

Selenoproteins*

Jun Lu, Arne Holmgren¹

From the Medical Nobel Institute for Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institute, SE-17177 Stockholm, Sweden

¹To whom correspondence should be addressed. Tel.: 46-8-52487686;

E-mail: Arne.Holmgren@ki.se;

Fax: 46-8-7284716

Selenium is an essential micronutrient for man and animals. The role of selenium has been largely attributed to its presence in selenoproteins as the 21st amino acid, selenocysteine (Sec, U). Sec is encoded by TGA in DNA. A unique mechanism is used to decode the UGA in mRNA to co-translationally incorporate Sec in the growing polypeptide since there is no free pool of Sec. In the human genome 25 genes for selenoproteins have been identified. Selenoproteins like glutathione peroxidases, thioredoxin reductases or iodothyronine deiodinases are involved in redox reactions and Sec is an active site residue essential for catalytic activity. Selenoproteins have biological functions in oxidoreductions, redox signaling, antioxidant defense, thyroid hormone metabolism, or immune responses. They thus possess a strong correlation with human diseases such as cancer, Keshan disease, virus infections, male infertility, or abnormalities in immune responses and thyroid hormone function.

Selenium was discovered by the Swedish chemist Jöns Jacob Berzelius in 1817 and has been recognized as an essential trace element for many life forms including man since 1957 (1,2). The main form of selenium in mammalian proteins is as selenocysteine encoded by the TGA codon. Sec is co-translationally incorporated within

the growing polypeptide chain by an unusually complex machinery first described in *E. coli* (3) and also well-characterized from mammalian cells (1,2,4). Selenocysteine differs from cysteine by a single atom (Se versus S) and has similar chemical properties, but the lower pKa value (5.3) and stronger nucleophilicity of selenocysteine make it much more reactive. There is no free pool of selenocysteine in cells and during protein catabolism, Sec is broken down to elemental Se. One reason for no free selenocysteine pool is the risk of misincorporation of this highly reactive amino acid in the place of cysteine. Another reason is that selenocysteine as well as other selenium compounds like selenite redox cycles with oxygen and mammalian thioredoxin and thioredoxin reductase resulting in rapid NADPH oxidation and reactive oxygen species (ROS) formation (5,6). Selenoproteins and selenium molecular biology is covered in books and reviews (1,2). This minireview will focus on some well-characterized selenoproteins and their functions.

Biosynthesis of Selenoproteins

The incorporation of selenium as Sec into a selenoprotein requires a specific mechanism to decode the UGA codon in mRNA, which normally operates in translation termination (4). Selenite and selenate from food and water are used by

mammalian cells as Se sources and selenite is reduced to selenide by the glutathione-glutaredoxin and the thioredoxin systems (5,6). The exact mechanism of selenate reduction is not yet clear. Selenide may also be generated from dietary selenomethionine and selenocysteine by lyase action and used as a selenium source for Sec biosynthesis. Via the catalysis by selenoprotein selenophosphate synthetase 2 (SPS 2), the selenide is converted to monoselenophosphate, which is the active selenium donor in the conversion from the Seryl-tRNA^{Sec} into Sec-tRNA^{Sec} (7), where the Seryl-tRNA^{Sec} refers that serine is loaded onto Sec-tRNA at the beginning. The selenoprotein synthesis machinery including a specific secondary structure in the 3' UTR of selenoprotein mRNAs, termed a SECIS element, Sec specific elongation factor, Sec-tRNA^{Sec} and SECIS binding protein 2 (SBP2), ribosomal protein L30 43-KDa RNA binding protein, soluble liver antigen protein, and selenophosphate synthetase 1 thus work in concert to incorporate the Sec into a nascent polypeptide at the site encoded by UGA codon in mammalian cells (1,4).

Structure and Activity of Mammalian Selenoprotein

Selenoproteins exist in archaea, bacteria and eukaryotes with Sec as a key catalytic group, however, not all the species in these kingdoms. Yeast and higher plants do not have selenoproteins and components of the selenoprotein synthesis machinery, instead they express cysteine-containing homologues (7,8). Mammalian selenoproteins can be mainly classified into two groups according to the location of Sec (9) (Fig. 1). One group of selenoproteins possess Sec in a site very close of C-terminus of protein, such as in thioredoxin reductases (TrxRs), selenoproteins S, R, O, I, K. The

