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Forum Review

Regulation of the Mammalian Selenoprotein Thioredoxin Reductase 1 in Relation to Cellular Phenotype, Growth, and Signaling Events

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ABSTRACT

Reactive oxygen species (ROS) are generated as toxic by-products of aerobic metabolism, but are also essential biomolecules in cell signaling. The thioredoxin (Trx) system is a major enzymatic system modulating ROS levels and is important for redox regulation of cellular function. It consists of Trx and thioredoxin reductase (TrxR), which reduces Trx using NADPH. Most, if not all, of the functions of Trx depend on the activity of TrxR. Mammalian TrxR enzymes are selenoproteins with broad substrate specificities, and alteration of cytosolic TrxR1 expression and activity is likely to be an important determinant for the control of cellular redox regulation. TrxR1 activity in cells seems to be modulated by an intricate interplay, involving a housekeeping type promoter in combination with alternative splice variants and transcriptional start sites, posttranscriptional regulation through AU-rich elements, inactivation by electrophilic agents and by itself modulating the effects of several key signaling molecules. TrxR1 activity is also intimately linked with several aspects of selenium metabolism, and hence selenoprotein function in general. Here, we summarize the current knowledge of these different levels of TrxR1 regulation in diverse cell types and in response to growth and signaling events.
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BACKGROUND

THE THIOREDOXIN (TXR) SYSTEM is found in nearly all living organisms and consists of Trx, thioredoxin reductase (TrxR), and NADPH. Trx is a small, ubiquitously expressed redox-active protein that is reduced by TrxR using NADPH, having a wide range of cellular functions (5, 79). Several isoforms of human Trx are known today (73, 87, 88, 103), but the classical form (Trx1) is yet by far the best studied. In most organisms, Trx is highly important for the synthesis of deoxyribonucleotide building blocks for DNA synthesis in its role as hydrogen donor for ribonucleotide reductase, although this particular function is not completely clear in all mammalian cell types (38). In mammals, many additional cellular functions are, however, known for Trx. These include important roles in antioxidant defense, both by direct catalysis of several antioxidant reactions (79) and by regeneration of other antioxidant enzymes such as peroxiredoxins (19) and methionine sulfoxide reductases (75). Trx is also important for gene regulation by modulating the activities of several transcription factors, including nuclear factor-κB (NFκB), Fos, and Jun (1, 94), as well as Ref-1 and p53 (42, 112). Furthermore, Trx indirectly affects the overall activity of mitogen-activating protein (MAP) kinases and their counteracting phosphoprotein phosphatases, as the latter are easily inhibited by reactive oxygen species (ROS), thereby allowing increased protein phosphorylation at events of oxidative stress, which is modulated by Trx (23, 95). Trx also directly controls apoptosis signal-regulating kinase 1 (ASK-1), a MAP kinase kinase kinase, by a specific inhibitory binding of reduced Trx to ASK-1. This binding is released when Trx is oxidized, thereby contributing to apoptotic induction at certain events

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of increased oxidative stress (89, 111). Moreover, Trx is involved in signaling mediated by nitric oxide (NO), by indirect effects linked to oxidative stress and redox regulation of NO synthase (NOS) isoenzymes (99), but also directly by nitrosylation of the structural cysteine 69 in Trx, a nitrosylation that seems to regulate the activity of Trx (37). These many functions of Trx may affect the cell in a most complex manner. Depending on the cellular (or subcellular) context in which Trx is active, it may lead to altered cellular function, increased viability, cellular proliferation or differentiation, or induction of apoptosis. Trx itself is also known to be subject to a complex pattern of regulation. The vitamin D3-up-regulated protein 1 (VDUP-1) is a natural endogenous inhibitor of Trx, which seems to play a highly important role in regulation of cellular function (50, 52, 78, 90, 102). Moreover, the promoter of the Trx gene is rather complex, responding to either hemin or phorbol 12-myristate 13-acetate (PMA) by differential effects of either Nrf2 or Fos and Jun at the same antioxidant responsive element (54). Furthermore, Trx may change from its cytosolic localization to the nucleus or extracellularly, where it may act in transcription factor control (43), or as either cytokine (for review, see 77) or chemokine (13), respectively. Several extensive reviews have been published on the function and regulation of Trx (46–48, 67, 77–79, 99), and this shall therefore not be discussed in further length in this article, where we instead will focus on the cellular regulation of TrxR1. However, we would like to emphasize that for most, if not all, of the functions of Trx its redox state is of essential importance, *i.e.,* whether the redox-active motif of Trx is in the disulfide or dithiol state will determine its function. Therefore, the activity of TrxR1 is an integral part of the many functions of Trx, as schematically summarized in Fig. 1.

Mammalian TrxR has a broad substrate specificity and is a selenoprotein containing a penultimate C-terminal selenocysteine residue necessary for the catalytic activity (28, 109, 118–120). Mammalian TrxR reduces the active site in oxidized Trx, but can also reduce several low-molecular-weight compounds, such as dithionitrobenzoic acid (45), lipoic acid (6), and selenite (59). This broad substrate specificity is explained by the C-terminally located tetrapeptide motif carrying the selenocysteine residue, with which a neighboring cysteine residue forms a reversible selenenylsulfide/selenolthiol redox-active motif, which should be easily accessible to the many substrates as well as inhibitors of the enzyme (10, 34, 79, 91, 120).

