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Forum Review

Redox Regulation of Human Thioredoxin Network

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ABSTRACT

Oxidative stresses are largely mediated by intracellular protein oxidations by reactive oxygen species (ROS). Host cells are equipped with antioxidants that scavenge ROS. The cellular reduction/oxidation (redox) balance is maintained by ROS and antioxidants. Accumulating evidence suggests that the redox balance plays an important role in cellular signaling through the redox modification of cysteine residues in various important components of the signal transduction pathway. Thioredoxin (TRX) is a small protein playing important roles in cellular responses, including cell growth, cell cycle, gene expression, and apoptosis, to maintain the redox circumstance. Moreover, many recent papers have shown that the redox regulation by TRX is deeply involved in the pathogenesis of various oxidative stress-associated disorders. This review focuses on TRX and its related molecules, and discusses the role of TRX-dependent redox regulation in oxidative stress-induced signal transduction. *Antioxid. Redox Signal.* 8, 1881–1890.

INTRODUCTION

CELLS ARE EXPOSED to various oxidative stresses induced by metals, chemicals, heat shock, osmotic stress, and hypoxia (16, 67). Against these oxidative stresses, eukaryotic cells have acquired "antioxidant systems" to maintain the reduction/oxidation (redox) balance by scavenging the reactive oxygen species (ROS). The cellular redox status regulates signal transductions for various cellular events, including activation, differentiation, proliferation, and apoptosis. Increasing evidence has indicated that the redox regulation of cell signaling is important to maintain the homeostasis of living cells (16). Especially, the redox regulation of the key cysteine residue in transcriptional factors promotes the gene transcription for the redox response against oxidative stress. Recently, evidence has accumulated that reducing molecules such as thioredoxin (TRX) play important roles in cellular signaling through the change of sulfhydryl reaction via reduction of cysteine residues of, as well as the interaction with, various important components of signal transduction pathways (11, 57). In this review, we introduce TRX and TRX-related systems in four sections: a) TRX and its related molecules; b) induction of TRX; c) TRX binding partners; and d) posttranslational modification of TRX, and focus on the oxidative modification of TRX in the redox regulation of cellular signaling.

THIOREDOXIN AND ITS RELATED MOLECULES

Thioredoxin (TRX), a ubiquitous 12 kDa redox protein, was originally identified in *Escherichia coli* as an electron donor for ribonucleotide reductase, an essential enzyme for DNA synthesis (26). Human TRX was cloned as an adult T cell leukemia (ATL)-derived factor produced by HTLV-I transformed T cell line ATL-2 cells (80, 94). TRX is preserved in many different types of prokaryotes and eukaryotes. Human TRX is a 105 amino acid protein with two redox-active cysteine residues in the active center (-Cys–Gly–Pro–Cys-) and operates together with NADPH and TRX reductase as an efficient reducing system of exposed protein disulfides (60). In addition, human TRX has critical roles in many cellular functions including activation, differentiation, proliferation, and apoptosis. Proteins that share the similar active site sequence as TRX: -Cys–Xxx–Yyy–Cys- are called members of the TRX family (24, 57).

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Glutaredoxin (GRX) is a member of the TRX family that was originally identified in *E. coli* lacking TRX. GRX directly protects the activation of Akt against stress-induced oxidation, and suppresses recruitment of protein phosphatase 2A, resulting in a sustained phosphorylation of Akt, and inhibits apoptosis (56). Protein disulfide isomerase (PDI) is also a member of the TRX family existing in the endoplasmic reticulum (ER) and possessing two TRX-like active sites.

Recently, many papers have reported new TRX family proteins and TRX-related molecules in different subcellular fractions in the mammalian system. Mammalian thioredoxin 2 (TRX2) has a mitochondrial insertion signal and is specifically localized in mitochondria (78). TRX2 has the same active site -Cys–Gly–Pro–Cys as cytosolic TRX with thiol-reducing activity, and is essential for cell viability, playing a crucial role in the scavenging ROS and regulating the mitochondrial apoptosis signaling pathway through the prevention of cytochrome c release and apoptosis-induced factor (81, 86).