other group including glutathione peroxidases (GPxs), iodothyronine deiodinases (DIOs), selenoproteins H, M, N, T, V, W, SPS2, and selenoprotein 15 have Sec in the N-terminal part and in most cases possess thioredoxin fold structure and some selenoproteins contain CXXU motif, corresponding to the thioredoxin active site CXXC motif (10-13). From their structure it is apparent that the functions of most selenoproteins should be involved in the redox related reactions. In fact, the transcription of several selenoproteins such as TrxR1 and GPx2 are regulated by the redox sensitive transcription factor Nrf2/Keap1 system (14,15). Moreover, severe oxidative stress induces nuclear accumulation of SBP2 and blocks the Sec incorporation (2,16). The two main protein thiol reduction systems, thioredoxin or glutathione-glutaredoxin systems, are potential electron donors for oxidized SBP2 and may thus protect the cells by regulating the selenoprotein synthesis via controlling the SBP2 redox state and trafficking (16). The precise functions of many selenoproteins are still so far unknown. Overall, TrxRs, GPxs and DIOs are the three best characterized selenoprotein families. These selenoproteins have different enzymatic activities, but all require reductants to provide the electrons to make their catalytic redox cycle running (Fig. 2).

Thioredoxin Reductases—TrxRs in mammalian cells are members of the pyridine nucleotide-disulfide oxidoreductase family and three TrxRs have been identified in mammals: TrxR1 in cytosol/nucleus (17,18), TrxR2 in mitochondria (19,20), and thioredoxin glutathione reductase (TGR) in the testis (21), the latter also possessing glutathione and glutaredoxin reductase activity (Fig. 1) (21,22). Three-dimensional crystal structure of TrxR is similar to

glutathione reductase with FAD and NADPH binding domains and an interface domain (23). Besides the N-terminal –Cys-Val-Asn-Val-Gly-Cys- dithiol/disulfide, mammalian TrxRs contain a 16 residue C-terminal elongation with the conserved active site sequence -Gly-Cys-Sec-Gly-OH (24). The two subunits in the active homodimeric TrxR have a head to tail arrangement and the N-terminal redox active dithiol in one subunit and the C-terminal selenothiol active site of the adjacent subunit form a redox active center (23). The proposed mechanism of mammalian TrxR involves the N-terminal active site disulfide reduction by NADPH via FAD, then electron transfer from N-terminal active thiol to C-terminal selenenylsulfide bond in the opposite subunit of TrxR, and finally from C-terminal active site to the substrates (24,25) (Fig. 2A). The accessibility and the high reactivity of C-terminal active site selenolate confer mammalian TrxRs to have a wide range of substrates from small molecules such as selenite, lipid hydroperoxides, ebselen, dehydroascorbate to proteins like thioredoxin (Trx), protein disulfide isomerases or glutathione peroxidase, etc (2).

TrxR is the only enzyme able to reduce oxidized thioredoxin. Trx provides electrons to ribonucleotide reductase, which is essential for DNA synthesis by converting ribonucleotide to deoxyribonucleotides. The exact role of thioredoxin and glutaredoxin systems for ribonucleotide reduction in mammalian tissues is yet unknown. Thioredoxin can also reduce methionine sulfoxide reductase, and thioredoxin peroxidase (peroxiredoxin), and thus is involved in the repair of methionine sulfoxide oxidized proteins, or redox signaling via hydrogen peroxide (26,27). In addition, the thioredoxin system participates

in many cellular signaling pathways by controlling the activity of transcription factors containing critical cysteines in their DNA-binding domains such as NF- κ B, AP-1, P53, or the glucocorticoid receptor (28). It is also known that reduced Trx can bind to and inhibit apoptosis signal regulating kinase 1 (ASK1), whereas the oxidization of Trx results in the activation of ASK1 and induction of ASK1 dependent apoptosis (28). Therefore, TrxRs are involved in the control of cellular proliferation, viability and apoptosis through the control of Trx activity and redox state. The discovery of mammalian TrxR as a selenoprotein (17,18) occurred after its identification as a selenite reducing activity (5,6) and was a big surprise since bacterial and plant TrxR are smaller specific Cys-containing enzymes of entirely different structure and functions (28).

Glutathione Peroxidases—GPxs are well known to be the major components of the human antioxidant defense. In humans, there are now five Sec containing GPxs: the ubiquitous cytosolic GPx (cGPx/GPx1), the gastro-intestinal specific GPx (GI-GPx/GPx2), the plasma GPx (pGPx/GPx3), the ubiquitous phospholipid hydroperoxide (PHGPx/GPx4), and the olfactory epithelium and embryonic tissues specific GPx (GPx6) (9). GPxs1-3 catalyze the reduction of hydrogen peroxide and organic hydroperoxides, while GPx4 can directly reduce phospholipid and cholesterol hydroperoxides. The GPx4 is also involved in sperm maturation and male fertility since it has been found to be a main structural component of the sperm mitochondrial capsule in mature spermatozoa as an enzymatically inactive, oxidatively cross-linked, insoluble protein (29).