Three separate TrxR isoenzymes are found in mammals: the classical cytosolic TrxR1, a mitochondrial (TrxR2) isoform (61, 72, 104), and one isoenzyme expressed mainly in testis (104), all sharing the same overall domain structure and selenocysteine-containing active-site motif. However, in contrast to TrxR1 and TrxR2, the testis-specific enzyme also has an additional N-terminal monothiol glutaredoxin domain and, in contrast to the other two isoenzymes, can also directly catalyze the reduction of glutathione disulfide. It was therefore named "TGR" for thioredoxin and glutathione reductase (105).

As briefly summarized above, rather much is known about the cellular effects of Trx and its regulation. As a complement to other reviews of the Trx system (referred to above and also found in the present Forum issue of *Antioxidants & Redox Signaling*), we shall here summarize our present understanding of the regulation of the cytosolic isoenzyme TrxR1 in relation to cellular phenotype, growth, and signaling events. Although several aspects of this regulation are yet unknown, recent findings suggest an intricate pattern of TrxR1 regulation. This is probably explained by its presumed dual role of a housekeeping antioxidant enzyme, as well as a key player in redox control of cellular function.

LEVELS OF REGULATION

All regulation of protein expression can be controlled at different levels for either immediate or long-term responses, which should be true also for the control of TrxR1. The transcriptional level of regulation involves proximal promoter regions with or without distal enhancers or regulation via histone acetylation and methylation (35). Subsequent control of gene expression may occur posttranscriptionally or posttranslationally, and quick regulation of mRNA levels may be mediated through elements in the 5′ or 3′ untranslated regions (UTRs) (9, 100). This type of regulation is also of importance for TrxR1. The genomic organization, different regulatory elements, and cDNA variants are schematically illustrated in Fig. 2. Furthermore, being an enzyme, TrxR1 may also be regulated by interactions with substrates or inhibitors of enzyme activity, and as a selenoprotein, it is dependent on an adequate selenium supply. Notably, the exposed selenolthiol of reduced TrxR makes the enzyme highly susceptible to a number of electrophilic compounds acting as efficient inhibitors due to rapid derivatization of the selenocysteine residue. We shall now summarize our current concept of the different levels of TrxR1 regulation, and the reader is referred to Figs. 1 and 2 throughout this summary.

REGULATION OF THE PROMOTER OF TRXR1

The proximal promoter region for human TrxR1 was recently identified (86). Deletion constructs revealed that the promoter activity was maintained in both HeLa and A549 cells within the −115 to +167 region; that narrow region was therefore considered to encompass the core promoter. The core promoter contained a POU motif that was shown to bind the Oct-1 transcription factor, and two GC-rich regions were found to bind Sp1 and Sp3. Lack of a classical TATA box in combination with an increased GC content with functional Sp1 sites, as well as a predicted CpG island close to the transcriptional initiation site, was a typical finding for a promoter of a housekeeping gene (51, 86, 108). Mutational studies of the human core promoter have subsequently shown that the transcriptional activity is not solely dependent on the presence of the previously found Sp1/Sp3 tandem motif, because ~50% of the transcriptional activity remained after mutations of these sites (our unpublished observations). Therefore, other not yet identified transcription factors must also be of importance for the basal transcriptional activity of the