Transmembrane TRX-related protein (TMX), another new TRX family protein localized in the ER, possesses an atypical active site sequence, -Cys–Pro–Ala–Cys-, and a potential transmembrane domain as a transforming growth factor-beta-responsive gene (50). TMX significantly suppresses ER stress-induced apoptosis. TMX has PDI-like activity to refold scrambled RNase (51). ERdj5, which is identified as JPDI, is also characterized as a novel human ER co-chaperone containing domains resembling DnaJ, PDI, and TRX domains (10, 28). ERdj5 is ubiquitously expressed and abundant in secretory tissues such as pancreas and testis. The most intriguing feature of this molecule is four CXXC motifs, such as DnaJ-, TRX-like, and PDI-like domains on the same polypeptide. An important question concerning ERdj5 is what domain is essential for the functions of this molecule. Three tissue-specific testicular TRXs named SpTRX-1, SpTRX-2, and SpTRX-3 are expressed in the tail of spermatozoa (32, 55, 72). During mammalian spermiogenesis in testis, seminiferous tubules, and later maturation in epididymis, extensive reorganization of disulfide bonds is required to stabilize cytoskeletal sperm structures. SpTRXs play a critical role in regulating the period of human spermiogenesis, since an expression pattern of SpTRX is restricted to the postmeiotic phase of spermatogenesis. TXL-2, a thioreodoxin-like protein 2, is ubiquitously expressed, with the highest levels of expression in the testis and the lung (73). This protein is associated with microtubular structures such as the lung airway epithelium cilia and the manchette and axoneme of spermatids. Another family member of TRX, nucleoredoxin, plays a role in the regulation of transcription factors (40).

TRX and its family member proteins regulate signal transductions via redox reaction in each compartment such as nucleus, ER, plasma membrane, and mitochondria (Fig. 1). Many investigators have reported on the TRX functions in or from the extracellular environment. TRX is released via a redox active site against various stimulations from the cell (38). Extracellular TRX can also enter into cells through a redox reaction and attenuate intracellular ROS generation and ROS-induced apoptosis (38, 59). Administration of recombinant TRX can also attenuate oxidative stress-induced injury in lung, heart, and brain (19, 27, 45, 58). The anti-inflammatory effect of TRX may be partly explained by its antichemotactic effect that suppresses neutrophil infiltration into the inflammatory site (5, 58, 84).

Another member protein of TRX released from cells, macrophage migration inhibitory factor (MIF), is a multifunctional protein involved in several inflammatory disorders, such as inflammatory lung diseases, and some autoimmune diseases (61, 62). MIF has the conserved sequence Cys–Ala–Leu–Cys and sequence-dependent oxidoreductase activity (70). Jung *et al*. reported that MIF bound to the PAG, a member peroxiredoxin (Prx) protein family, and this association significantly affected the inhibition of antioxidant activity for PAG via disulfide formation (34). Glycosylation inhibiting factor (GIF) shares an identical gene with MIF. GIF is modified posttranslationally with cysteinylation in cysteine of MIF at position 60 and this consequent conformational change is responsible for the generation of GIF bioactivity (87). Evidence has suggested that redox regulation of the cysteine is involved in the differential control of MIF/GIF function. Moreover interestingly, the expression of TRX and MIF are reciprocally regulated (39). It suggested that the expression of TRX family molecules is associated with cellular signaling. Witte *et al*. reported that protein kinase C-θ (PKCθ)-interacting protein termed PICOT (for PKC-interacting cousin of thioredoxin), displays an N-terminal TRX homology domain that interacts with PKC (89). PICOT inhibits the activation of c-Jun N-terminal kinase and the transcription factors AP-1 or NF-κB, suggesting that PICOT plays a role in regulating the function of the TRX system. Thus, the TRX system is composed of many molecules forming a network of interaction through its active site, cysteine residues.

