Naturwissenschaften (2006) 93: 259–266
DOI 10.1007/s00114-006-0106-1

REVIEW

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Thioredoxins in bacteria: functions in oxidative stress response and regulation of thioredoxin genes

Published online: 23 March 2006

Abstract Thioredoxins fulfill a number of different important cellular functions in all living organisms. In bacteria, thioredoxin genes are often regulated by external factors. In turn, thioredoxins influence the expression of many other genes. The multiple and important functions of thioredoxins in cells necessitate to appropriately adjust their level. This review outlines different strategies that have evolved for the regulation of bacterial thioredoxin genes. It also summarizes effects of thioredoxins on gene regulation and presents a recent model for a redox-dependent gene regulation that is mediated by thioredoxins.

Introduction

Thioredoxins are small ubiquitous proteins with a highly conserved active site sequence [(Cys-Gly-Pro-Cys) (Holmgren 1985, 1995a; Martin 1995)]. These proteins share a common 3-D 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). Thioredoxins are part of the thioredoxin system, in which electrons are transferred from NADPH to thioredoxin reductase and finally to the thioredoxin (Trx). Because of their low redox potential [−270 to −330 mV in *Escherichia coli* (Krause et al. 1991; Aslund et al. 1997)], thioredoxins are efficient thiol-disulfide reductants. Thus, thioredoxins, together with the glutaredoxins, are responsible for maintaining a cellular reducing environment and, thereby, can regulate the activity of enzymes. Over the last years, thiol switches have emerged as a major regulatory mechanism in redox-dependent signal transduction (reviewed in, e.g., Paget and Buttner 2003). Apart from the function as thiol-disulfide reductases, thioredoxins also interact with other proteins to form functional protein complexes (reviewed in, e.g., Holmgren 1989).

The thiol-reducing activities of thioredoxins have been best characterized in *E. coli*, which comprises two thioredoxins, Trx 1 and Trx 2, encoded by the *trxA* and *trxC* genes, respectively (Laurent et al. 1964; Miranda-Vizuete et al. 1997; reviewed in Carmel-Harel and Storz 2000). In *E. coli*, a number of unique structural and regulatory features distinguish the thioredoxin 2 subfamily from the much larger thioredoxin 1 family. Trx 2 contains an additional N-terminal domain of 32 amino acids including two additional Cys-X1-X2-Cys motives compared to Trx 1 (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). Although the two *E. coli* thioredoxins are equivalent for most of their in vivo functions, the transcriptional regulation of *trxA* and *trxC* is different (Ritz et al. 2000). While both *trx* genes are not essential for viability of *E. coli* [both genes can be deleted from the genome (Ritz et al. 2000)], Trx 1 is required for viability of a number of other bacteria, e.g., *Rhodobacter sphaeroides* (Pasternak et al. 1997), *Bacillus subtilis* (Scharf et al. 1998), *Anacystis nidulans* (Muller and Buchanan 1989), *Synechocystis* sp. PCC 6803 (Navarro and Florencio 1996).

Several reviews have addressed the general structure and function of thioredoxins (e.g., Aslund and Beckwith 1999; Arner and Holmgren 2000; Carmel-Harel and Storz 2000; Ritz and Beckwith 2001). The fact that cancer cells have high levels of thioredoxin and that reduced cellular thioredoxin levels can cause cancer-prone disease (reviewed in Kontou et al. 2004) emphasizes the importance of this protein in humans. In plants, the thioredoxin system is particularly complex because at least 20 thioredoxin isoforms have been found (reviewed in, e.g., Gelhaye et al. 2005). Different pathways allowing thioredoxin reduction coexist in plants involving ferredoxin–thioredoxin reductase and thioredoxin reductases (Gelhaye et al. 2005). There are far too many reports on thioredoxins and their function to give a single comprehensive overview. There-

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fore, this review is restricted to bacterial thioredoxins and focuses on the role of thioredoxins in gene regulation and on the regulation of thioredoxin genes.

