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Bacterial Thioredoxins - Genes and Regulation

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ABSTRACT

Thioredoxins are small, ubiquitous proteins with a dithiol/disulfide active site (CGPC) and have been characterized in a wide variety of prokaryotic and eukaryotic cells. In the thioredoxin system, thioredoxin reductase serves to reversibly reduce oxidized thioredoxin using NAD(P)H as electron donor. In 1964, thioredoxin was originally discovered as electron donor for ribonucleotide reductase in *Escherichia coli*. By now, many thioredoxins are identified to fulfil a number of important cellular functions, e.g. they are the major cellular protein disulfide reductases, controlling the cellular redox potential. The multiple and important functions of thioredoxins necessitate to adjust their cellular levels according to the requirements. Despite the importance of thioredoxin functions, only little is known about the regulation of thioredoxin genes. The present review therefore considers bacterial genes encoding thioredoxins. We give an overview on thioredoxin genes and their regulation in different bacteria. Furthermore, we will review the current knowledge about the participation of thioredoxin proteins in the regulation of gene expression and protein activity.

Keywords: bacteria, gene expression

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INTRODUCTION

Many metabolic, signalling and transcriptional processes inside cells are mediated by the cellular redox state. Protein thiols in form of cysteine residues are key players in redox sensing and regulation (Holmgren *et al*. 2005).

Thioredoxins are small ubiquitous proteins with a highly conserved active site sequence [(Cys-Gly-Pro-Cys) (Holmgren 1985, 1995a; Martin 1995)] and share a common 3D architecture known as the thioredoxin motif, consisting of four α-helices and five β-sheets (Eklund *et al*. 1991; Holmgren 1995b; Martin 1995; Capitani *et al*. 2000). The low redox potential of thioredoxins [-270 mV to -330 mV in *Escherichia coli* (Krause *et al*. 1991; Aslund *et al*. 1997)] makes these proteins efficient thiol-disulfide reductants, utilizing the two cysteine residues in their active site. The reduction of the resulting active site disulphide in thioredoxins is catalyzed by the thioredoxin reductase, which uses NADPH as an electron donor. Together, thioredoxin, thioredoxin reductase and NADPH constitute the thioredoxin system (**Fig. 1**). Thus, thioredoxins, together with the glutathione/glutaredoxin system are responsible for maintaining protein cysteines in a reduced state and thereby can regulate the activity of proteins/enzymes.

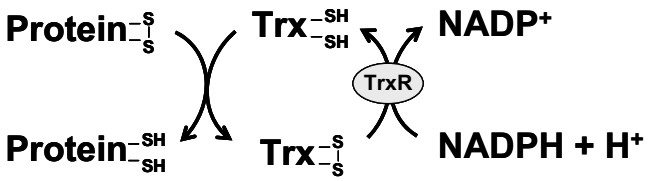

Fig. 1 The thioredoxin system. As efficient thiol-disulfide reductases, thioredoxins reduce protein-disulfides, thereby utilizing the two cysteine residues in their active site. The reduction of the resulting active site disulfide in thioredoxins is catalyzed by the thioredoxin reductase, which uses NADPH as electron donor. Together, thioredoxin (Trx), thioredoxin reductase (TrxR) and NADPH comprise the thioredoxin system.

However, the function of thioredoxins is not limited to the function as protein disulfide reductases. In *E. coli*, thioredoxin was first described as an electron donor for ribonucleotide reductase (Laurent *et al*. 1964; Orr and Vitols 1966). Nowadays, thioredoxins are known to function in many cellular processes [e.g. as hydrogen donor for phosphoadenosine-phosphosulfate reductase and methionine reductase (Gonzalez Proqué *et al*. 1970; Lillig *et al*. 1999), as an essential component in the life cycle of some bacteriophages (Mark and Richardson 1976; Russel and Model 1985; Lim *et al*. 1985; Huber *et al*. 1987), in the oxidative stress response (e.g. Das and Das 2000; Zeller and Klug 2006a, 2006b)]. Some of the most important functions of thioredoxins are summarized in **Table 1**.