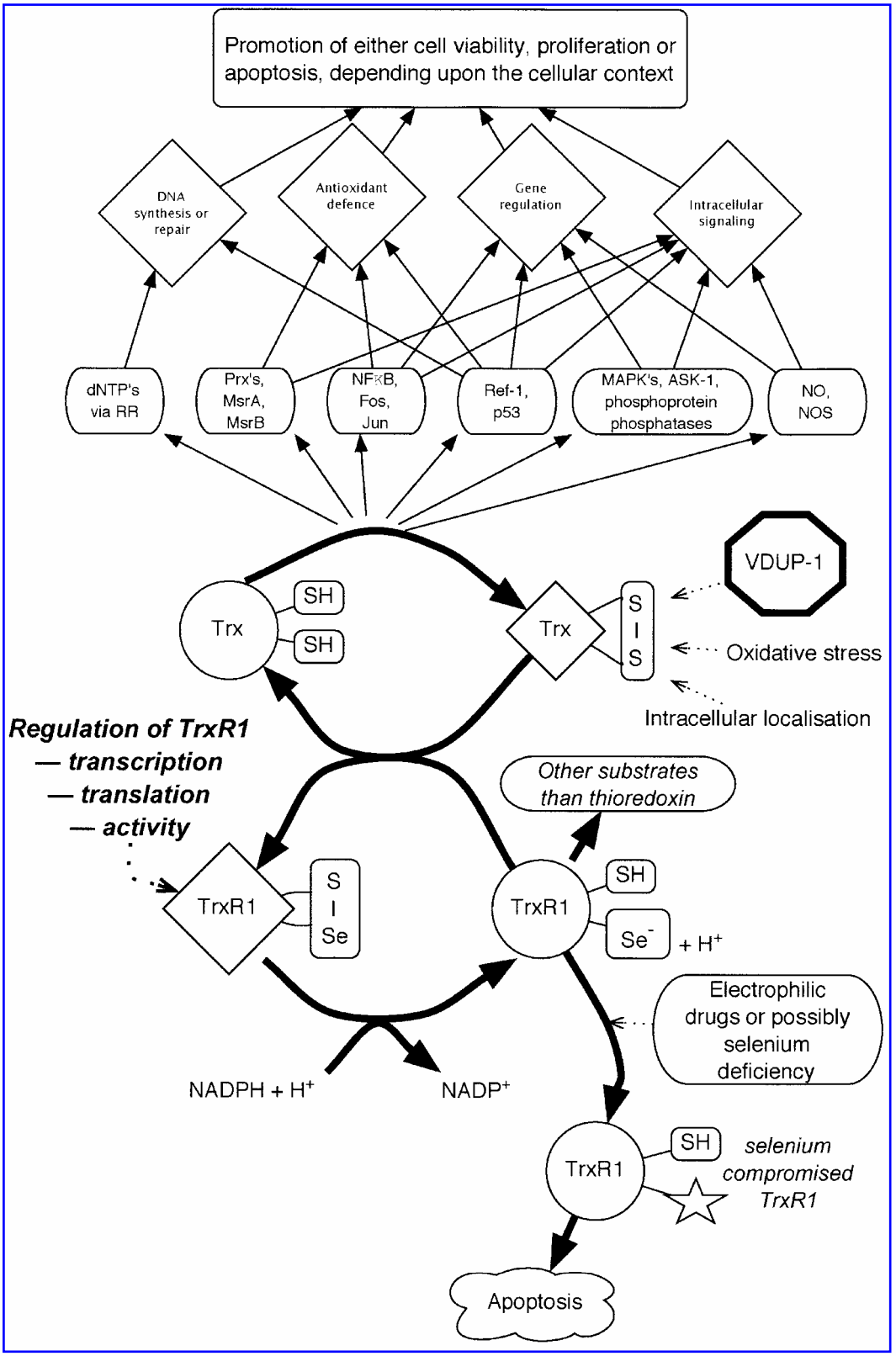

FIG. 1. The Trx system and its targets. A schematic figure illustrating the many functions of the Trx system in mammalian cells. These diverse functions are likely to be affected by the regulation of TrxR1 expression and activity, being the subject of this review. Please see text for further details.