Functions of bacterial thioredoxins

Many important functions are fulfilled by bacterial thioredoxins, which are summarized in Fig. 1. Thioredoxins are involved in the reduction of a number of enzymes. As hydrogen donor to ribonucleotide reductase (Orr and Vitols 1966) and methionine sulfoxide reductase (Gonzalez Porqué et al. 1970; Boschi-Muller et al. 2000), thioredoxin fulfills an important role in DNA synthesis and protein repair, respectively. As hydrogen donor for phosphoadenosine–phosphosulfate reductase (Lillig et al. 1999), it is implicated in sulfur assimilation (Gonzalez Porqué et al. 1970; Russel et al. 1990).

Thioredoxins are not only involved in reducing cytoplasmic proteins but can directly reduce hydrogen peroxide, H_2O_2 (Spector et al. 1988; Kang et al. 1998). Kang et al. (1998) were able to show that the thioredoxin system provides reducing equivalents to peroxiredoxins that in turn reduce H_2O_2. Furthermore, thioredoxins function as singlet oxygen quencher and hydroxyl radical scavenger (Das and Das 2000) and act as hydrogen donor for peroxidases (Chae et al. 1994). These features imply an important function of thioredoxin in the oxidative stress response. Oxidative stress is defined as a disturbance of the pro-oxidant–antioxidant balance in favor of pro-oxidants (Sies 1985). It is caused by reactive oxygen species (ROS) that are generated by auto-oxidation of components of the respiratory chain and other cellular compounds (Gonzalez-Flecha and Demple 1995; Imlay and Fridovich 1991; Messner and Imlay 1999; Seaver and Imlay 2004) or by exposure of aerobically grown cells to metals, redox-active chemicals [such as Butyl-hydroperoxide (*t*-BOOH) or diamide], or by radiation. Oxidative stress conditions promote disulfide bond formation of redox-sensitive proteins resulting in the functional modulation of these proteins (reviewed in Imlay 2003). The oxidative stress response is aimed to prevent, to counteract, and to repair damages caused by ROS. A role of thioredoxins in the oxidative stress response has been shown for several bacterial species. An *E. coli* double mutant, lacking both Trx 1 and Trx 2, was shown to be more sensitive to the disulfide bond-inducing agent diamide, suggesting an active role of thioredoxins in dealing with the accumulation of nonnative disulfide bonds. Surprisingly the same mutant was found to be more resistant to high levels of H_2O_2 (Ritz et al. 2000). This was explained by the fact that the cytoplasmic redox potential of this mutant is more oxidized, which in turn results in the activation of the oxidative stress response (e.g., induction of catalase). This activation of the stress response results in a higher resistance toward H_2O_2. The deletion of the *trxC* gene alone results in a more sensitive phenotype in response to H_2O_2 in *E. coli* implicating a role of Trx 2 in the oxidative stress response (Ritz et al. 2000). A number of proteins that participate in the oxidative stress response (superoxide dismutase, hydrogen peroxidase I, alkyl hydroperoxide reductase) or have key regulatory functions in the oxidative stress response (ferric uptake regulator, aconitase) were found to be associated with thioredoxin 1 in *E. coli* (Kumar et al. 2004).

Beside the functions for redox regulation and oxidative stress defense, thioredoxin is an essential subunit of the bacteriophage T7 DNA polymerase (Huber et al. 1987; Mark and Richardson 1976) and is essential for the assembly of several filamentous phages (Russel and Model 1985). The Trx 1 of *Synechocystis* sp. PCC 6803 is required for both photoautotrophic and heterotrophic growth (Navarro and Florencio 1996). An interaction analysis of the *Synechocystis* thioredoxin indicated numerous thio-