Several reviews have addressed the general structure and function of thioredoxins in prokaryotes and eukaryotes (e.g. Aslund and Beckwith 1999; Arner and Holmgren 2000; Carmel-Harel and Storz 2000; Ritz and Beckwith 2001; Meyer *et al*. 2005; Ago and Sadoshima 2006; Arner

Received: 5 June, 2007. Accepted: 25 August, 2007.

Invited Mini-Review

Table 1 Main functions of thioredoxins in prokaryotes and eukaryotes.

Function	Reference (e.g.)
Hydrogen donor	Laurent *et al*. 1964; Orr and Vitols 1966; Gonzalez Proqué *et al*. 1970; Lillig *et al*. 1999
Ribonucleotide reductases	
Phosphoadenosine-phosphosulfate reductases	
Methionine reductase	
Oxidative stress response	Spector *et al*. 1988; Chae *et al*. 1994; Kang *et al*. 1998; Das and Das 2000; Vieira dos Santos and Rey 2006; Zeller and Klug 2006a
Reduction of protein disulfides (redox regulation)	
ROS scavenging	
Electron donor for peroxiredoxins and peroxidases	
Transcriptional regulation	Schenk *et al*. 1994; Müller *et al*. 1997; Saitoh *et al*. 1998; Nordberg and Arner 2001; Kumar *et al*. 2004; Li *et al*. 2004b
Influence on gyrase supercoiling activity	
Redox regulation of transcriptional factors (AP-1, NFκB)	
Photosynthesis	Clement-Metral 1979; Buchanan 1984; Pasternak *et al*. 1999; Li *et al*. 2003a; Gelhaye *et al*. 2005
Regulation of light-dependent activation of enzymes	
Regulation of photosynthesis genes	
Regulation of δ-aminolaevulinic acid	
Involvement in viral life cycle	Mark and Richardson 1976; Lim *et al*. 1985; Russel and Model 1985; Huber *et al*. 1987
Subunit of T7 DNA polymerase	
Assembly of filamentous phages	
Involvement in virulence	Bjur *et al*. 2006
Involvement in protein folding/refolding (chaperone activity)	Kern *et al*. 2003; McGee *et al*. 2006
Involvement in diseases	Rubartelli *et al*. 1995; Saito *et al*. 1996; Yoshida *et al*. 1999; Nakamura *et al*. 2001; Nordberg and Arner 2001; Ago and Sadoshima 2006; Arner and Holmgren 2006

and Holmgren 2006; Haendeler 2006; Vieira dos Santos and Rey 2006). The present review mainly addresses bacterial genes encoding thioredoxins, their regulation in different bacteria and under different conditions, and considers the influence of bacterial thioredoxins on gene expression and protein activity.

BACTERIAL THIOREDOXINS, THIOREDOXIN GENES AND GENE ORGANIZATION

Thioredoxin 1 (TrxA, also known as Trx1), first discovered in *E. coli* in 1964, is encoded by the *trxA* gene, contains 109 amino acids and has a central core of five strands of twisted β-pleated sheet flanked by four α-helices and the active site located in a protrusion of the protein (Gleason and Holmgren 1988; Miranda-Vizuete *et al*. 1997). In 1997, a novel thioredoxin, TrxC (Trx2), was identified in *E. coli* by Miranda-Vizuete *et al*., which is encoded by the gene *trxC*. Both thioredoxins are equivalent for most of their *in vivo* functions (Stewart *et al*. 1998), but in contrast to TrxA, TrxC contains an additional N-terminal domain of 32 amino acids including two additional Cys-X1-X2-Cys motives (Miranda-Vizuete *et al*. 1997). The four cysteines of these two Cys-X1-X2-Cys motives function to coordinate one zinc atom (Collet *et al*. 2003). Available information on the abundance of thioredoxin proteins indicates that TrxA is an essential and ubiquitously distributed protein whereas TrxC may have limited distribution to circumvent certain environmental conditions (Li *et al*. 2003a; Sarin and Sharma 2006). The existence of at least one thioredoxin has been described in various bacterial species, including e.g. *Rhodobacter sphaeroides* [TrxA (Clement-Metral 1979)]; *Rhodobacter caspulatus* [TrxA and TrxC (Li *et al*. 2003a)]; *Streptomyces* sp. [TrxA and TrxC (Horecka *et al*. 1996; Stefankova *et al*. 2006)]; *Desulfovibrio desulfuricans* [TrxA and TrxC (Sarin and Sharma 2006)]; *Bacillus subtilis* [TrxA (Scharf *et al*. 1998)], *Helicobacter pylori* [TrxA and TrxC (Windle *et al*. 2000; Baker *et al*. 2001; Comtois *et al*. 2003)]. Interestingly, up to eight thioredoxin genes can be found in cyanobacterial genomes (Florencio *et al*. 2006). Primary structure analysis reveals that there are four distinct groups of thioredoxins in cyanobacteria. Three groups are shared between cyanobacteria and photosynthetic eukaryotes including *m*-type (TrxA), *x*-type (TrxB) and *y*-type thioredoxins (TrxQ). The fourth group of the cyanobacterial thioredoxins, the *c*-type (TrxC), is unique to cyanobacteria (Florencio *et al*. 2006.)