GPxs1-3 are homotetrameric proteins with a subunit molecular weight about 22-25 kDa, whereas GPx4 is a 20-22 kDa

monomeric enzyme. All known GPxs subunit structure exhibits the typical structure motif of thioredoxin fold (30-32). The core structure of the GPxs subunit thus consists of central β strands surrounded by several α -helices (Fig. 1). One helix connects anti-parallel β strand to neighboring β strand and forms a $\beta\alpha\beta$ substructure. The catalytically active Sec is normally located at the N-terminal end of the helix. The conserved catalytic triad of all these GPxs contains Sec, Gln, and Trp. The catalytic redox cycle involves the oxidation of Sec into selenenic acid by hydrogen peroxide and organic hydroperoxides and reduced into selenolate anion form by GSH (33)(Fig. 2B).

Iodothyronine Deiodinases—Three DIOs have been identified with a tissue and subcellular localization (34). DIO1 is found primarily in liver, kidney, and thyroid; DIO2 is in brain, pituitary, throid, skeletal muscle and brown adipose tissue; DIO3 is found in cerebral cortex and skin, and expressed at a very high level in placenta and pregnant uterus. DIO1 and DIO2 catalyze the deiodination of thyroxine (T4), the major thyroid hormone secreted by the thyroid gland, into active hormone 3,5,3'-triiodothyronine (T3), DIO 3 convert T4 into reverse-3,5,3'-triiodothyronine (rT3), and also T3 into T2. DIO 1 and 2 can also convert rT3 into T2 (34,35).

All the three DIOs are integral membrane protein of 29-33 KDa and share significant structural similarity; they belong to the thioredoxin fold protein family and contain a glycoside hydrolase clan –A-like structure (Fig. 1). DIO1 and DIO3 are localized at the plasma membrane, while DIO2 resides in the ER membrane. A common striking feature is the presence of active center in the pocket thioredoxin fold $\beta\alpha\beta$ motif (Fig. 1). The proposed

deiodination mechanism involved in the generation of oxidized DIO-SeI intermediate and thus the intermediate is reduced by thiol containing reductants and release iodide (Fig. 2C) (36). The identity of the DIOs reductant is currently unknown with the thioredoxin and glutaredoxin systems as prime candidates.

Some of the other selenoproteins have been cloned and characterized. For example, Sep 15 is also a member of the thioredoxin-like fold superfamily of proteins, highly homologous to the ER protein disulfide isomerase (PDI) and containing a surface-accessible, Sec-containing redox active motif (-CXU-). Sep 15 has been proposed to be involved in glycoprotein folding in ER, with a similar role as protein-disulfide isomerase (PDI). SelR, methionine-R-sulfoxide reductase (Msr) B1 (MsrB1), catalyzes the reduction of oxidised methionine (Met) residues (methionine sulfoxides). The oxidation of protein methionine occurs under oxidative stress and can lead to protein damage. SelR was shown to specifically reduce methionine-R-sulfoxides, and the Sec residue is crucial for enzymatic activity (37). Selenoprotein P is the selenoprotein with multiple Sec residues per protein subunit, in all 10 Sec residues, and present in the human plasma. The main role of SelP is to transport and delivery of selenium to the tissues. The additional role may serve as a heavy metal chelator or antioxidant (38).

Physiological and Pathophysiological Functions of Selenoproteins

Selenoprotein physiological and pathological effects are closely related with selenium status. Selenium deficiency leads to a dramatic loss of activity of selenoproteins including TrxRs, GPxs and DIOs. However, the expression of

selenoproteins exhibits a hierarchy style during selenium deprivation and repletion, the significance of specific selenoprotein in the specific tissues may determine the priority of the mRNA level and protein expression (39). For example, under selenium deficient condition, the activities of most selenoprotein in liver, kidney and lung decrease, whereas selenoprotein activities in brain remain at the similar level as during normal selenium supplementation. While selenium deficiency leads to a rapid loss of GPx 1 mRNA and protein level in liver, PHGPx and TrxR mRNA level are kept at a higher degree (39).