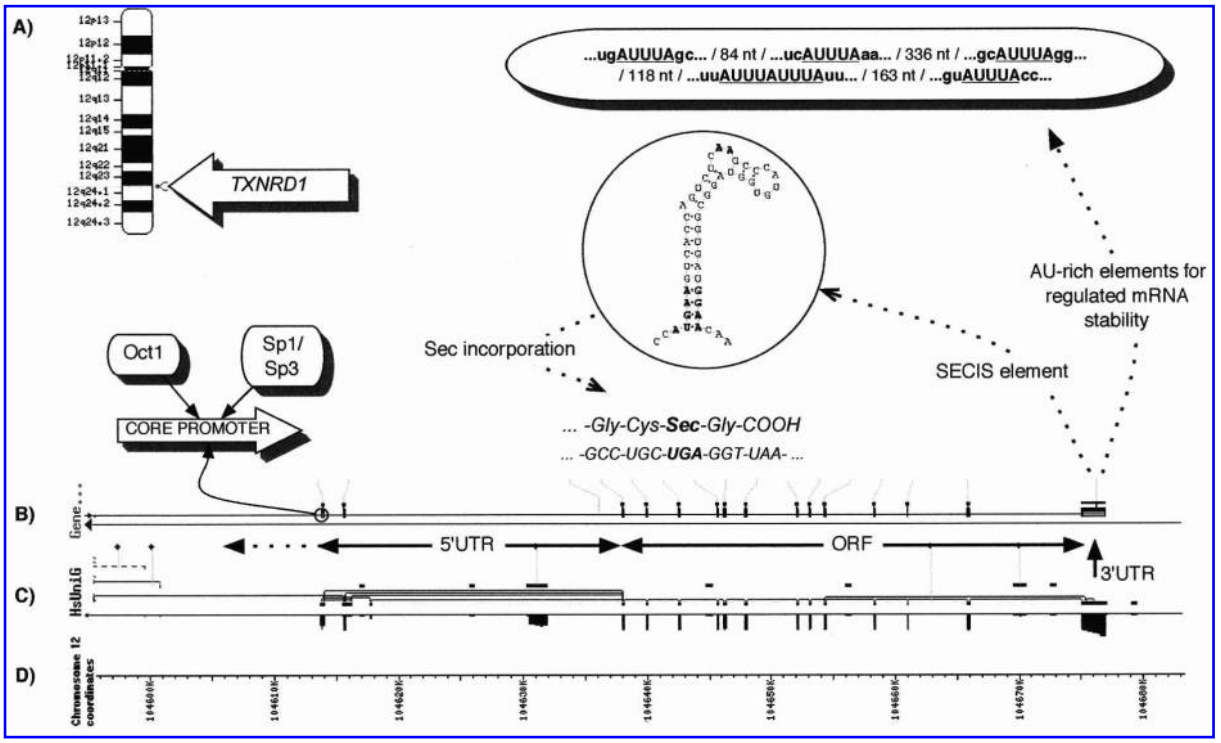

FIG. 2. Scheme of the human TrxR1 gene and its regulation. (A) The localization of the *TXNRD1* gene on human chromosome 12 is indicated, as given by NCBI (http://www.ncbi.nlm.nih.gov/blast) and experimentally verified as being located to 12q23–12q24.1 using *in situ* hybridization (26). **(B)** The exon organization of a typical TrxR1 transcript is schematically shown, indicating the localization of the core promoter, as well as the exons forming the 5′-UTR, the open reading frame (ORF), and the 3′-UTR. Shown also is the localization of the SECIS element in the 3′-UTR as well as its secondary structure, as given by the SECISearch algorithm (56, 57; http://genome.unl.edu/SECISearch.html). The SECIS element is necessary for selenium incorporation as selenocysteine (Sec) at the C-terminal redox-active tetrapeptide motif –Gly-Cys-Sec-Gly-COOH, with Sec endoced by a UGA codon. In the 3′-UTR, the human transcript for TrxR1 also carries six AREs (AUUUA motifs) that are important for regulation of the mRNA stability; the core of these motifs and their distance from each other within the 3′-UTR are indicated in the figure. Most transcripts for TrxR1 arise from the housekeeping-type core promoter found in humans to involve the Oct1, Sp1, and Sp3 transcription factors, as indicated in the figure. Note, however, that transcripts may also arise from other transcriptional start sites and, in addition, the TrxR1 mRNA arising from the core promoter seems also to be spliced in several different variants. This is indicated in **(C)** summarizing the alignment of the different EST variants of the UniGene TrxR1 cluster Hs.13046 (http://www.ncbi.nlm.nih.gov/UniGene) to the genomic sequence. Splice variants are shown by the different horizontal lines, with the frequency of each separate exon in the EST cDNA sequences being indicated by the inverted bar graph. **(D)** The chromosomal coordinates are given, showing that the exons of the most common variants of TrxR1 span ~65,000 nucleotides, whereas rare primary transcripts may be considerably longer. See text for further details.

TXNRD1 gene. Furthermore, housekeeping-type promoters also may have additional responsive promoter elements and distant enhancers or silencers, and the *TXNRD1* promoter is far from fully characterized. Interesting to note is that Sp1 and Oct-1 are known to be able to interact (36), and this may be one mechanism taking part in executing and also regulating the basal activity of the TrxR1 promoter. It is furthermore known that both Sp1 and Sp3 usually bind to the same GC boxes, as in the core promoter for TrxR1, and that Sp3 may act as either a repressor or an activator depending on the cellular context (for review, see 107). Variation in the ratio between Sp1 and Sp3 has been proposed as a mechanism for promoter regulation, and like many other transcription factors, both Oct-1 and Sp1 are known to be sensitive to their redox status (64, 115), which adds to the complexity of TrxR1 regulation. Alignment of the genomic *TXNRD1* upstream region in mouse with the corresponding human sequence revealed two conserved AP1 binding sites and a conserved CAAT box (upstream of the proposed core promoter), while the mouse sequence seemed to lack Sp1/Sp3 and Oct-1 sites corresponding to those that are active in the human core promoter (82).

Several variants of TrxR1 with different 5′ regions originating from alternative transcriptional start sites have been identified (82, 85, 106). It is likely that differential splicing and/or alternative transcriptional start sites play an important role in the regulation of TrxR1 expression, although the mechanisms or details of this level of regulation are yet unknown. However, we can state that transcription initiation at the previously characterized core promoter appears to be the most common event in many cell types, hence generating the clear majority of the transcripts for TrxR1 (unpublished observations).

POSTTRANSCRIPTIONAL REGULATION OF TRXR1

Mammalian TrxR1, as well as the mitochondrial TrxR2, was recently shown to exhibit alternative splicing around the first exon (62, 82, 85, 106) (Fig. 2C). In mouse and rat, at least three forms differing in the 5′-end have been identified. One of the splice variants harbors an additional upstream ATG that can encode an N-terminally elongated protein of 67 kDa instead of the common 55-kDa form (106). In humans, five different 5′ cDNA variants have been reported and a human TrxR1 variant protein with an apparent mass of 67 kDa was detected (106), which could possibly correspond to the murine splice variant, although this has not been confirmed. The function of different first exon splice variants of TrxR1 is far from clarified, but could possibly be coupled to tissue- and/or cell-specific regulation of expression at the mRNA level.

The 3′-UTR of all mammalian TrxR isoenzymes contains a selenocysteine insertion sequence (SECIS) element (Fig. 2B) that is necessary for selenocysteine incorporation (22, 27, 53, 62, 119). The SECIS element of TrxR1 has also been shown to be moderately responsive to selenium supplementation, but seems to be highly active under standard cell culturing conditions (27). Selenium may affect TrxR1 on many levels; this is discussed in more detail below.