TRX can also regulate cell signaling to associated other systems such as peroxidases. TRX-dependent peroxidases (peroxiredoxins; Prxs) are thought to be members of a family acting against intracellular hydrogen peroxide (91). Prxs share the same basic catalytic mechanism, in which an active site cysteine (the peroxidatic cysteine) is oxidized to a sulfenic acid by the peroxide substrate (71, 90). Although located primarily in the cytosol (PrxI, II), Prxs are also found within mitochondria (Prx III), peroxisomes, associated with membranes, and in at least one case, exported (Prx IV) (14, 25). These proteins are also divided into three classes: typical 2-Cys Prxs; atypical 2-Cys Prxs; and 1-Cys Prxs. Typical 2-Cys Prxs are obligate homodimers containing two identical active sites. Recently, studies of several typical 2-Cys Prxs have revealed the dramatic changes in oligomeric state (dimer and decamers) linked to changes in the redox state. The second class of Prxs are the atypical 2-Cys Prxs, which have the same mechanism as typical 2-Cys Prxs but are functionally monomeric. The last class of Prxs, the 1-Cys Prxs, conserves only the peroxidatic cysteine and does not contain a resolving cysteine (9). Prxs exert their protective antioxidant role in cells through the peroxidase activity. A range of other cellular roles has also been reported in mammalian Prx family members, including cell proliferation, differentiation, and apoptosis (91). These reports suggest that TRX family proteins exist in each organelle, and the crosstalks among TRX family members play crucial roles in the cellular responses against oxidative stresses.

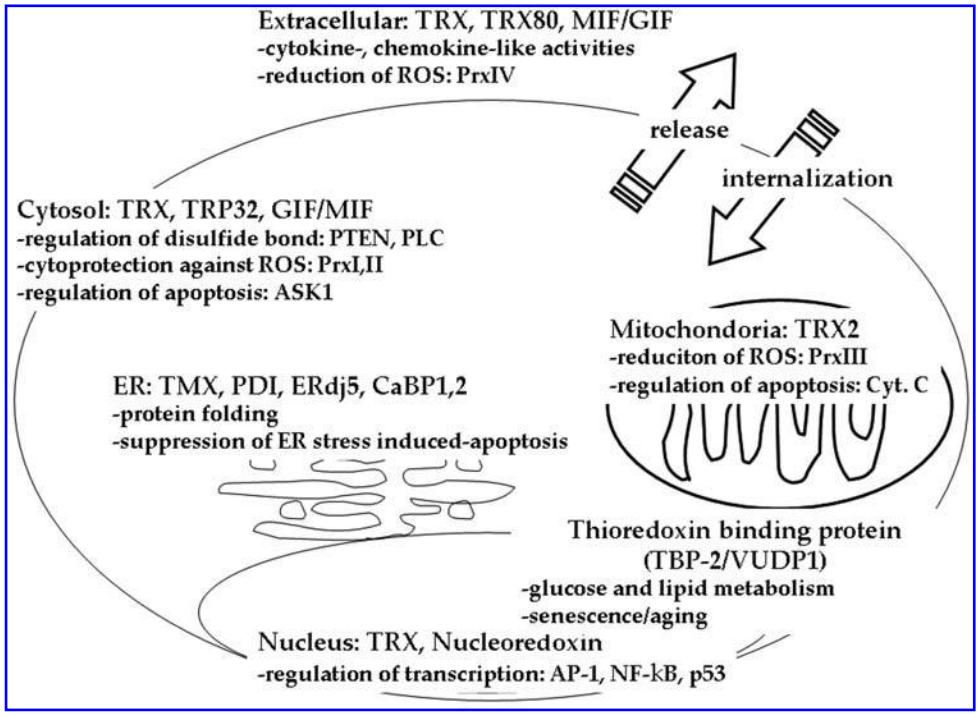

FIG. 1. Localization of TRX and its related proteins. TRX and its family molecules are localized in extracellular and intracellular compartments. MIF, macrophage migration inhibitory factor; GIF, glycosylation inhibitory factor; Prx, peroxiredoxin; ROS, reactive oxygen spices; TRP32, thioredoxin-related protein 32; TMX, transmembrane thioredoxin-related protein; PLC, phospholipase C; PDI, protein disulfide isomerase; Cyt, cytochrome c; TBP2, thioredoxin binding protein-2; VUDP1, vitamin D-upregulated protein 1.

INDUCTION OF THIOREDOXIN

Thioredoxin is induced by a variety of stresses, including virus infection, mitogens, phorbol myristate acetate (PMA), X-ray and ultraviolet irradiation, hydrogen peroxide, and ischemic reperfusion. Reports regarding the promoter analysis of TRX recently have been increasing. The promoter region of TRX contains ARE (antioxidant responsive element), CRE (cyclic AMP responsive element), and SP-1. In the erythroleukemia cell line K562 cells, we identified the differential mechanism for TRX gene activation through the hemin-dependent binding of Nrf2 on the antioxidant responsive element (ARE) (36) and PMA-induced binding of AP-1 on the same element. Moreover, we also reported that overexpression of TRX enhanced the ARE-mediated TRX gene activation by *tert*-butylhydroquinone (tBHQ) (37). Retinol (vitamin A) transcriptionally induces expression of TRX in monkey tracheobronchial epithelial cells (3). Estradiol, or prostaglandin (PG) E_1, increases TRX expression (47, 48). TRX is significantly augmented by PGI_2. Both PGE_1 and PGI_2 partly enhance the signal transduction via a cyclic AMP-dependent pathway (93).