While both *trx* genes are not essential for viability of *E. coli* (Ritz *et al*. 2000), TrxA is required for viability of a number of bacteria, e.g. *R. sphaeroides* (Pasternak *et al*. 1997), *B. subtilis* (Scharf *et al*. 1998), *Anacystis nidulans* (Muller and Buchanan 1989), *Synechocystis* sp. PCC 6803 (Navarro and Florencio 1996). To our knowledge, TrxC has not been described to be essential in bacteria.

A quite diverse organization of *trx* genes is found among various bacterial genomes. In most bacterial species, the *trxA* gene is clustered with the gene encoding thioredoxin reductase (*trxB* or *trxR*), whereas the *trxC* gene is unlinked to other thioredoxin genes. Nevertheless, in some bacterial chromosomes, *trxA* genes are unlinked to *trxB* genes.

The genes *trxA* and *trxB* constitute an operon in *Streptomyces* (Cohen *et al*. 1993; Gal-Mor *et al*. 1998). In *S. coelicolor*, both genes are contained as a cluster on a cosmid H24 that carries *oriC* and several genes involved in DNA replication. The *trxA/trxB* locus is positioned approximately 9.4 kb from *oriC*. The arrangement of genes near the *trxA/trxB* region resembles that in *Mycobacterium leprae* and *M. tuberculosis* (Gal-Mor *et al*. 1998).

The genomic organisation of thioredoxin genes in *D. desulfuricans* revealed that *dstrx1* (*trxA*) and *dstrxR* (thioredoxin reductase) genes are in close proximity to each other. The stop codon TAA of the *dstrx1* ORF overlaps with the start codon of *dstrxR* ORF indicating translational coupling. However, the *dstrx2* gene (*trxC*) is positioned elsewhere (and on the complementary strand) and is located downstream to an open reading frame encoding an ATP dependent zinc protease gene (Sarin and Sharma 2006).

In the genome of *H. pylori* the gene encoding thioredoxin reductase (*trxR*) is positioned just downstream from *trxA*. *trxC* (HP1458) is not found near *trxA* (HP0824) or *trxR* (HP0825) (Comtois *et al*. 2003).

At least three modes of organization of thioredoxin genes exist within the bacterial genus *Mycobacterium*: i) in the majority of mycobacterial strains the genes coding for thioredoxin and thioredoxin reductase are located on separate sites of the genome, ii) in *M. tuberculosis* strains both genes are found on the same locus, overlapping in one nucleotide, iii) in the pathogen *M. leprae*, thioredoxin and thioredoxin reductase are encoded by a single gene and, therefore, are expressed as a fusion protein (MlTrxR-Trx), with the N-terminal part of the protein corresponding to thioredoxin reductase and the C-terminal part to TrxA (Wieles *et al*. 1995).

In contrast, in the chromosome of several *Staphylococcus* species, *trxA* and *trxB* genes are mapped to quite differ-

ent sites. In *S. aureus*, *trxA* is located in a cluster of conserved genes, *mutS2-trxA-uvrC* (transcribed in the same direction), and *trxB* is located in a gene cluster just downstream of the *uvrAB* genes (Uziel *et al*. 2004). A similar organization of *trx* genes occurs in *S. epidermidis* and *S. xylosus* (Uziel *et al*. 2004).