The 3′-UTR of TrxR1, in addition, contains a cluster of AUUUA sequences [AU-rich elements (AREs)] (Fig. 2B), which in untreated cells lead to a rapid TrxR1 mRNA turnover (27, 55). Koishi *et al.* in fact cloned TrxR1 (called KDRF) as an ARE-containing rapidly responding mRNA, using screening with a TAAAT-rich probe of a cDNA library from KM-102 cells stimulated with PMA and calcium ionophore (55). AREs are typically found in cytokine, protooncogene, transcription factor, and other mRNA having rapid posttranscriptional up- or down-regulation in response to signaling events (20). Regulation via AREs enables quick expression responses to various stimuli, mediated by a specific block in mRNA degradation through ARE-interacting proteins, in turn responding to altered intracellular signaling (20). Promotion of cellular transformation and oncogenesis has been connected to inactivation of AREs in growth factors and protooncogenes. For example, stabilization of *c-myc* mRNA by deletion of the AREs promotes oncogenic transformation *in vitro* and is linked to human T-cell leukemia (2). A TrxR1 shorter mRNA variant lacking the AREs was cloned as cDNA from tissue of rat neuroblastoma (119), and subsequent transfection studies showed that a similar shorter cDNA (containing the SECIS and lacking the AREs) resulted in higher TrxR1 mRNA, protein, and activity levels (22). This could thereby be an indication of yet an alternative regulation at the posttranscriptional level of TrxR1. The 3′-UTR of the mitochondrial TrxR2 does not contain AREs.

POSTTRANSLATIONAL REGULATION OF TRXR1—INHIBITION OF THE ENZYME

In cells, the TrxR1 protein was reported to be rapidly inactivated by ROS targeting the selenocysteine residue, and the enzyme was thus proposed to work as a redox sensor of cells (104). ROS are important mediators of signal transduction pathways (for reviews, see 39, 110), and direct oxidation of the selenol group of TrxR1 with subsequent oxidation of Trx may affect many cellular components dependent on reduced Trx (Fig. 1). The "redox sensor" view of TrxR1 is thereby an attractive model linking ROS and signaling events. However, the TrxR1 protein is not inactivated by ROS *in vitro* (16, 118), and the mechanism for inactivation of TrxR1 in cells is therefore not clear.

Recently, electrophilic prostaglandin derivatives and other lipid aldehydes were demonstrated to target rather specifically and directly the TrxR1 protein and hence inhibit the enzyme (74). A number of other nonendogenous electrophilic compounds were already known inhibitors of mammalian TrxR1. These include low-molecular-weight compounds such as iodoacetic acid (80), arsenicals (65, 66), and gold compounds used in the treatment of rheumatoid arthritis (33). Several electrophilic anticancer drugs also have TrxR as a target for inhibition, for example, quinones (68, 69), nitrosoureas (32, 93), and cisplatin (7, 92). Dinitrohalobenzenes are another group of inhibitors of TrxR1 that, uniquely, also yield a derivatized enzyme with an increased NADPH oxidase activity that may play a role in their immunostimulatory properties (80). Inhibited TrxR1 may have many effects on cellular function linked to repressed Trx activity, as is clear from the scheme in Fig. 1. However, inhibited or selenium-deficient TrxR1 may also directly induce apoptosis, which is discussed below.

TRXR1 REGULATION AND FUNCTION IN RELATION TO CANCER

TrxR1 is widely expressed in many diverse tissues (26, 81, 84, 85). Elevated levels of TrxR1 have been found in a number of human cancer cell lines, including Jurkat and A549 cells (109), and TrxR1 protein and total activity was shown to be increased in colorectal tumors compared with normal mucosa (12). Expression patterns of TrxR1 were also examined in tumors and normal livers of TGFa/c-myc transgenic mice and in prostate cell lines derived from matched tumor and normal tissues, which also showed an increase of TrxR1 protein in tumors compared with normal tissues or cells (29). According to the expressed sequence tag (EST) cDNA occurrences for TrxR1 in relation to all other cDNA sequences, its transcript seems to be increased in many cancer forms, most notably liver, neuronal, and prostate cancer, whereas some cancer forms seem to have a lowered percentage of TrxR1 transcripts, such as skin cancer (Fig. 3). The fact that TrxR1 may be up-regulated in many tumors, together with the finding that TrxR1 mRNA is repressed in p53-overexpressing cells (29), indicates that p53 could be a negative regulator of the TrxR1 gene. This is further complexed by the redox regulation of p53, in which Trx and TrxR1 are vital components (112). The requirement of an active TrxR1 for normal and correct p53 maturation was recently demonstrated (74). Furthermore, selenium-compromised TrxR1 was recently shown to induce apoptosis when introduced into A549 cells. This

