochemiluminescence in Thiophenyl-Substituted Boron-Dipyrromethene Dyes. *Chemistry - A European Journal* **12**:3, 689-700. [CrossRef]
147. Andreas J. Meyer, Rüdiger Hell. 2005. Glutathione homeostasis and redox-regulation by sulfhydryl groups. *Photosynthesis Research* **86**:3, 435-457. [CrossRef]
148. 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]
149. Valerie Noguera, Olivier Walker, Nicolas Rouhier, Jean-Pierre Jacquot, Isabelle Krimm, Jean-Marc Lancelin. 2005. NMR Reveals a Novel Glutaredoxin–Glutaredoxin Interaction Interface. *Journal of Molecular Biology* **353**:3, 629-641. [CrossRef]
150. A DAIZO, Y EGASHIRA, H SANADA. 2005. Suppressive effect of corn bran hemicellulose on liver injury induced by D-galactosamine in rats. *Nutrition* **21**:10, 1044-1051. [CrossRef]
151. Michael Thiele , Prof. Jürgen Bernhagen . 2005. Link Between Macrophage Migration Inhibitory Factor and Cellular Redox Regulation. *Antioxidants & Redox Signaling* **7**:9-10, 1234-1248. [Abstract] [Full Text PDF] [Full Text PDF with Links]
152. Rebecca A. Wingert, Jenna L. Galloway, Bruce Barut, Helen Foott, Paula Fraenkel, Jennifer L. Axe, Gerhard J. Weber, Kimberly Dooley, Alan J. Davidson, Bettina Schmidt, Barry H. Paw, George C. Shaw, Paul Kingsley, James Palis, Heidi Schubert, Opal Chen, Jerry Kaplan, The Tübingen 2000 Screen Consortium, Leonard I. Zon. 2005. Deficiency of glutaredoxin 5 reveals Fe–S clusters are required for vertebrate haem synthesis. *Nature* **436**:7053, 1035-1039. [CrossRef]
153. Ken'ichi Ogawa . 2005. Glutathione-Associated Regulation of Plant Growth and Stress Responses. *Antioxidants & Redox Signaling* **7**:7-8, 973-981. [Abstract] [Full Text PDF] [Full Text PDF with Links]
154. Thomas D. Lockwood . 2005. The Transfer of Reductive Energy and Pace of Proteome Turnover: A Theory of Integrated Catabolic Control. *Antioxidants & Redox Signaling* **7**:7-8, 982-998. [Abstract] [Full Text PDF] [Full Text PDF with Links]
155. Ylva Hamnell-Pamment, Christina Lind, Carina Palmberg, Tomas Bergman, Ian A. Cotgreave. 2005. Determination of site-specificity of S-glutathionylated cellular proteins#. *Biochemical and Biophysical Research Communications* **332**:2, 362-369. [CrossRef]
156. 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]
157. Hajime Nakamura . 2005. Thioredoxin and Its Related Molecules: Update 2005. *Antioxidants & Redox Signaling* **7**:5-6, 823-828. [Abstract] [Full Text PDF] [Full Text PDF with Links]
158. Pamela Maher. 2005. The effects of stress and aging on glutathione metabolism. *Ageing Research Reviews* **4**:2, 288-314. [CrossRef]
159. Andreas Barthel, Lars-Oliver Klotz. 2005. Phosphoinositide 3-kinase signaling in the cellular response to oxidative stress. *Biological Chemistry* **386**:3, 207-216. [CrossRef]
160. Yingang Feng, Nicolas Rouhier, Jean-Pierre Jacquot, Bin Xia. 2005. Letter to the Editor: 1H, 15N, and 13C resonance assignments of reduced glutaredoxin C1 from Populus tremula x tremuloides. *Journal of Biomolecular NMR* **31**:3, 263-264. [CrossRef]
161. Yvonne Janssen-Heininger, Karina Ckless, Niki Reynaert, Albert van der Vliet. 2005. SOD Inactivation in Asthma. *The American Journal of Pathology* **166**:3, 649-652. [CrossRef]

162. Mari Enoksson, Aristi Potamitou Fernandes, Stefanie Prast, Christopher Horst Lillig, Arne Holmgren, Sten Orrenius. 2005. Overexpression of glutaredoxin 2 attenuates apoptosis by preventing cytochrome c release. *Biochemical and Biophysical Research Communications* **327**:3, 774-779. [CrossRef]

163. Bita Sahaf, Kartoosh Heydari, Leonard A. Herzenberg, Leonore A. Herzenberg. 2005. The extracellular microenvironment plays a key role in regulating the redox status of cell surface proteins in HIV-infected subjects. *Archives of Biochemistry and Biophysics* **434**:1, 26-32. [CrossRef]

164. A. Yu. Andreyev, Yu. E. Kushnareva, A. A. Starkov. 2005. Mitochondrial metabolism of reactive oxygen species. *Biochemistry (Moscow)* **70**:2, 200-214. [CrossRef]

165. Martijn A. Huynen, Chris A.E.M. Spronk, Toni Gabaldón, Berend Snel. 2005. Combining data from genomes, Y2H and 3D structure indicates that BolA is a reductase interacting with a glutaredoxin. *FEBS Letters* **579**:3, 591-596. [CrossRef]

166. Thomas D. Lockwood. 2004. Cys-His proteases are among the wired proteins of the cell. *Archives of Biochemistry and Biophysics* **432**:1, 12-24. [CrossRef]

167. Maddalena Fratelli, Elisabetta Gianazza, Pietro Ghezzi. 2004. Redox proteomics: identification and functional role of glutathionylated proteins. *Expert Review of Proteomics* **1**:3, 365-376. [CrossRef]

168. Sylke Müller. 2004. Redox and antioxidant systems of the malaria parasite Plasmodium falciparum. *Molecular Microbiology* **53**:5, 1291-1305. [CrossRef]

169. Hajime Nakamura . 2004. Thioredoxin as a Key Molecule in Redox Signaling. *Antioxidants & Redox Signaling* **6**:1, 15-17. [Citation] [Full Text PDF] [Full Text PDF with Links]

170. Patricia J. Kiley, Gisela Storz. 2004. Exploiting Thiol Modifications. *PLoS Biology* **2**:11, e400. [CrossRef]

171. Elise R. Hondorp, Rowena G. Matthews. 2004. Oxidative Stress Inactivates Cobalamin-Independent Methionine Synthase (MetE) in Escherichia coli. *PLoS Biology* **2**:11, e336. [CrossRef]

172. Dipak K. Das Methods in Redox Signaling . [Citation] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]