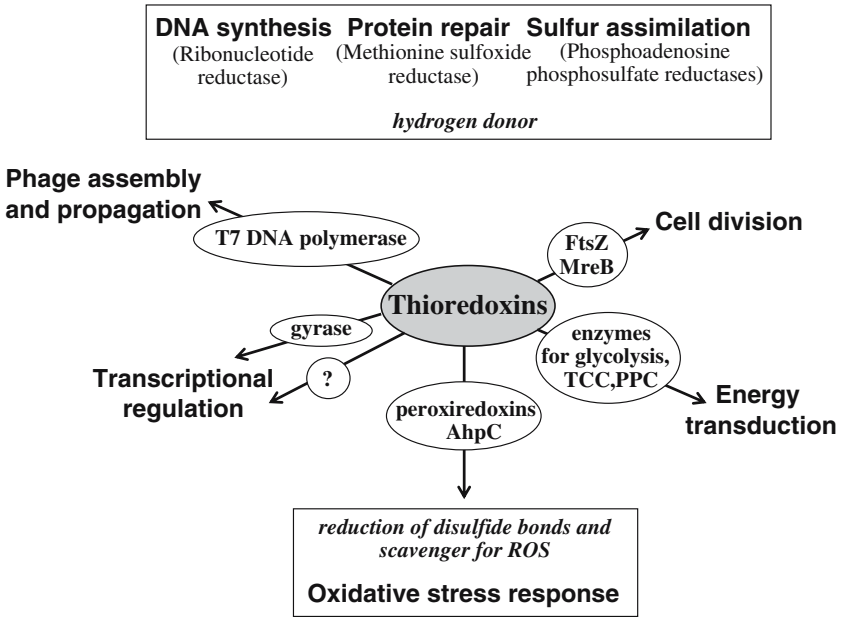

Fig. 1 Functions of thioredoxin. *Rectangles* include those functions for which the mechanisms of thioredoxin action are known and which involve direct interaction with target molecules. *Arrows* indicate functions that include the interaction of thioredoxin with other proteins (the interaction partners are *circled*). *ROS* reactive oxygen species; *TCC* tricarboxylic acid cycle; *PPC* pentose phosphate cycle; *AhpC* alkyl hydroperoxide reductase; *FtsZ* cell division protein, tubulin homolog; *MreB* cell division protein, actin homolog

redoxin-linked processes in Cyanobacteria, such as glycogen synthesis, sugar-nucleotide metabolism, oxidative stress response, and light harvesting (Lindahl and Florencio 2003). In *E. coli*, a proteome analysis resulted in the identification of many thioredoxin-targeted proteins (Kumar et al. 2004). A total of 80 proteins was found to be associated with the *E. coli* Trx 1, implicating the involvement of thioredoxin in at least 26 distinct cellular processes that include cell division, transcriptional regulation, energy transduction, protein folding and degradation, and several biosynthetic pathways.

Recent studies addressed the role of thioredoxins in facultatively photosynthetic bacteria, which provide an excellent model system to study the oxidative stress response of free-living bacteria. Bacteria of the facultatively phototrophic genus *Rhodobacter* are metabolically highly versatile and can rapidly adapt to changes in their environment. *Rhodobacter* species are found in aquatic environments, where the oxygen concentration may rapidly change due to external conditions or the metabolic activities of other organisms. While *Rhodobacter capsulatus*, like *E. coli,* contains Trx 1 and Trx 2, *R. sphaeroides* lacks Trx 2. Although *trxA* is essential in *Rhodobacter* (Pasternak et al. 1999; Li and Klug, unpublished results), strains that produce lower amounts of *trxA* could be constructed and analyzed (Pasternak et al. 1999). An *R. sphaeroides* strain with decreased Trx 1 level shows higher sensitivity to diamide and H_2O_2 than the wild type; however, it shows higher resistance to the superoxide anion-generating agent paraquat and to the glutathione depleting and oxidizing organic peroxide *t*-BOOH (Li et al. 2003b). The *trxC* deletion mutant of *R. capsulatus* is more sensitive to all oxidative-stress generating agents tested (H_2O_2, paraquat, *t*-BOOH, and diamide) than the isogenic wild-type strain (Li et al. 2003a). These results implicate that in *Rhodobacter*, TrxA and TrxC have a role in the oxidative stress response.

