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Mini Review

Thioredoxin and Its Related Molecules: Update 2005

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ABSTRACT

Studies on thioredoxin (Trx) and its related molecules have expanded dramatically recently. Proteins that share the similar active-site sequence, -Cys-Xxx-Yyy-Cys-, are called the Trx family, and the number of Trx family members is increasing. Trx reductase, which reduces oxidized Trx in cooperation with NADPH, has three isoforms, and peroxiredoxin, which is Trx-dependent peroxidase, has six isoforms. In addition to a role as an antioxidant, Trx and its related molecules play crucial roles in the redox regulation of signal transduction. The classical cytosolic Trx1 and truncated Trx80 are released from cells. Plasma/serum levels of Trx1 are good markers for oxidative stress. Exogenous Trx1 shows cytoprotective and antiinflammatory effects and has a good potential for clinical application. This is an update review on Trx and its related molecules. *Antioxid. Redox Signal.* 7, 823–828.

STUDIES ON THIOREDOXIN (Trx) and its related molecules are expanding. According to PubMed, we have roughly 3,400 articles on "Trx" in total and more than half of them have appeared in the 6 years since 1999. We had a *Forum* issue on Trx in this journal last year. This is an update review on the Trx field.

The original Trx system was composed of NADPH, Trx reductase (TrxR), and Trx. We have now so many members of the Trx family sharing the similar active-site sequence, -Cys-Xxx-Yyy-Cys-, as shown in Fig. 1. The classical cytosolic thioredoxin-1 (Trx1) has been most intensively studied in mammals. It plays a crucial role in reduction/oxidation (redox) regulation in signal transduction and is secreted from cells in response to oxidative stress (40). Trx1 knockout mice are embryonic lethal, suggesting that Trx1 is an essential protein for mammals (30). Trx2 is a mitochondria-specific member of the Trx family, and it is also an essential protein for cell survival like Trx1 (47, 61). Glutaredoxin (Grx) is a glutathione-dependent member of the Trx family. There are two isoforms of Grx in mammals. Whereas the classical Grx1 exists in the cytosol, Grx2 is in the nucleus and mitochondria (6, 28). Reduction of glutathionylated substrate by Grx2 in mitochondria is dependent not only on glutathione, but also on TrxR and NADPH (18). Down-regulation of Grx2 mRNA by short interfering RNA enhances the sensitivity to doxorubicin (25). Endoplasmic reticulum (ER) has several members of the Trx family, including protein disulfide isomerase (PDI). ERdj5 contains the J domain and four Trx domains and is identical to JPDI (3, 14). TMX is a transmembrane Trx-related protein with anti-ER stress activity and shows PDI-like function to refold scrambled RNase (31, 32). Trx-like protein 2 (Txl-2) is a unique member of the Trx family binding to microtubules (51). Glycosylation-inhibiting factor (GIF) is a cystinylated protein at Cys^{60} of macrophage migration inhibitory factor (MIF), which is also a Trx family member with redox-active dithiols (21, 67). The two different biological activities of MIF and GIF may be redox-regulated. Tissue-specific members of the Trx family were reported and reviewed by Miranda-Vizuete *et al.* in the previous *Forum* issue (17, 35). More recently, a plasma cell-specific member was reported as plasma cell Trx-related protein (PC-TRP) (69).

As for mammalian TrxR, a selenoprotein containing a penultimate C-terminal selenocysteine necessary for its catalytic activity, there are three isoforms: the classical cytosolic TrxR1, mitochondrial TrxR2, and Trx and glutathione reductase (TGR). TGR reduces not only Trx1, but also oxidizes glutathione and exists mainly in the testis (35, 58) Mammalian cytosolic TrxR1 and mitochondrial TrxR2 have alternative splicing variants (50, 59). In human, five different 5′ cDNA variants have been reported. One of the splicing variants exhibits a 67-kDa pro-