In *E. coli*, *trx* genes map in widely different positions on the genome. The *E. coli* gene for TrxC is positioned at 58.5 min, far away from the *trxA* gene, which is located at 84 min in the *E. coli* chromosome (Lim *et al*. 1985; Miranda-Vizuete *et al*. 1997). The gene encoding thioredoxin reductase (*trxB*) is located at 20-21 min on the *E. coli* chromosome (Haller and Fuchs 1984).

The only thioredoxin gene of *R. sphaeroides* (*trxA*; RSP1529) is located on chromosome 1 next to the gene RSP1527 (encoding a helicase, *uvrD/REP*) in the 5′ direction and is transcribed in the same orientation as RSP1527. In the 3′ direction of *trxA* an unknown open reading frame (RSP1530) is located and transcribed in the opposite direction. The gene encoding thioredoxin reductase (RSP1576) is located at a different position on the chromosome 1 and transcribed on the reverse strand (www.rhodobacter.org). A similar gene organization is found in the closely related bacterium *R. capsulatus*. The *trxA* gene (RRC03345) is located next to RRC3344 (helicase, *uvrD/REP*) in the 5′ direction and to RRC3346 (ATP-dependent protease, *hsIV*) in the 3′ direction. Here, all three genes are transcribed in the same direction (Integrated Genomics, www.ergo-light.com/ERGO). The *trxC* gene of *R. capsulatus* (RRC00979) is located in a different region of the chromosome. A gene encoding a thymidine kinase is found upstream of *trxC* and is transcribed in the same direction. Downstream of *trxC* a tRNA-coding gene is located (Ala-CGC-tRNA).

REGULATION OF BACTERIAL THIOREDOXIN GENE EXPRESSION

Despite the importance of thioredoxins in many cellular functions (**Table 1**), our knowledge of *trx* gene regulation in response to external stimuli is still limited.

The response to one important stimulus, oxidative stress, has been examined in various bacteria. Oxidative stress is defined as a disturbance of the prooxidant–antioxidant balance in favour of prooxidants (Sies 1985) and is caused by reactive oxygen species (ROS) generated in the respiratory chain and other cellular compounds or in the environment (Imlay and Fridovich 1991; Gonzalez-Flecha and Demple 1995; Messner and Imlay 1999; Seaver and Imlay 2004). As in many other respects, enteric bacteria served as the first bacterial systems to study the oxidative stress response. In *E. coli*, two key factors involved in the adaptive responses to oxidative stress have been characterized, OxyR and SoxR. OxyR, a transcriptional regulator of the LysR family, binds to its target sites (Toledano *et al*. 1994) in its oxidized or reduced form and activates gene expression (Tao *et al*. 1993; Storz and Zheng 2000; Zheng *et al*. 2001; Zeller *et al*. 2007). In some cases, however, repression of gene expression by OxyR was observed (Zheng *et al*. 2001). The second regulon for the oxidative stress response in *E. coli* is the SoxRS regulon. In this system, SoxR and SoxS serve as regulators of the response to superoxide (reviewed in, e.g., Nunoshiba 1996; Demple 1996; Storz and Zheng 2000).

Since oxidative stress conditions change the cellular redox-state and promote disulfide bond formation of redox-sensitive proteins and one major function of thioredoxins is the reduction of such disulfides, a regulation of *trx* genes by ROS and the oxygen level is expected. Indeed, many reports have been published, showing the regulation of *trx* genes under oxidative stress conditions. Ritz *et al*. (2000) showed that the expression of the *E. coli trxC* gene is induced by H_2O_2 and is regulated by OxyR. In contrast, *trxA* expression is not increased by H_2O_2 in *E. coli* and is not under control of OxyR (Michan *et al*. 1999; Garrido and Grant 2002). It was described that the *trxA* gene of *E. coli* is under control of guanosine 3′, 5′-bispyrophosphate (ppGpp), is expressed in the stationary phase (Lim *et al*. 2000) and is negatively regulated by cyclic AMP (Sa *et al*. 1997). Interestingly, TrxA seems to contribute to the regulation of SoxR transcriptional activity by affecting the disassembly and reassembly of the [2Fe-2S] clusters (Ding and Demple 1998). Although *trxA* gene expression seems not to be regulated by ROS, TrxA might contribute to the oxidative stress defence by influencing SoxR activity.