In *Lactococcus lactis*, the thioredoxin system was believed to be essential because this organism does not produce glutathione. However, cells lacking thioredoxin reductase were viable, even under aerobic conditions (Vido et al. 2005). This strongly suggests that other molecules besides thioredoxin and glutathione can maintain the cytoplasmic redox potential in *L. lactis*.

Reactive oxygen and nitrogen molecules are generated by mammalian cells and plant cells as a defense strategy against bacterial infections. Therefore, thioredoxins are not only important proteins for the oxidative stress response in nonpathogenic bacteria, but they may also influence the survival of pathogens in host cells. *Mycobacterium leprae* harbors a thioredoxin–thioredoxin reductase hybrid gene that increases intracellular survival of *Mycobacterium smegmatis* (Wieles et al. 1997). *Helicobacter pylori trxA* or *trxA2* (for Trx 2) mutants show increased sensitivity to agents generating oxidative stress (Comtois et al. 2003; McGee et al. 2006). In other bacteria, a role of thioredoxins in the oxidative stress response has not been demonstrated by mutant analysis, but an increased expression of *trx* genes in the presence of ROS implies their role in oxidative stress defense [e.g., *B. subtilis* (Scharf et al. 1998); *Oenococcus oeni* (Jobin et al. 1999)].

Regulation of *trx* gene expression in response to external stimuli is important in all bacteria, but different strategies have evolved to properly adjust the level of thioredoxins. An overview about the different strategies used by bacteria to regulate expression of *trx* gene is addressed below.

Regulation of bacterial thioredoxin gene expression

Despite the importance of thioredoxins in many cellular functions, our knowledge on the regulation of *trx* genes is still limited and restricted to few species. As in many other respects, enteric bacteria served as the first bacterial

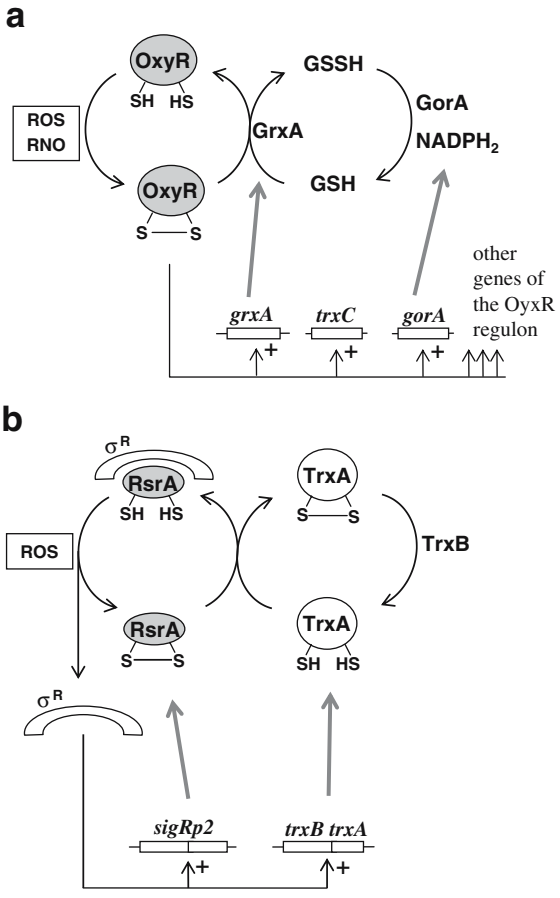

Fig. 2 Regulation of thioredoxin genes in **a** *Escherichia coli* and **b** *Streptomyces coelicolor* by oxidative stress. **a** Oxidized OxyR regulates expression of the OxyR regulon in response to oxidative and nitrosative stress, thereby activating expression of *trxC*, *grxA*, and *gorA*. Oxidized OxyR is reduced by glutaredoxin 1 accompanied by the consumption of glutathione, resulting in a feedback loop for OxyR-regulated genes. **b** The activity of σ^R is controlled by the anti-sigma factor RsrA. Oxidative stress induces intramolecular disulfide bond formation in RsrA. In this form, RsrA releases σ^R that activates expression of *trxBA*. Reduced thioredoxin A oxidizes RsrA, allowing the formation of the σ^R–RsrA complex and thereby establishing a feedback loop of regulation. *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *GrxA* glutaredoxin A, *GorA* glutathione reductase, *GSSH*/*GSH* oxidized/reduced glutathione, *TrxA* thioredoxin A, *TrxB* thioredoxin reductase