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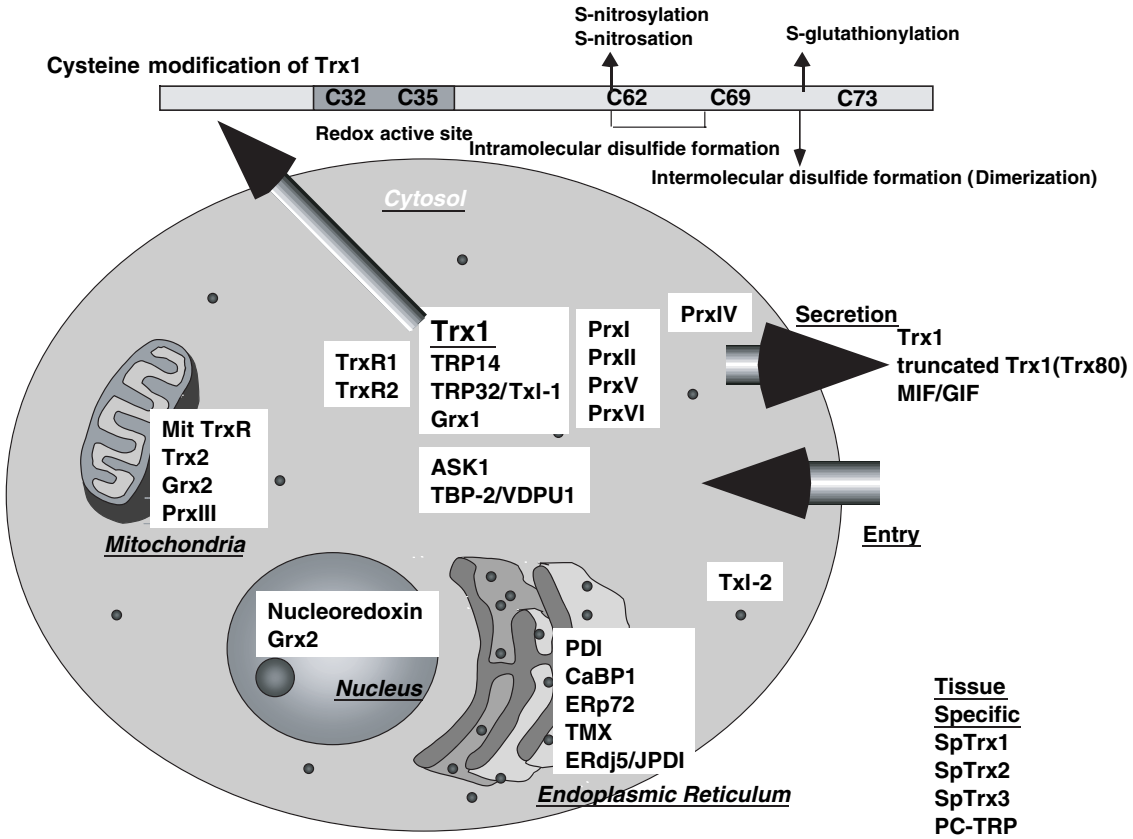

FIG. 1. Cysteine modifications of Trx1 and subcellular localizations of the Trx family and related proteins.

tein with N-terminal elongation instead of the common 55-kDa protein. The functions and meanings of these splicing variants of TrxR are to be clarified.

Peroxiredoxins (Prxs) are Trx-dependent peroxidases and are now divided into six isoforms. Whereas Prx I and Prx II exist in the cytosol, Prx III is in the mitochondria and Prx IV is secreted from cells. Prx V exists in mitochondria and microsome. Prx VI is a one-cysteine type. Prx I-deficient mice have shortened life span with hemolytic anemia and some malignancies (45). Prx II knockout mice also show anemia (24).

Posttranslational modifications of Trx1 have been reported. C-terminal truncated Trx1 composed of 1–80 or 1–84 N-terminal amino acids (Trx80) is secreted from cells and shows more cytokine-like functions (49). *S*-Nitrosylation of Trx1 at Cys^{69} is important for its antiapoptosis effect (7). HMG-CoA reductase inhibitors, which are commonly used for the prevention of atherosclerosis, augment *S*-nitrosylation of Trx1 at Cys^{69} and reduce oxidative stress (8). Glutathionylation occurs at Cys^{73}, which is also the site responsible for the dimerization induced by oxidation (2). In addition to the original active site between Cys^{32} and Cys^{35}, another dithiol/disulfide exchange is observed between Cys^{62} and Cys^{69} (68). Cys^{35} and Cys^{69} of Trx1 are reported to be the target for 15-deoxyprostaglandin-J_2 (53).

Trx and its related molecules play important roles in intracellular signal transduction. Upon oxidative stress, Trx1 translocates from cytosol into nucleus and augments the DNA-binding activity of several transcriptional factors, including nuclear factor-κB, activator protein-1, and p53 (10, 11, 66). In cooperation with redox factor-1, Trx1 induces p53-dependent p21 transactivation leading to cell-cycle arrest and DNA repair (65, 66). Trx1 regulates the signaling for apoptosis by suppressing the activation of apoptosis signal-regulating kinase-1 (ASK1) (33, 52, 65). Trx2 is a critical regulator of mitochondrial cytochrome *c* release and apoptosis (61). Trx1 and 14-kDa Trx-like protein (TRP14) reactivate PTEN, a protein tyrosine phosphatase reversing the action of phosphoinositide 3-kinase, by the reduction of the disulfide reversibly induced by hydrogen peroxide (15, 16, 23). Grx1 plays a crucial role in maintaining the activation of a serine kinase Akt for cell survival (39). We previously reported that Trx-binding protein-2 (TBP-2), which is identical to vitamin D3 up-regulated protein 1 (VDUP1), is an endogenous negative regulator of Trx1. TBP-2/VDUP1 is deeply involved in tumor suppression (46) and aging (70). Interestingly, the gene for TBP-2/VDUP1 is mutated in spontaneously hyperlipidemic mice (1). Now the relationship between lipid metabolism and tumor suppression is under investigation.

