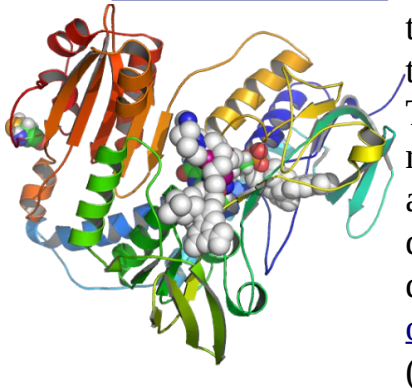
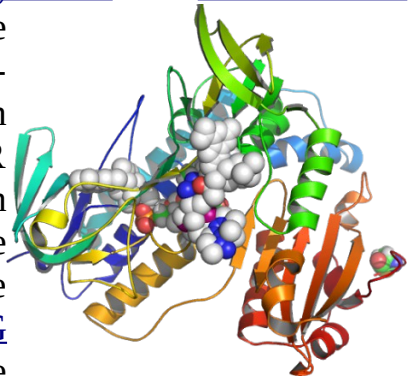
Thioredoxin reductase: Selenotetrapeptide sequences with specificity for thioredoxin and glutathione systems

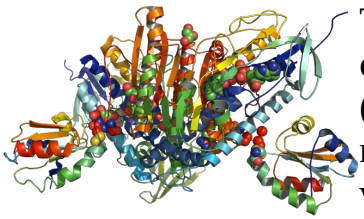
Thioredoxin reductase (EC 1.6.4.5) TXNRD1 (Alternate Symbols: GRIM-12, TR, TRXR) chromosomal position 12q23.3-q24.1 (§, ‡) is a homodimeric selenocysteine-containing enzyme. Secys a selenocysteine residue is an essential TR isozyme component, located near the C-terminus region [cysteine (Cys)-497,Secys-498] of the intracellular, redox cellular environments center in the catalytically active enzyme site, Gly-499 is the actual C-terminal amino acid. In their N-terminal sequences Cys-59, Cys-64 links the thiol/disulfide oxidoreductase dependent pathway reductases from there to the flexible C-terminal part (Secys) of the other sub cellular subunit by which Selenocystine is efficiently reduced and induce RNR (Ribonucleotide reductase) for replication and repair, where Trx reductase (TR) or oxidized GSH (GSSG) reductase further supply electrons for RNR. The protein reversibly modulates specific signal transduction cascades, to regulate multiple downstream intracellular redox-sensitive proteins that links NADPH and thiol-dependent processes which catalyzes NADPH-dependent reduction in the presence of the redox protein-Trx and thioredoxin reductase (TR) maintain cysteine residues in numerous proteins in the reduced state. There are three TXNRD selenoproteins 5-prime end variants essential for mammals, one V3 (TXNRD1) encodes an N-terminal glutaredoxin (GRX) these variants code for thioredoxin glutathione reductases (TGR). V3 associates with and triggers formation of Filopodia (cytoplasmic filaments) can guide actin in migrating cells, the emerging protrusions of cell membrane restructuring involved is in 'deglutathionylation values" for mitochondrial and cytosolic thioredoxin reductase (TR) domains. Characterization of the TR native Thioredoxin and glutathione systems (TGR) suggests that the lifecycle of E. granulosus and Schistosoma mansoni a phylum of Platyhelmintha, involves the TXNRD1_v3 isoform containing a fused (Grx) glutaredoxin domain which is abolished by deglutathionylation' targeted to either mitochondria or the nucleus in the reduction of glutathionylated substrates, in leishmaniasis (disease) glutathione reductase system (TGR) is replaced by the trypanothione reductase (TcTR) system in mammalian cells, essential as these TR3 are significant as a recognized drug target of these (TcTR) human protozoan parasites. Cytosolic TR1, mitochondrial - TR3 and TrxR2 (locus 22q11.21) where TrxR1 and TrxR2 are consdered as the respective cytosolic and mitochondrial



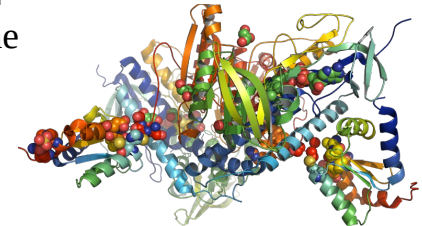
thioredoxin reductases, plus the thioredoxin glutathione reductases-TGR systems most likely can reduce (Trx) by fusion of the TR and an N-terminal glutaredoxin domains. As a pyridine nucleotide disulfide oxidoreductase of the oxidized GSH and GSSG (selenodiglutathione) reductase



TGR structures enzyme stability, are linked to the previously characterized two thioredoxin reductases cytosolic TR1 and TR3, and one mitochondrial variant. Selenols are key metabolites at mammalian TXNRD1's active (SeCys 498) site. Thioredoxin undergoes NADPH-dependent reduction (NTRs) and reduce oxidized cysteine groups on mitochondrial TXNRD1 proteins similar to the cytosolic enzyme, from the FAD binding domain where the active cystines and the NADPH binding domain are contained, plus an interface domain (ID) of the C-terminal interface homologous to glutathione reductase identifies a mechanism of p53 mediated cell death regulation involving (TrxR) enzymes of redox homeostasis reactions to overcome the oxidative stress generating reactive oxygen species (ROS) on a complex combination of decreased apoptosis to prevent permanent cell damage and cell death that tumor cells use to evade the redox-sensitive signaling factors, or resistance to therapy. End products of lipid-peroxidation, 4-HNE-(4-Hydroxynonenal) can induce oxidative stress, other isoforms are more water-soluble adducts detoxifying such a buildup, peroxidation might be limiting their (selenoproteins) proper expression. Thioredoxin reductase (TrxR) is the homodimeric flavoenzyme that catalyzes reduction of thioredoxin disulfide (Trx) one of the major redox control systems, involving a second interaction between NAD(P)H and/or (quinone reductase) NQO1 via the FAD-containing enzyme (TR), thioredoxin reductase forms an oxidoreductase system. TrxRs are able to reduce a number of substrate proteins other than Trx.