ROS and oxygen tension also affect the expression of thioredoxin genes in the related facultatively photosynthetic bacteria *R. sphaeroides* and *R. capsulatus*. The *trxA* genes of both *R. sphaeroides* and *R. capsulatus* are induced by an increase of oxygen, while the *trxC* gene of *R. capsulatus* is slightly repressed (Pasternak *et al*. 1996; Li *et al*. 2003a). All *Rhodobacter* thioredoxin genes also respond to oxidative stress. Expression of *trxA* and *trxC* in *Rhodobacter* is strongly induced in response to various ROS-inducing agents (Zeller *et al*. 2006b). Expression studies of *trx* genes in *oxyR* mutants of *Rhodobacter* indicate an involvement of OxyR in the regulation of the *trxC* gene under oxidative stress conditions (Zeller *et al*. 2006b). In contrast to the regulation of *trxC*, and in agreement with the situation in *E. coli*, expression of *trxA* is not regulated by OxyR. So far, the mechanism of *trxA* regulation in *Rhodobacter* under oxidative stress conditions is unknown. Although many Gram-positive bacteria encode OxyR homologues, they use other regulators to control *trx* gene expression under oxidative stress. In *Bacillus subtilis*, the essential *trxA* gene is under control of the vegetative sigma factor σA and is also transcribed by the general stress sigma factor σB (Scharf *et al*. 1998). Transcription initiating at the σA-dependent promoter is induced by H_2O_2 (Scharf *et al*. 1998). In addition, induction of the *B. subtilis trxA* and *trxB* (encoding the thioredoxin reductase) genes by disulfide stress (induced by diamide; Leichert *et al*. 2003) depends on the global regulator Spx (Nakano *et al*. 2003; Zuber 2004). This activation requires a direct interaction between the RNA polymerase alpha-subunit and the active form of Spx that has an intermolecular disulfide bond (Nakano *et al*. 2005). The mechanism of Spx-dependent transcriptional activation is unique in that it does not involve initial Spx-DNA interaction (Nakano *et al*. 2005).

In *Streptomyces coelicolor trxA* and *trxB* (encoding thioredoxins reductase) constitute an operon that is under direct control of the alternative sigma factor σ^R (Paget *et al*. 1998; Li *et al*. 2002, 2003b). The *trxC* gene was also found to be a member of the σ^R regulon (Paget *et al*. 2001; Li *et al*. 2002). The activity of σ^R is controlled by the anti-sigma factor RsrA. Oxidative stress induces intramolecular disulfide bond formation in RsrA, which causes it to lose affinity for σ^R, thereby releasing σ^R to activate transcription of *trxBA* (Kang *et al*. 1999; Li *et al*. 2002; Bae *et al*. 2004). Interestingly, oxidized RsrA is a direct substrate for reduced thioredoxin, which allows the formation of the σ^R-RsrA complex, thereby establishing a feedback loop of regulation (Kang *et al*. 1999; Li *et al*. 2002, 2003b).

Reactive oxygen and nitrogen molecules are generated by mammalian and plant cells as a defence strategy against bacterial infections. Therefore, thioredoxins are not only important proteins for the oxidative stress response in non-pathogenic bacteria, but they may also influence the survival of pathogens in host cells.

An alternative sigma factor, SigH, is involved in the regulation of the *trxC* and *trxB2* genes in the intracellular pathogen *Mycobacterium tuberculosis* (Raman *et al*. 2001; Manganelli *et al*. 2002). SigH regulates the expression of the stress-responsive (heat and oxidative stress) sigma factors SigE and SigB, suggesting a central role of SigH in a network regulating heat and oxidative stress responses (Raman *et al*. 2001; Manganelli *et al*. 2002).

In *S. aureus* several oxidative stress compounds (diamide, *t*-BOOH and the redox cycling agent menadione) induce the *trxA* and *trxB* genes, while no effect of H_2O_2 was observed (Uziel *et al*. 2004). As in *B. subtilis*, the induction

Table 2 Regulation of bacterial thioredoxin genes by different stimuli and/or different conditions.
? indicates unknown regulator; brackets indicate a putative but so far not established regulator. See text for detailed description.