systems to study the oxidative stress response. Two key regulons of the adaptive responses to oxidative stress were defined by the analysis of a number of genes with known or predicted functions in the oxidative stress response. The OxyR regulon comprises genes that respond to H_2O_2 including genes encoding thioredoxin 2 (*trxC*), catalase (*katG*), alkyl hydroperoxidase (*ahpCF*), a small RNA (*oxyS*), glutaredoxin 1 (*grxA*), and the glutathione reductase gene, *gorA* (Storz et al. 1990; Zheng et al. 2001). OxyR, a transcriptional regulator of the LysR family, binds to its target sites (Toledano et al. 1994) in its oxidized form and, in most cases, activates gene expression by contacting the alpha subunit of DNA polymerase (Tao et al. 1993). In some cases, however, repression of gene expression by OxyR was observed (Zheng et al. 2001). Oxidized OxyR is reduced by glutaredoxin 1 accompanied by the consumption of glutathione, resulting in a feedback loop for OxyR-regulated genes (Zheng et al. 1998; Storz and Zheng 2000, Fig. 2a). In addition, the Stamler group was able to show that OxyR not only responds to oxidative stress but can also be activated by nitrosative events by S-nitrosylation (Hausladen et al. 1996; Kim et al. 2002). 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 in enteric bacteria (reviewed in, e.g., Nunoshiba 1996; Demple 1996; Storz and Zheng 2000). Interestingly, thioredoxins seem to contribute to SoxR regulation by affecting the disassembly and reassembly of the [2Fe-2S] clusters (Ding and Demple 1998).

As described above, *E. coli* thioredoxins are involved in the response to oxidative stress. Therefore, it is of no surprise that the expression of the *trxC* gene is induced by H_2O_2 and that *trxC* is a member of the OxyR regulon (Ritz et al. 2000; Fig. 2a). 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 thioredoxin 1 gene of *E. coli* (*trxA*) is under the 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).

Oxygen tension and ROS also affect the expression of thioredoxin genes in the related facultatively photosynthetic bacteria *R. sphaeroides* and *R. capsulatus*. Both *Rhodobacter* strains have OxyR homologues, but no SoxRS homologues. 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 *trxC* in *R. capsulatus* is strongly induced in response to diamide (20-fold, 1.5 mM final concentration), moderately induced by paraquat (1 mM final concentration), and shows little response to *t*-BOOH (0.6 mM final concentration) and H_2O_2 [1 mM final concentration (Zeller, Li, and Klug, unpublished results)]. The response of the *R. capsulatus trxA* gene to oxidative stress is quite different from that of the *trxC* gene. It most remarkably shows very little response to diamide (twofold). The addition of *t*-BOOH results in threefold increase of *trxA* expression, while the response to paraquat and H_2O_2 is similar to the *trxC* response (Zeller, Li, and Klug, unpublished results). Similar to the *trxC* gene of *R. capsulatus* the *trxA* gene of *R. sphaeroides* shows a strong response to diamide. It increases about sixfold after addition of *t*-BOOH and two- to threefold after exposure to paraquat or H_2O_2 (Li et al. 2003b). Apparently, glutathione depletion (induced by *t*-BOOH) is a stronger stimulus for *trxA* expression in *R. sphaeroides* than reactive oxygen species. Expression studies of *trx* genes in *oxyR* mutants of *Rhodobacter* indicate an involvement of OxyR in the regulation of the *trxC* gene (Zeller, Li, and Klug, unpublished results). The exact mechanisms of this regulation in *Rhodobacter* are currently under study.