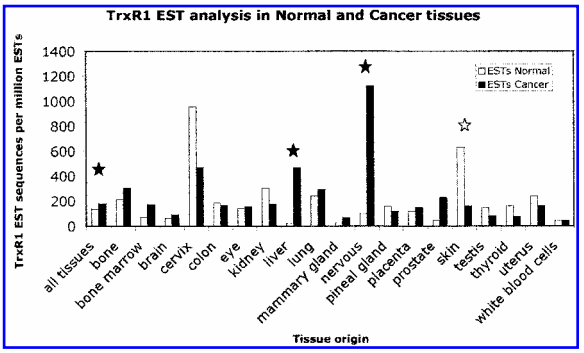

FIG. 3. TrxR1 EST analysis in normal and cancer tissues. Analysis comparing the frequency of TrxR1 EST clones (TrxR1 sequences per million ESTs) originating from selected normal (open columns) or cancer (filled columns) tissues. The tissues where the increase of TrxR1 EST clone frequency was statistically significant in cancer tissue are denoted with a black star (*i.e.,* all tissues combined, liver, nervous system, or prostate), whereas TrxR1 mRNA appears to be specifically down-regulated in skin cancer, as judged from this EST analysis (open star). These data were compiled from the "Virtual Northern" feature within the cancer genome anatomy project, NCI, using Unigene cluster Hs.13046. (see http://cgap. nci.nih.gov/Tissues/ VirtualNorthern).

was surprising because the effect occurred in substoichiometric amounts compared with the endogenous TrxR1 levels and hence probably not through an inhibition of the endogenous Trx system (4). The apoptosis-inducing effects of selenium-compromised TrxR1 corresponded well, however, with prior studies of the "GRIM-12" gene inducing apoptosis in a dominant manner, because the GRIM-12 constructs encoded a TrxR1 lacking the selenocysteine residue (4, 44). As selenocysteine in endogenous TrxR1 is a target for alkylation by several anticancer drugs (see above), the so generated selenium-compromised TrxR1 may hence directly promote apoptosis as part of the anticancer effect of such drugs (4). To conclude, the relation of TrxR1 regulation to cancer development or treatment is likely to be complex and not solely an issue of different TrxR1 levels. As TrxR1 may promote antioxidant defense and cell viability, this may naturally explain its overexpression in cancer cells and role as an anticancer drug target. On the other hand, the necessity of a functional TrxR for p53 maturation supports a role for TrxR1 as a protein protecting against development of cancer through actions of p53. The protective effects of selenium against cancer development (21) may therefore possibly be linked to the ref-1-dependent selenomethionine-induced maturation of p53 as a DNA repair enzyme (98). For this to occur, selenomethionine may possibly lead to an increased activity or synthesis of TrxR1, subsequently leading to an increased ref-1-dependent modulation of p53 by Trx (74, 112, 113).

TRXR1 REGULATION IN RESPONSE TO DIVERSE EXOGENOUS STIMULI

TrxR1 is known to display significant and fast modulation of protein as well as mRNA levels upon treatment of cells with different exogenous agents. We shall briefly summarize here some of these effects. Some of the published experiments using individual cell types are also listed in Table 1.

Incubation of the human epidermoid carcinoma cell line A431 with either epidermal growth factor or hydrogen peroxide resulted in a significant increase in the intracellular abundance of TrxR1 protein, although it may have been inhibited (104). A similar effect on the TrxR1 levels was also seen with 1-chloro-2,4-dinitrobenzene (DNCB) treatment (104). The mechanism for the induction of TrxR1 protein in these cases is not known. Human thyrocytes and HepG2 cells incubated with calcium ionophore (A23187) and PMA showed a marked increase in expression of TrxR1 (49), which has also been observed in mouse skin (58). PMA and A23187 together stimulate activation of the calcium-phosphoinositol cascade (114), and this suggests that an increase of TrxR1 expression can be triggered by calcium. Increased expression induced by A23187 has also been seen in human umbilical vein endothelial cells (HUVECs), although less pronounced probably due to the >10-fold higher basal TrxR1 levels in HUVECs as compared with thyrocytes and HepG2 cells (3). It was however proposed that the increased expression of TrxR1 seen upon use of calcium ionophore may not be the direct result of calcium signaling, but rather due to a general stress effect caused by A23187 (3). Incubation of HUVECs with PMA resulted in decreased TrxR1 levels (3), in contrast to the increase obtained with thyrocytes or HepG2 cells (49). In human bone marrow-derived stromal cells (KM-102), PMA alone and in combination with A23187 rapidly and significantly increased the TrxR1 mRNA levels within 4 h (55), which decreased thereafter (55). Incubation of these cells with lipopolysaccharides or interleukin-1β also resulted in a significant increase of TrxR1 mRNA after 4 h, which thereafter decreased to basal levels (55). In peripheral blood monocytes and myeloid leukemia cells (97), as well as in osteoblasts (96), TrxR1 mRNA levels were shown to be increased above basal levels in a fast but transient manner by vitamin D3 treatment.

Peroxynitrite is a highly cytotoxic NO-derived compound that may be formed by reaction of NO with superoxide (11). Peroxynitrite is a powerful oxidant and may react with a variety of biomolecules and with relatively high reaction rate constants with selenoproteins in general (8, 101). In HUVECs, peroxynitrite was consequently demonstrated to inactivate TrxR1 with a subsequent up-regulation of TrxR1 mRNA and protein levels (83). The up-regulation of TrxR1 in response to the initial inactivation of the enzyme by peroxynitrite may constitute a protective mechanism in HUVECs (83), but in another study exposure to NO gas lowered TrxR1 mRNA and protein levels in lung endothelial cells (116).