The 3' UTR of selenocysteine-containing genes have a common stem-loop structure, the sec insertion sequence (selenocystine-SECIS, PDB: 2ZZ0), that is necessary for the recognition of a catalytically active Sec codon rather in the values for mitochondrial and cytosolic thioredoxins reductase (TR) domains. The Sec residue is protonated at a different pka than in comparison to that of Cysteine. Cys59-Cys64 two cysteines pair also was oxidized in the N-terminal FAD domain essential for thioredoxin-reducing activity, and the need for Sec-498 (PDB: 2J3N) to be in complex with the FAD and NADP(+) during catalysis to the N-terminal active site cysteine residues Cys59-Cys64 and from there to the C-terminal part of the other subunit which have selenotetrapeptide sequences from the other module (PDB: 2J3N). Secys498 forms, (Human PDB 3QFB,) can both be identified at active site of the enzyme Gly-499 of the subunits active Cys-497-TRXR1 (the TR1 structure PDB: 3QFB) are the mechanism(s) for the incorporation of Se into TrxRs as the amino acid selenocysteine (Sec), as well as for delivery to a variety of secondary substrates or TRX (PDB: 3QFB) in nuclei provide means to quantify glutathione (GSH) (PDB: 3H8Q) conditions of the active GRX functonally and structurally analogus to TGR (selenodiglutathione) reductase. These two were modeled parts of TGR were linked to V3 (_TXNRD1) encodes an N-terminal inter-specific glutaredoxin (PDB: 1JHB). From the



FAD binding domain-(PDB: 1ZKQ) active cystines and the NADPH binding domain where they are contained, plus an interface domain (ID) of the C-terminal ID in complex with its substrate thioredoxin (Trx-PDB: 1TRX, TXNRD1-3QFB) bringing Cys32 in Trx1 close to Cys497 in 3H8Q to quantify glutathione (GSH) that helped in characterizing what was separately modeled as the Thioredoxin reductase (TXNRD1) domain which are consdered as the respective cytosolic and mitochondrial thioredoxin reductases units with a model obeying standard geometry that is conceivable of human thioredoxin reductase 1-2 and 3's structures glutaredoxin domain 3H8Q in complex with the FAD and NADP(H) when replaced by the TcTR (PDB: 2W0H) trypanothione/trypanothione reductase system involves a phylum of Platyhelmintha, where a glutathione (GSH) isoform containing a fused (Grx) glutaredoxin domain (PDB: 1JHB) is essential for the parasite survival. The intricate substrate specificities for the thioredoxin (Trx) system which consists of native Trx and the respective cytosolic mitochondrial thioredoxin reductase (TrxR) enzymes are likely to be of central importance to these observations as a determinant of TrxR function in general, each (the thioredoxin reductase/thioredoxin pathway) can reduce a number of different types of substrates or cross-reactive-bound enzyme fractions as active with thioredoxin.

[1.] Selenium yeast: seleno yeast PMID: 16857846
[2.] Sulforaphane From Broccoli PMID: 16377050, 12742546, 20204301, 12949356, 19595745, 17150329, 15740016, 12663510, 15998110, 17300148
[3.] Chlorella vulgaris: corresponding to a chloroplast NADPH-dependent thioredoxin reductase gene (NTR-C), in Chlorella PMID: 18029787
[4.] Scutellarin: It can be found in Scutellaria barbata and S. lateriflora. PMID: 15131321
[5.] Curcumin (TURMERIC plant of the ginger family): PMID: 21782934, 20160040, ~15879598
[6.] Experiments in E. huxleyi genus phytoplankton PMID: 20032866
[7.] Gambogic Acid pigment of gambooge resin from tree species Garcinia gummi-gutta. PMID: 24407164
[8.] Shikonin an antioxidant (no longer approved for use,: targets the Sec residue [13.] in TrxR1 to inhibit its physiological function. see: (Methane-) methylseleninic acid (MSA)) obtained from the extracts of plant [9.] Lithospermum erythrorhizon. PMID: 24583460
[10.] Black tea extract (BTE) theaflavin (TF) PMID: 19059456
[11.] Green tea extract-epigallocatechin-3-gallate (EGCG) PMID: 19020731
[12.] Eicosatetraenoic acid, (Mortierella Alpina Oil) Arachidonic acid (AA) all-cis-5,8,11,14-eicosatetraenoic acid, 5-Hydroxyicosatetraenoic_acid_and_5-oxo-eicosatetraenoic_acid PMID: 15123685
[13.] Juglone: In the food industry known as C.I. Natural Brown 7 and C.I. 75500. (DTNB assay, a synthetic approach for Cys and Sec residues.) PMID: 21172426, 11170645, 18382651 ... a 5,5'-[dithiobis Pyritinol: analogue, Sulbutiamine]

[14.] The antioxidant ubiquinol-10 (Q10) PMID: 12435734
[15.] Rottlerin, conductance potassium channel (BKCa++) opener, source the Kamala tree. PMID: 17581112
[16.] Ajoene a chemical compound available from garlic. PMID: 9986706