One of TRX inducers is geranylgeranylacetone (GGA), which is widely used as an antiulcer drug. TRX was induced by GGA in hepatocytes and gastric mucosal cells, and prevented ethanol-induced cytotoxicity in these cells (23). Dekigai *et al*. also confirmed the cytoprotective effects of GGA against ischemia and reperfusion injury in hepatocytes and intestinal cells (12). We ourselves demonstrated that expression of TRX induced by GGA prevented the 1-methyl-4-phenylpyridinium ion (MPP^+)-induced cell death in a rat pheochromocytoma cell line (PC12), and attenuated light-induced damage in retina via maintenance photoreceptor cell integrity (4, 82).

Sulforaphane, which is isothiocyanate highly concentrated in cruciferous vegetables such as broccoli, is also known as a TRX inducer. Administration of sulforaphane into intraperitoneal and oral induces TRX protein, and attenuates light damage in the neural retina and retinal pigment epithelium (RPE) of mice (83). As described above, TRX-inducing chemical compounds play roles in the signal transduction of cytoprotection in a variety of diseases caused by oxidative stresses.

THIOREDOXIN BINDING PARTNERS

TRX is associated with a variety of cellular proteins. In the nucleus, the activation of NF-κB and AP-1 is inhibited under oxidizing conditions (15). In contrast, reduced TRX increases the NF-κB activation more significantly compared with other reducing agents such as glutathione, *N*-acetylcysteine (NAC), 2-mercaptoethanol, or dithiothreitol (DTT) (15, 20, 66, 75). NF-κB activation requires the reduction of the cysteine at