Species	Stimulus or condition	Gene	Regulator
Escherichia coli	Oxidative stress	*trxC*	OxyR
	Stationary phase	*trxA*	cAMP, ppGpp
Rhodobacter	Oxidative stress	*trxA*, *trxC*	OxyR; ?
	Oxygen tension	*trxA*, *trxC*	?
	Blue light	*trxC*	?
Bacillus	Oxidative stress	*trxA*	σ^A,σ^B, Spx
Streptomyces	Oxidative stress	*trxA*, *trxC*	σ^R
Mycobacterium	Oxidative stress, heat stress	*trxC*	Sig H
Staphylococcus	Oxiative stress	*trxA*	Spx
Helicobacter	Oxidative stress	*trxA*, *trxC*	?
Oenococcus	Oxidative stress, heat stress	*trxA*	?
Desulfovibrio	Anaerobic growth conditions	*trxA*, *trxC*	?
Synechocystis	Photosynthetic electron transport, light, glucose availability	*trxA*	(cytochrome b_6f complex), ?

of *trxA* and *trxB* seems to be dependent on Spx activity but does not involve the stress sigma factor σ^B (Uziel *et al*. 2004; Pamp *et al*. 2006).

In other bacteria, a role of thioredoxins in the oxidative stress response has been shown, the mechanism of *trx* regulation under these conditions however, remains in most cases elusive [e.g. *H. pylori* (Windle *et al*. 2000; Comtois *et al*. 2003; Baker *et al*. 2001); *Oenococcus oeni* (Jobin *et al*. 1999); *M. leprae* (Wieles *et al*. 1997); *D. desulfuricans* (Sarin and Sharma 2006)].

Expression of *trx* genes is not only regulated under oxidative stress conditions. Reports are available that show an involvement of electron flow and light on *trx* gene expression. In the photoheterotrophic cyanobacterium *Synechocystis* sp. PCC 6803, expression of the *trxA* gene has been described to be transcriptionally regulated by the photosynthetic electron transport (Navarro *et al*. 2000). In this study it was shown that *trxA* expression is regulated in response to light and glucose availability, indicating that an active electron transport is required. Primer extension analysis strongly suggested that *trxA* is transcribed from two proximal promoters containing a -10 TATA box similar to the *E. coli* consensus promoters (Navarro *et al*. 2000). Unlike the *trxA* mRNA, the amount of thioredoxin protein was not regulated by light indicating that thioredoxin protein is very stable and that the *trxA* expression is likely to be primarily regulated at the transcriptional level, rather than at the protein level (Navarro *et al*. 2000).

Regulation of thioredoxin genes in response to light and photosynthetic electron flow has also been suggested in the facultatively photosynthetic bacterium *Rhodobacter* (Zeller T., Li K., Metz S. and Klug G, unpublished results). In this organism, *trxC* expression appears to be specifically regulated by blue light. OxyR, shown to regulate the transcription of *trxC* in response to the redox state and oxidative stress in *R. capsulatus* (Zeller *et al*. 2006b) as well as the TrxC protein itself and DNA gyrase (see below), seem not to be involved in this light-dependent regulation of *trxC*. The exact mechanism of this regulation is currently under study. An overview of thioredoxin genes, their regulation and regulators involved is given in **Table 2**.

INFLUENCE OF THIOREDOXINS ON GENE EXPRESSION AND PROTEIN ACTIVITY

Beside their function as thiol-disulfide reductases, thioredoxins seem also to influence gene expression and to participate in regulation of protein activity.

An influence of thioredoxins on gene expression has mostly been demonstrated by mutant or depletion analysis. Significantly increased expression of the genes *grxA*, *fpg* (DNA repair glycosylase Fpg), *nrdA* and *nrdB* (ribonucleotide reductase) were observed in *E. coli* strains lacking both TrxA and glutathione reductase or TrxA and glutaredoxin 1 (Gallardo-Madueno *et al*. 1998; Prieto-Alamo *et al*. 2000). In *R. capsulatus*, the *trxC* mutant shows much stronger H_2O_2-induced expression of *acnA* (aconitase A), *fur* (ferric uptake regulator), *gorA*, *katG* and stronger paraquat induced expression of *acnA*, *fpr* (ferredoxin/flavodoxin reductase), *fur*, *gorA*, and *katG* than the wild type (Li *et al*. 2004a). Smits and colleagues (2005) also reported the effects of thioredoxin depletion on global transcription levels in *B. subtilis*. Since thioredoxins have so far not been reported to act as transcriptional regulators, it is likely that these reported transcriptional changes represent indirect effects of thioredoxin, probably by an altered cellular redox state due to thioredoxin depletion (Li *et al*. 2004a; Zeller *et al*. 2006b). Nevertheless, reports accumulate showing that thioredoxins also directly participate in gene expression and protein activity.