The bile acid taurochenodeoxycholic acid and the secondary bile acid deoxycholic acid were shown to up-regulate TrxR1 mRNA levels in a gastric carcinoma cell line (St 23132) and in colon cancer cells (HT-29) (60). The up-regulation of TrxR1 after deoxycholic acid treatment was similar to the effect of PMA (60). PMA is known to cause oxidative stress and was also shown to up-regulate TrxR1 mRNA levels in mouse skin (58). Deoxycholic acid was also shown to cause an oxidative burst, resulting in an up-regulation of TrxR1 mRNA and protein, which suggested a linkage between TrxR-dependent antioxidant defense systems and oxidative stress induced by bile acids (60).

TABLE 1. REGULATION OF TRXR1 IN DIFFERENT CELL LINES IN RESPONSE TO DIFFERENT EXOGENOUS STIMULI

Effect on TrxR levels	*Treatment*	*Detection method*	*Cell type*	*Origin*	*Reference*
Increased	A23187 (0.5 μ*M*)	Se75, western	HUVECs	Human umbilical vein endothelial	3
	A23187 (0.1 μ*M*)	Se75, western	Thyrocytes	Human thyrocytes	49
	Bile acids (TCDCA/DCA)	mRNA	St 23132	Human gastric cancer	60
	Bile acids (DCA)	mRNA/western	HT-29	Human colon cancer	60
	DNCB (30 μ*M*)	Immunoblot	A431	Human epidermoid carcinoma	104
	EGF (500 ng/ml)	Immunoblot	A431	Human epidermoid carcinoma	104
	Etoxomosir (1 m*M*)	RT-PCR	HepG2	Human hepatoma	70
	H_2O_2 (0.2 m*M*)	Immunoblot	A431	Human epidermoid carcinoma	104
	Hypoxia	mRNA	HT-29	Human colon cancer	12
	IL-1β (25 units/ml)	mRNA	KM-102	Human bone marrow	55
	Isothiocyanate (6 μ*M*)	mRNA	HepG2	Human hepatoma	117
	Isothiocyanate (6 μ*M*) + selenite (0.12 μ*M*)	mRNA/RIA/ activity	HepG2	Human hepatoma	117
	LPS (1 μg/ml)	mRNA	KM-102	Human bone marrow	55
	Peroxynitrite (0.2–1 m*M*)	mRNA/western	HUVECs	Human umbilical vein endothelial	83
	PMA (0.1 μ*M*)	Se75, western	Thyrocytes	Human thyrocytes	49
	PMA (10 ng/ml) + A23187 (0.2 μ*M*)	mRNA	KM-102	Human bone marrow	55
	PMA/A23187	Se75, western	HepG2	Human hepatoma	49
	PMA/A23187	Se75, western	HUVECs	Human umbilical vein endothelial	3
	PMA/A23187	Se75, western	Thyrocytes	Human thyrocytes	49
	Selenite (1 μ*M*)	Activity	A549	Human lung cancer	24
	Selenite (40 n*M*)	Activity	EAhy926	Human endothelial	63
	Selenite (1 μ*M*)	Activity	HT-29	Human colon cancer	24
	Selenite (40 n*M*)	Activity	HUVECs	Human umbilical vein endothelial	71
	Selenite (1 μ*M*)	Activity	MCF-7	Human breast cancer	24
	Selenite (0.1 μ*M*)	mRNA/activity	THP1	Human monocytic leukemia	97
	Selenite (0.12 μ*M*)	RIA/activity	HepG2	Human hepatoma	117
	Serum (10%)	mRNA	MCF-7	Human breast cancer	12
	PMA (0.1 μg/ml)	mRNA	HT-29	Human colon cancer	60
	Vitamin D3 (0.1 μ*M*)	mRNA/activity	THP1	Human monocytic leukemia	97
	Vitamin D3 (0.1 μ*M*)	mRNA (ddPCR)	FOB	Human fetal osteoblasts	96
Decreased	Gold thioglucose (10 μ*M*)	Activity	EAhy926	Human endothelial	63
	H_2O_2 (1 m*M*	Activity	IEC-6	Rat small intestine	40
	NO (8.5 ppm)	mRNA/activity	PAECs	Porcine pulmonary artery endothelial	116
	Peroxynitrite (0.2–1 m*M*)	Activity	HUVECs	Human umbilical vein endothelial	83
	PMA (0.5 μ*M*)	Se75, western	HUVECs	Human umbilical vein endothelial	3
	Zinc	mRNA	Rat intestine	Rat intestine	18
No change	Selenite (1 μ*M*)	Activity	HL-60	Human leukemia	24
	Selenite (1 μ*M*)	Activity	Jurkat	Human leukemia	24
	Selenite (0.12 μ*M*)	mRNA	HepG2	Human hepatoma	117
	Vitamin D3 (0.1 μ*M*)	Activity	FOB	Human fetal osteoblasts	96

DCA, deoxycholic acid; DNCB, dinitrochlorobenzene; EGF, epidermal growth factor; H_2O_2, hydrogen peroxide; IL-1β, interleukin-1β; LPS, lipopolysaccharide; TCDCA, taurochenodeoxycholic acid.