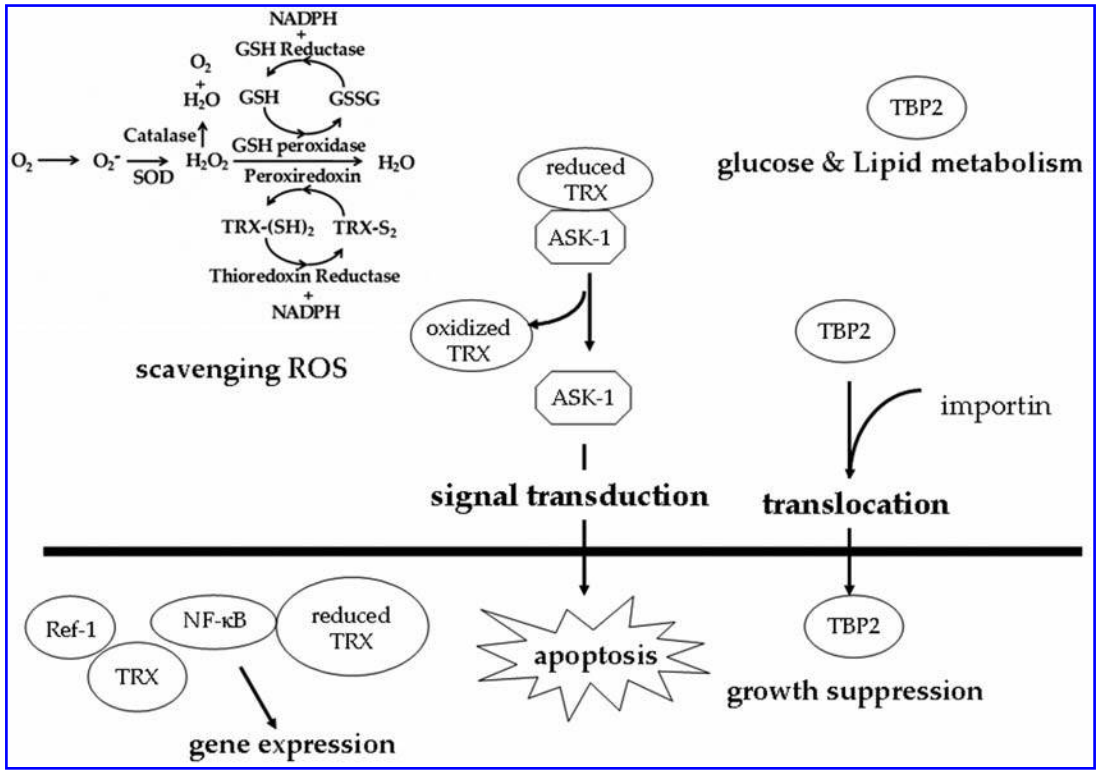

FIG. 2. Redox regulation by TRX and its related proteins. TRX regulates cell signals to interact with many proteins through redox status.

position 62 in the p50 subunit be reduced (52). In this NF-κB system, direct binding between reduced TRX and NF-κB is involved in the nuclear translocation of NF-κB (22). The transcription factor AP-1 is also redox regulated (1, 54, 75). DNA binding of AP-1 is increased by the reduction of a single conserved cysteine residue in the DNA binding domain of each of the homodimers (33). Transfected TRX causes an increase in AP-1 activity (13). TRX increases AP-1 activity but does so through another nuclear redox protein Ref-1 (21, 92). TRX was shown to interact directly with Ref-1/APEX nuclease, a ubiquitous nuclear protein, when UV irradiation promptly induced the translocation of TRX into the nucleus. This translocation of TRX and association with Ref-1 may support the function of p53 against oxidative stress. p53 is a tumor suppressor protein and transcriptional factor found to be deleted in a large number of human cancers (41). The binding of p53 to DNA is not only enhanced by phosphorylation, but also is affected by the redox status. The mutation of the cysteine in DNA binding domain of p53 markedly decreases the activity in response to DNA damages against mitomycin C. Ueno *et al*. reported that TRX increases the DNA binding of p53 and also potentiates Ref-1-enhanced p53 activity, depending on the redox active site (85). Apoptosis can be considered as a finely regulated mechanism to maintain genome stability by eliminating cells with severe DNA damage caused by oxidative stress. Jun kinase/SAP kinase and p38 kinase are also reported to play important roles in oxidative stress-induced apoptosis (30). A protein to which TRX binds and that has received attention is apoptosis signal-regulating kinase 1 (ASK-1), which is an activator of the c-Jun N-terminal kinase (JNK) and p38 MAP kinase pathways (74). The reduced TRX, but not oxidized TRX, binds to ASK-1, and inhibits the apoptosis process. It is well known that ASK-1 is required for TNF-α-induced apoptosis, and TRX also prevents apoptosis induced by TNF-α (44, 49). Therefore, the reduced TRX binds to ASK-1 to inhibit ASK-1-dependent apoptosis, whereas TNF-α, or stress-induced generation of ROS, leads to dissociation of TRX and the activation of ASK-1. Interestingly, Liu *et al*. also reported that ASK-1 ubiquitination is enhanced by the formation of an ASK-1–TRX complex (46). They reported that the binding of both reduced TRX and ASK-1 promoted ubiquitination/degradation; however, apoptosis was enhanced through the activation or ASK-1 via disassociation with TRX when cells were exposed to TNF-α or ROS. This phenomenon was confirmed by using single mutant TRX, TRX-C32S, or TRX-C35S.

Recently, Lee *et al*. reported redox regulation of tumor suppressor PTEN by TRX (42). PTEN, phosphatidylinositol (3, 4, 5) trisphosphate (P_3) 3-phospatase, regulates cell migration, growth, and survival by modulating the PI 3-kinase pathway. The reduced form of PTEN inhibits activation of Akt by preventing formation of phosphatidylinositol-biphosphate to tri-phosphate.(42, 43, 53). They reported that TRX is more efficient than glutathione, glutaredoxin, or 14 kDa thioredoxin-like protein with regard to the reduction of oxidized PTEN *in vitro*. Another TRX binding protein, TBP-2, which is identical to vitamin D3-upregulated protein 1 (VDUP1), has been reported. The reduced TRX but not