Although many gram-positive bacteria encode OxyR homologues, they use other regulators to control *trx* gene expression under oxidative stress. The essential *trxA* gene of *B. subtilis* is not only under control of the vegetative sigma factor σ^A but is also transcribed by the general stress sigma factor σ^B (Scharf et al. 1998). Transcription initiating at the σ^A-dependent promoter is induced by H_2O_2 (Scharf et al. 1998). The induction of the *B. subtilis trxA* and *trxB* (encoding the thioredoxin reductase) genes by disulfide stress (induced by diamide, Leichert et al. 2003) involves the Spx protein that also represses activator-stimulated transcription by interacting with the C-terminal domain of RNA polymerase alpha subunit (Nakano et al. 2003a,b). A *B. subtilis* Spx mutant is hypersensitive to diamide (Nakano et al. 2003b). It was proposed that Spx, on one hand, functions as an activator that mobilizes the operations necessary to reverse oxidative stress, but on the other hand, serves as a negative regulator that causes the postponement of developmental programs and energy-consuming functions while the cells cope with stress (Nakano et al. 2003b). Disulfide stress causes an increase of Spx level, possibly due to posttranscriptional regulation (Nakano et al. 2003b). The transcriptional activation by Spx requires formation of an intramolecular disulfide bond within a highly conserved Cys-X1-X2-Cys motif (Nakano et al. 2005). A similar motif is present at the C-terminal end of the transcriptional repressor PerR, another regulator of the oxidative stress response in *Bacillus* (Bsat et al. 1998; Herbig and Helmann 2001).

In *Streptomyces coelicolor*, *trxB* and *trxA* constitute an operon that is under direct control of the alternative sigma factor σ^R (Paget et al. 1998; Li et al. 2002; Li et al. 2003c). 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; Li et al. 2003c) (Fig. 2b). While

OxyR is a positive regulator that is active in its oxidized form, RsrA is a negative regulator and the reduced form of the protein is active (Fig. 2).

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 *Staphylococcus 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). This induction is independent of the stress sigma factor σ^B, but the regulators involved in this response remain to be identified.

Thioredoxins can influence the expression of genes

A direct effect of thioredoxins in the oxidative stress response is expected because of their capability to reduce oxidized proteins. However, thioredoxins can also participate in the oxidative stress response by affecting the expression of other genes involved in this response. As outlined in the previous paragraph and shown in Fig. 2, thioredoxins are part of regulatory feedback loops including the sigmaR/RsrA proteins in *S. coelicolor*. Therefore, thioredoxins affect the regulation of other genes that are under the control of sigmaR/RsrA.

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 thioredoxin 1 and glutathione reductase or thioredoxin 1 and glutaredoxin 1 (Gallardo-Madueno et al. 1998; Prieto-Alamo et al. 2000). The *trxC* mutant of *R. capsulatus* 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). The induction of *acnA* by superoxide in *E. coli* results in the synthesis of higher levels of aconitase A, which is resistant to superoxide and can therefore keep the tricarboxylic acid cycle functional (Varghese et al. 2003). The *fur* gene encodes a regulatory protein, which represses genes required for iron uptake. Upon oxidative stress a stronger repression of iron uptake can prevent the formation of hydroxyl radicals by the Fenton reaction. *gorA* encodes glutathione reductase, an important component of the glutathione/glutaredoxin system. *katG* encodes catalase, an important enzyme for the detoxification of H_2O_2. These findings confirm an interplay of different defense systems.

Smits et al. (2005) reported the effects of thioredoxin depletion on global transcription levels in *B. subtilis*. The results of this study indicate that changes in thioredoxin A level cause transcriptional changes in *B. subtilis*. Because thioredoxins have so far not been reported to act as transcriptional regulators, the authors suggest that these transcriptional changes are likely to represent indirect effects of thioredoxin A (e.g., interaction or influence on transcription factors or other proteins).

In *Rhodobacter*, thioredoxins have been demonstrated to be involved in the redox-dependent regulation of photosynthesis genes (Clement-Metral 1979; Pasternak et al. 1999; Li et al. 2003b). Oxygen tension is the major factor that determines the regulation of photosynthesis genes and, consequently, the formation of photosynthetic complexes in *Rhodobacter*. Decreased levels of Trx 1 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). The *puf* and the *puc* operon encode pigment-binding proteins and other proteins required for the formation of photosynthetic complexes. 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). This finding of a signal from thioredoxin to transcription of photosynthesis genes resulted in the discovery of a new signaling pathway.