Serum/plasma levels of Trx1 are good for evaluating the oxidative stress in a variety of disorders. In human immunodeficiency virus (HIV) infection, plasma levels of Trx1 are elevated in association with decreased levels of intracellular glutathione in lymphocytes and poor prognosis (41, 43). Recently, the importance of Trx1 in the entry of HIV into T cells

has been discussed (34). Among chronic liver diseases, the pathogenesis of not only hepatitis C virus (HCV) infection, but also nonalcoholic steatohepatitis (NASH), is deeply associated with oxidative stress. Serum levels of Trx1 are valuable to estimate the oxidative stress in NASH (57), as well as in HCV infection (29, 56). In cardiovascular disorders, serum levels of Trx1 are elevated not only in acute ischemic heart disease (37, 38), but also in chronic heart failure (20), and may be valuable for estimation of chronic oxidative stress (55).

Transgenic mice overexpressing human Trx1 systemically under β-actin promoter are more resistant to various oxidative stresses and survive longer than control C57BL/6 mice (36). Compared with control C57BL/6 mice, Trx1 transgenic mice are more resistant to cerebral infarction (60), retinal photooxidative damage (62), adriamycin-induced cardiotoxicity (54), bleomycin or inflammatory cytokine-induced lung injury (13), influenza viral pneumonia (44), renal ischemia–reperfusion (19), thioacetamide-induced acute hepatitis (48), and so on. When embryos of control mice were cultivated *in vitro* under 25% oxygen, growth was significantly disturbed and various anormalies were induced. In contrast, embryos of Trx1 transgenic mice can grow normally even under such oxidative stress. The importance of the Trx system in the neonatal period is reviewed by Das (5).

Exogenous Trx1 can enter into cells and attenuate intracellular reactive oxygen species generation and cellular apoptosis (22). Administration of recombinant human Trx1 is beneficial for clinical application, including acute lung injury associated with leukocyte infiltration (13, 42). Recently, we reported that exogenous Trx1 attenuates autoimmune myocarditis (26), which was cited in the Editorial in *Circulation* (27). Tao *et al.* also reported that Trx1 attenuates myocardial infarction and *S*-nitrosation of Cys^{69} enhances the cardioprotective effect (64). Continuous infusion of recombinant Trx1 attenuates cerebral infarction (9). We have just started a translational research program to treat patients with acute lung injury by administration of recombinant human Trx1 protein.

The expression of Trx1 is diminished in the aorta in spontaneously hypertensive rats (63). Trx1-inducing agents may be beneficial for the prevention of metabolic syndromes, including hypertension. We previously reported that geranylgeranylacetone (GGA) induces Trx1, as well as heat shock protein-72 (12). Trx1 plays an important role in ischemic preconditioning (4). GGA pretreatment suppresses several oxidative stress-associated cytotoxicities by induction of Trx1. Now we have more possible inducers of Trx1, especially among foods. Ebselen is a seleno-organic compound with Prx-like activity and also another good candidate to attenuate oxidative stress as an antioxidant (71).

The research on Trx and its related molecules is rapidly ongoing. We will have more novel news in this field next time.

ABBREVIATIONS

ASK1, apoptosis signal-regulating kinase 1; ER, endoplasmic reticulum; GGA, geranylgeranylacetone; GIF, glycosylation-inhibiting factor; Grx, glutaredoxin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MIF, macrophage migration inhibitory factor; NASH, nonalcoholic steatohepatitis; PC-TRP, plasma cell thioredoxin-related protein; PDI, protein disulfide isomerase; Prx, peroxiredoxin; TBP-2, thioredoxin-binding protein 2; TGR, thioredoxin and glutathione reductase; TMX, transmembrane thioredoxin-related protein; TRP14, 14-kDa thioredoxin-like protein; Trx, thioredoxin; TrxR, thioredoxin reductase; Txl-2, thioredoxin-like protein 2; VDUP1, vitamin D3 up-regulated protein 1.

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