oxidized TRX interacted with TBP2 *in vitro* and *in vivo* (8, 35, 64). Interestingly, the expression of TBP-2 is lost in human T-cell leukemia virus type-I (HTLV-I)-positive cell (Nishinaka Cancer Res., 2004 ref. 68), which has high expression of TRX, and is also downregulated in human cancers (6, 18). Expression of TBP-2 is lost in HTLV-I-positive, interleukin-2-independent T-cell lines but maintained in HTLV-I-positive, interleukin-2-dependent T-cell lines, as well as HTLV-I-negative T-cell lines (63). Recently, one of the mechanisms was shown to be the epigenetic silencing of the TBP-2 gene through DNA methylation and histone deacetylation (2). In TBP-2-overexpression cells, a G_1 arrest was observed in association with an increase of p16 expression and reduction of retinoblastoma phosphorylation (63). Therefore, the decreased expression of TBP-2 in cells was closely associated with cancer promotion, HTLV-I transformation, and ATL leukemogenesis.

We also generated mice with target inactivation of TBP2 (TBP-$2^{-/-}$ mice). These mice show a phenotype that is quite compatible with the pathology of Reye syndrome with severe bleeding. Serum biochemical analyses indicated that plasma free fatty acids, ketone bodies, and pyruvate and lactate levels are higher, whereas glucose levels are lower. These results suggest that Krebs cycle-mediated fatty acid utilization is impaired in these mice (65). A similar phenotype was reported in a spontaneous hyperlipidemia mouse strain, HcB-19 (29). These reports suggest that TBP-2 plays an important role in fatty acid utilization.

POSTTRANSLATIONAL MODIFICATION OF THIOREDOXIN

Two signaling systems, based on the principle of posttranslational modification of proteins, are conserved throughout evolution and influence most aspects of cellular physiology. One is phosphorylation and the other is redox regulation. Both are exemplary regulations of protein function by reversible modification, and they govern many of the same signal transduction pathways through overlapping sets of cellular targets. In the TRX systems, many reports maintain that TRX is modified at cysteines by redox-based compounds through disulfide bonds. TRX has three additional structural cysteines (Cys 62, 69, and 73) besides the active site two cysteines Cys 32 and Cys 35. A recent report shows that the dithiol/disulfide exchange is also observed between Cys 62 and Cys 69 in TRX molecule (88).

S-nitrosylation, an NO-related posttranslational modification, is an important mechanism in the dynamic regulation of protein function. Some proteins are regulated by *S*-nitrosylation of a single critical cysteine residue within an acid-base or hydrophobic structural motif, which may also be subject to oxygen- or glutathione-dependent modification. Haendeler *et al*. reported that TRX *per se* is *S*-nitrosylated at cysteine 69 under basal conditions, and this modification is required for scavenging ROS and for preserving the redox regulatory activity of TRX (17). Moreover, TRX can suppress not only TNF-α-induced apoptosis signaling via ASK-1 dependent pathway, but also *S*-nitrosylation on Cys 69 of TRX can contribute strongly anti-apoptotic activity compared to wild-type TRX (17). In contrast, Sumbayev reported that amounts of *S*-nitrosylated TRX is increased to incubate with *S*-nitrosoglutathione (GSNO) in a time-dependent manner, and causes DNA fragmentation, the marker of apoptosis via ASK-1 activation (79). The inhibition of *S*-nitrosylation for TRX by glutathione (GSH) or NAC does not lead to the activation of ASK-1. Since TRX regulates TRX activity through the active site of it, this mechanism was considered the correlation the modification of two redox active site modification. These results suggest that the *S*-nitrosylated TRX plays a critical role in the regulation of the apoptosis pathway by the change of *S*-nitrosylated position of cysteine residues for TRX.

Glutathionylation is known as another modification via SH groups. Mixed disulfides are formed between glutathione and cysteines in proteins, which is known to occur after oxidative stress. Glutathionylation occurs by thiol–disulfide exchange between protein sulfhydryls and oxidized glutathione (GSSG). This reversible process can be catalyzed by glutaredoxin. Glutathionylated proteins also can be formed by reaction with *S*-nitrosoglutathione, a pathway requiring the formation of this compound from nitric oxide. In an oxidative condition, such as when the cells exposed by diamide, the cysteine at position 73 of TRX is modified by glutathione (7). Glutathionylation of TRX abolished its enzymatic activity as insulin disulfide reductase. Interestingly, Cys 73 is also involved in the dimerization of TRX, which may occur under