In a search for proteins interacting with *Rhodobacter* thioredoxins, the gyrase B subunit was identified by a yeast-two hybrid screening (Li et al. 2004b). A model in which thioredoxin affects gene expression by modifying gyrase activity was experimentally confirmed (Li et al. 2004b). TrxA mutants of *Rhodobacter* exhibit lower supercoiling activity than the wild type; in contrast, the TrxC mutant exhibits higher supercoiling activity. In vitro experiments supported the modulation of gyrase supercoiling activity by thioredoxin. Because the expression of many genes is influenced by the supercoiling status of the

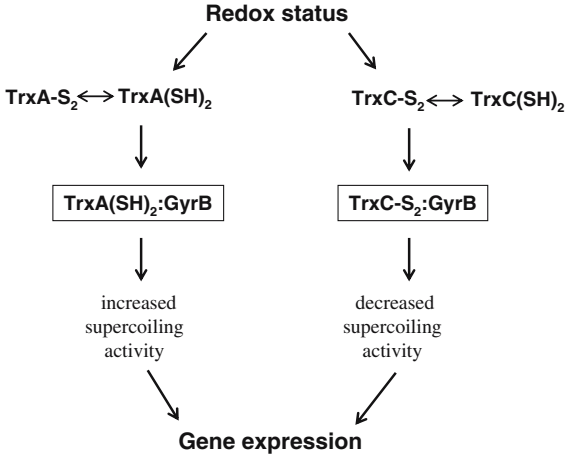

Fig. 3 Model for redox regulation on gene expression through thioredoxins as established for the thioredoxins of *R. sphaeroides* and *R. capsulatus*. The redox status of the cell determines the ratio of reduced to oxidized thioredoxin. The redox switch of thioredoxins alters the supercoiling activity of gyrase, which further affects gene expression. Reduced but not oxidized thioredoxin A binds to gyrase and increases its supercoiling activity. Oxidized but not reduced thioredoxin C binds to gyrase and decreases its supercoiling activity. *TrxA* thioredoxin A, *TrxC* thioredoxin C, *GyrB* subunit B of gyrase. S_2 and $(SH)_2$ indicate oxidized or reduced redox state of thioredoxins, respectively

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. A model for the action of thioredoxins on gene expression is shown in Fig. 3. Reduced, but not oxidized, Trx 1 interacts with the gyrase B subunit and increases its supercoiling activity. In contrast, oxidized, but not reduced, Trx 2 interacts with gyrase B and decreases its supercoiling activity. Because a reduced supercoiling leads to decreased *puf* and *puc* transcription (Zhu and Hearst 1988), a reduction of oxygen tension results in increased gyrase activity and, consequently, in increased *puf* and *puc* transcription. The same opposite effect of Trx 1 and Trx 2 on gyrase activity was observed in *E. coli* (Li et al. 2004b). This strongly suggests that the gyrase-mediated effect of thioredoxins on gene expression is a common redox-dependent signalling pathway in bacterial adaptation. Based on the above-mentioned model, one can also speculate that by regulating photosynthesis genes via gyrase, thioredoxins may also be involved in the regulation of ROS generation in *Rhodobacter*. Because the simultaneous presence of pigments, light, and oxygen results in the formation of toxic ROS, the effect of thioredoxins on the gyrase activity decreases the expression of photosynthesis genes under high oxygen tension and therefore limits the generation of ROS.

Concluding remarks

The elucidation of the regulation of bacterial thioredoxin genes and the effects of thioredoxin on gene regulation is still in an early phase. Nevertheless, the available data demonstrate that thioredoxins are parts of complex regulatory networks that control the bacterial oxidative stress response and, most likely also, many additional physiological functions. The intensified studies on the functions of bacterial thioredoxins will most likely reveal further strategies to build up such regulatory networks to maintain many 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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