The exact molecular mechanisms mediating these fast responses of TrxR1 mRNA or protein levels to different exogenous signaling stimuli are not known.

REGULATION OF TRXR BY SELENIUM COMPOUNDS

The role and regulation of TrxR1 in cells are intimately linked to the effects and metabolism of selenium compounds. Not only is TrxR1 a selenoprotein and therefore dependent on an adequate selenium supply for its own synthesis, as discussed above, but the enzyme has also the capacity itself to metabolize a number of selenium compounds. The enzyme reduces selenite to selenide (17)—needed for selenoprotein synthesis—and also selenodiglutathione (14), a major intracellular selenium metabolite. TrxR1 may also directly reduce the active site of another selenoprotein, plasma glutathione peroxidase (15). Furthermore, methylated selenium was proposed to be an inhibitor of TrxR1 (25), but was later found to be an efficient substrate of the enzyme (31). Here, we shall

not discuss further the selenium-metabolizing properties of TrxR1, but instead summarize the known effects of selenium compounds on the regulation of TrxR1 expression or activity in a cellular context.

Selenium in the form of selenite (1 μ*M*) was shown to increase the TrxR1 mRNA levels two- to fivefold, linked to an increased stability of the mRNA with a longer half-life of 21 h as compared with 10 h in the absence of selenium (24). In contrast, Trx mRNA levels, stability, or protein levels were not affected by this selenium treatment. The same study also suggested that an increase in TrxR activity caused by selenium was first due to increased TrxR1 mRNA levels, followed by a subsequent increase in TrxR1 selenoprotein levels (24). Effects of selenium deprivation have been studied in rats fed a selenium-deficient diet, where TrxR activity decreased dramatically in kidney and liver, but TrxR activity in brain was not affected (41). This finding was interesting also in view of the possible neuroblastoma-derived variant of TrxR1 mRNA with shorter 3′-UTR lacking the AREs (see discussion above). Specific loss of TrxR activity upon selenium deficiency (and not the loss of other selenoproteins) was recently shown to cause an induction of heme oxygenase-1 (76).

Sodium selenite added to serum-free growth medium was shown to induce TrxR activity in several cancer cell lines, including MCF-7 breast cancer cells, HT-29 colon cancer cells, and A549 lung cancer cells (24). Surprisingly, Jurkat and HL-60 leukemia cells showed no increase in TrxR activity by selenium addition (24). Increased protein levels and activity of TrxR1 by selenium treatment were also demonstrated in HepG2 cells, where a synergy effect between sulforaphane and selenite was observed, which in turn protected against paraquat-induced cell death (117). Sulforaphane up-regulated the TrxR1 mRNA levels, whereas selenium addition did not affect the mRNA amount in that study, but instead induced TrxR1 at the translational level (117). Although selenite did not induce TrxR1 mRNA it could, however, delay the degradation of sulforaphane-induced TrxR1 mRNA. Moreover, the up-regulation of TrxR1 mRNA caused by sulforaphane was glutathione- and protein kinase C-dependent (117). Response to protein kinase C appears to differ between cell types, because its activation with phorbol esters causes a down-regulation of TrxR1 in HUVECs (3), but an up-regulation in thyrocytes (49) and mouse skin (58). Interestingly, TrxR1 may possibly reduce and thereby activate oxidized protein kinase C, which would suggest not an indirect, but a direct link between the activity of TrxR1 and signaling through protein kinase C (30).

CONCLUSION

We have summarized here our current concept of TrxR1 regulation in relation to cellular signaling events. It is clear that many details of this regulation are still unknown. It is nonetheless evident that the enzyme plays an important role in both antioxidant defense and redox regulation of signaling events. This may possibly explain the complex setup of intricate regulatory mechanisms that seem to act for this enzyme. As we have summarized, these appear to involve a combination of a basal housekeeping type transcription with alternative splicing events, alternative transcriptional start sites, posttranscriptional regulation of its mRNA levels, rapid interactions of the selenocysteine-containing active site with endogenous and exogenous electrophilic agents, and an intimate link to several levels of selenium metabolism. Detailed knowledge of which specific mechanism is the most important regulator of TrxR1 levels at a certain signaling event or in a particular cell type is yet to be aquired.

ABBREVIATIONS

AREs, AU-rich elements; ASK-1, apoptosis signaling kinase 1; DNCB, 1-chloro-2,4-dinitrobenzene; EST, expressed sequence tag; HUVEC, human umbilical vein endothelial cell; MAP, mitogen-activated protein; NFκB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; PMA, phorbol 12-myristate 13-acetate; ROS, reactive oxygen species; SECIS, selenocysteine insertion sequence; Trx, thioredoxin; TrxR, thioredoxin reductase; UTR, untranslated region; VDUP-1, vitamin D3-up-regulated protein 1.

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