In 2004, a new signalling pathway from thioredoxin to transcription of photosynthesis genes via the influence of thioredoxins on gyrase activity was discovered in *Rhodobacter* (Li *et al*. 2004b). In this organism, thioredoxins have been demonstrated to be involved in the redox-dependent regulation of photosynthesis genes (namely the *puf* and *puc* operon) (Clement-Metral 1979; Pasternak *et al*. 1999; Li *et al*. 2003c). Decreased levels of TrxA lead to lower increase of *puf* and *puc* mRNA levels after a drop of oxygen tension compared to wild type strains in *R. sphaeroides* and *R. capsulatus* (Pasternak *et al*. 1999; Li *et al*. 2004b). Surprisingly, a *trxC* deletion mutant of *R. capsulatus* showed a stronger increase of *puf* and *puc* mRNA levels after drop of oxygen tension (Li *et al*. 2003a). In search for proteins interacting with *Rhodobacter* thioredoxins, the gyrase B subunit was identified by a yeast-two hybrid screening (Li *et al*. 2004b). The authors showed that *trxA* mutants of *Rhodobacter* exhibit lower gyrase supercoiling activity than the wild type. In contrast, the *trxC* mutant exhibits higher gyrase supercoiling activity. *In vitro* experiments supported the view of modulation of gyrase supercoiling activity by thioredoxin. Reduced but not oxidized TrxA can interact with the gyrase B subunit and increases its supercoiling activity. In contrast, oxidized but not reduced TrxC interacts with gyrase B and decreases its supercoiling activity. Since the expression of many genes is influenced by the supercoiling status of the DNA (Dorman *et al*. 1988; Franco and Drlica 1989; Schneider *et al*. 2000), this implies an important function of thioredoxins on the expression of many genes. The same effect of thioredoxins on gyrase activity as in *Rhodobacter* was found in *E. coli*, suggesting that the gyrase-mediated effect of thioredoxins might be a common redox-dependent signalling pathway in bacterial adaptation (Li *et al*. 2004b). A model for the action of thioredoxins on gene expression is shown in **Fig. 2**.

Interestingly, in the same organism (*R. sphaeroides*), TrxA was also shown to influence the expression of photosynthesis genes independently of gyrase activity. In this case, the influence of TrxA seems to result from its effect on cellular redox state (Han Y and Klug G., unpublished results).