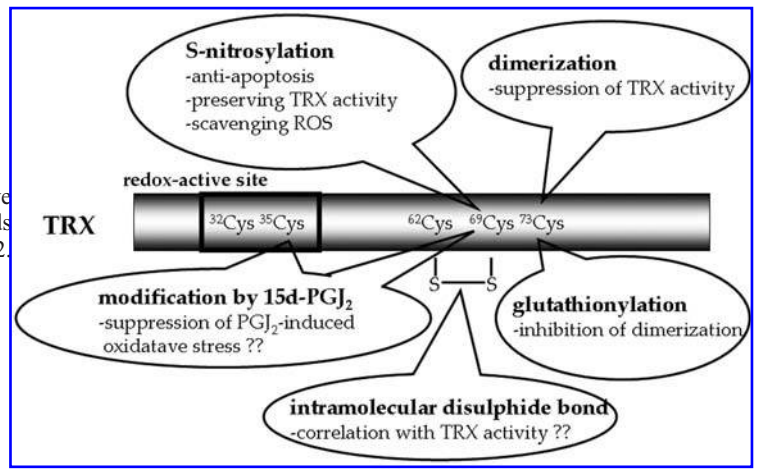

FIG. 3. Cysteine modification of TRX. Five cysteines of TRX are modified by small compounds such as NO, GSH, and PGJ2. PGJ2, prostaglandin J2.

oxidative conditions, confirming that Cys 73 can be oxidized. These results suggested that glutathionylation of TRX prevents the dimerization.

Shibata *et al.* also reported that 15d-prostaglandin (PG) J_2, a potent electrophile that causes intracellular oxidative stress and redox alteration, directly modified the endogenous TRX (76). Overexpression of TRX significantly suppresses the 15d-PGJ_2-induced oxidative stress. Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) and electrospray ionization-liquid chromatography (ESI-LC) analysis showed that the cysteines at positions 35 and 69 in TRX is identified to be modified by 15d-PGJ_2. TRX may be a direct sensor of the electrophilic PGs (31).

TRX is not only modified by some small compounds, but also cleaved at position 80 (69, 77). Pekkari *et al*. first reported that truncated TRX (TRX80) had a potent mitogenic activity in peripheral blood mononuclear cells (69). TRX80 was originally reported as eosinophil cytotoxicity enhancing factor produced by PMA-activated U937 cells (77). Since TRX80 was similar to TRX in its secondary structure, it could form the dimer. However, it lacked redox activity. It was proved that CD14-positive monocytes, but not B, or T lymphocytes were activated by TRX80 in dose-dependent manner, and TRX80 induced the secretion of IL-12 from CD40-positive monocytes (68). The reported concentration of TRX80 in plasma (2–175 ng/ml) is roughly comparable to the levels of TRX in plasma, which are 20–30 ng/ml in healthy volunteers, and up to 100 ng/ml in many patients with oxidative stress-associated disorders. These results suggested that TRX80 directed the immune system in favor of a Th1 response via IL-12 production. As mentioned above, TRX *per se* not only regulates a variety of molecules and signal transduction via redox change, but also obtains the new activities by the modifications of small chemical compounds, including *S*-nitrosylation and glutathionylation.

CONCLUSIONS

The TRX system, composed of several related molecules, protects cells against oxidative stress. TRX appears to be a regulator/modulator involved in cellular signaling against oxidative stimuli. Thus, redox modification by TRX itself and posttranslational modification of TRX is deeply involved in many signal transduction pathways. Moreover, the analysis of new secured activities of modified TRX may approach clinical therapy.

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ABBREVIATIONS

ASK-1, apoptosis-regulating kinase-1; ATL, adult T cell leukemia; ER, endoplasmic reticulum; GIF, glycosylation inhibiting factor; HTLV-I, human T cell leukemia virus type-I; MIF, macrophage migration inhibitory factor; PDI, protein disulfide isomerase; PG, prostaglandin; PICOT, protein kinase C-interacting protein; PTEN, phosphatidylinositol (3,4,5) trisphosphate (P_3) 3-phosphatase; Prx, peroxiredoxin; ROS, reactive oxygen species; TBP2, thioredoxin binding protein 2; TMX, transmembrane TRX-related protein; TRX, thioredoxin; redox, reduction/oxidation; TXL2, thioredoxin-like protein 2; VDUP1, vitamin D3-upregulated protein 1.

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