Further evidence of the participation of thioredoxins in

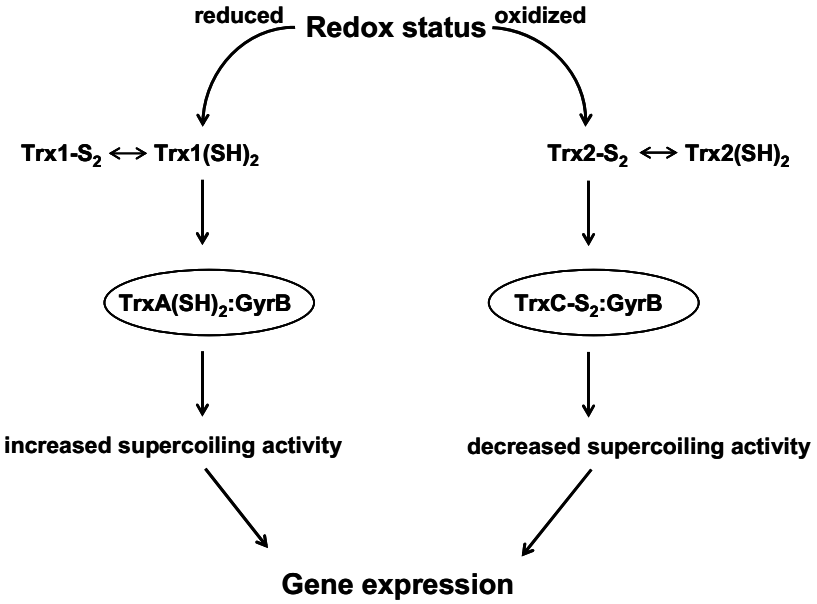

Fig. 2 Model for signal transduction from thioredoxins to gene expression as established for *Rhodobacter sphaeroides* and *Rhodobacter capsulatus*. Ratio of reduced and oxidized thioredoxin is determined by the cellular redox status. The redox switch of thioredoxins alters gyrase supercoiling activity, thereby affecting gene expression. Reduced but not oxidized thioredoxins 1 binds to gyrase and increases supercoiling activity. Oxidized but not reduced thioredoxin 2 binds to gyrase and decreases supercoiling activity. Trx1: thioredoxin 1; Trx2: thioredoxin 2; GyrB: subunit B of gyrase; S_2 and $(SH)_2$: oxidized or reduced redox state of thioredoxins, respectively.

regulatory pathways was provided by Kumar *et al*. (2004), who characterized the thioredoxin-associated *E. coli* proteome. In this study, a total of 80 proteins associated with thioredoxin were identified, implicating the involvement of thioredoxin in at least 26 distinct cellular processes including transcriptional regulation, cell division, oxidative stress, energy transduction, protein folding and several biosynthetic pathways. Several transcription factors (NusG, OmpR and RcsB) were also found to be associated with thioredoxin (Kumar *et al*. 2004).

A Chaperon-like activity of thioredoxins has been reported in *E. coli* and *H. pylori* (Kern *et al*. 2003; McGee *et al*. 2006). By this activity, thioredoxins are involved in the regulation of protein activity. In *E. coli*, thioredoxin and thioredoxin reductases interact with folded and unfolded proteins and promote the functional folding of several proteins (Kern *et al*. 2003). The chaperone properties of thioredoxin are at least partially independent from the active-site cysteines and therefore independent form the oxidoreductase activity of thioredoxin (Kern *et al*. 2003). In *H. pylori*, arginase activity is post-translationally stimulated by TrxA but not the homologous TrxC (McGee *et al*. 2006). In this bacterium, TrxA has chaperone activity that renatures urea- or heat- denatured arginase back to the catalytically active state. Thereby, the mechanism of TrxA mediated stimulation of arginase is not likely due to redox control for cysteines. Since most oxygen- and nitrogen intermediates inhibit arginase activity; this damage is reversed by TrxA Thus TrxA although not acting in a redox role, protects *H. pylori* arginase form oxidative and nitosative stress (McGee *et al*. 2006).

Thioredoxin-linked processes have also been identified in cyanobacteria. In *Synechocystis* sp. PCC 6803, Lindahl and Florencio (2003) have screened cytosolic and peripheral membrane protein complements for proteins interacting with the cyanobacterial TrxA. They identified 18 cytosolic and 8 membrane-associated proteins as substrates for TrxA. One of the targets, phosphoglucomutase, which represents a metabolic branch point between storage and utilization of carbohydrates, was found to be activated by TrxA (Lindahl and Florencio 2003).

CONCLUSIONS

Thioredoxins are important protein thiol/disulfide reductases. In addition to this established role as disulfide reductases, thioredoxins possess functions important for many cellular processes including transcriptional regulation, cell division, oxidative stress, energy transduction, and protein folding. Despite their many functions, elucidation of the regulation of bacterial thioredoxin genes and the effects of thioredoxins on gene and/or protein regulation is still in an early phase. Nevertheless, available data demonstrate that expression of several thioredoxins is regulated in response to environmental changes. Continued expansion in knowledge of the regulation of bacterial thioredoxins and their involvement in gene regulation and protein activity will reveal additional intriguing mechanisms. This will help to build up regulatory networks for the maintenance of important cellular functions under changing environmental conditions.

ACKNOWLEDGEMENTS

The work from the authors was supported by the Deutsche Forschungsgemeinschaft (Kl563/16), the Fonds der chemischen Industrie, the BMBF and the DAAD.

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