One example of severe selenium deficiency causing a human disease is Keshan disease, a potentially fatal form of cardiomyopathy which was firstly found in northeast of China (1). The disease occurred under the selenium deficiency combined with infection by Coxsackie B virus and has been prevented by selenium supplementation. A cardiomyopathy that resembles Keshan disease occurred when GPx1 knockout mice infected with a benign Coxsackievirus, suggesting that GPx1 is closely associated with the protection against virus infection (40).

Another good example to view the overall selenoprotein function in man is the SBP2 mutation (41). The defect in SBP2 induces a global decrease of selenoproteins activity and results in abnormal thyroid hormone metabolism. The amino acid substitution at R540Q resulted from a homozygous missense mutation and produced an abnormal thyroid phenotype associated with reduction in DIO2 enzyme activity and pre-pubertal growth retardation (41). This mutation lead to elevated total T4, free T4, and rT3 metabolites, but a low total and free T3 in three children of a Bedouin Saudi family. Another child from an unrelated

family exhibits the similar abnormal thyroid metabolism phenotypes and has a genetically prematurely terminated SBP2 protein lacking the C-terminal domain (41).

More specific roles of selenoproteins have been revealed by recent investigations by gene knockout techniques and several selenoproteins mutant human disease cases. Mutations of selenoprotein N cause rigid spine muscular dystrophy and the classical phenotype of multimimicore disease (42,43). One promoter genetic variation in selenoprotein S impaired SelS expression and influenced the production of inflammatory cytokines such as TNF- α , IL-6, IL-1 β , suggesting that selenoprotein SelS is involved in regulating inflammation (44). At least three selenoproteins TrxR1, TrxR2 and GPx4 are involved in embryogenesis, since deletions of the genes for these proteins for mice result in embryonic death. All GPx1, DIO1, and DIO2 knock out mice grow, develop and reproduce normally under laboratory conditions (40). However, GPx1 knock out mice are more sensitive to paraquat- and H₂O₂-induced oxidative stress. DIO2 knock out mice have impaired auditory function and thermogenesis, as well as mild brain function defects and temporary growth retardation (40). DIO1 knock out mice had abnormal excretion patterns of thyroid hormone metabolites including iodide. The DIO3 knock out model exhibited reduced viability, significant growth retardation, impaired fertility and hypothyroid symptoms with significantly reduced T3 and increased T4 levels (40). These studies reveal that selenoproteins play critical roles in antioxidant defense, fertility, thyroid hormone metabolism, immune response, and muscle development and functions.

Selenoproteins has been believed to be close linked with cancer and carcinogenesis

because there are numerous epidemiological reports on inverse correlation between selenium intake and occurrence of cancer risk for review see (2). However, the exact mechanism of how selenium intake protects from cancer is yet unknown. Large scale clinical trials with supplementation is under way against prostate cancer (2). As described above, many selenoproteins are involved in the antioxidant reaction, and can thus participate in the protection of normal cells against oxidative stress. On the other hand, when normal cell turns into a tumor cell, selenoproteins in the tumor switch their role to protect the malignant phenotype. It is therefore not surprising that TrxR and Trx have been found to be over-expressed in many aggressive tumors. Moreover, the tumor cell may require enough electrons from the Trx system for ribonucleotide reductase to keep up a constant DNA synthesis. Thus, the selenocysteine-containing mammalian TrxRs have emerged as new targets for anticancer drug development (45,46). The selenol has a low pKa value and selenocysteine in the open C-terminal –Gly-Cys-Sec-Gly active site of TrxR make the C-terminal easily attacked by electrophilic agents. Many anticancer compounds including clinical drugs such as the alkylation agents cisplatin, cyclophosphamide, or arsenic trioxide have been shown to be strong inhibitors of mammalian TrxR (46,47) and other various potent anticancer compounds curcumin, myricetin, and quercetin have strong irreversible inhibition on mammalian TrxR (48,49). The elucidation of TrxR and Trx roles in cancer biology may yield some promising anticancer paradigms for new cancer therapeutic agent development.

Abbreviations used are: Sec, selenocysteine;

Sec-tRNA^{Sec}, Selenocysteine tRNA; SBP2, SECIS binding protein 2; TrxR, thioredoxin reductase; Trx, thioredoxin; GPx, glutathione peroxidase; DIO, iodothyronine deiodinase; TGR, thioredoxin glutathione reductase; ASK1, apoptosis signal regulating kinase 1.

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Figure legends

FIGURE 1. Schematic representation of some selenoproteins. Selenoproteins can be divided into two groups according to the location of Sec: Sec is located in the very close of C-terminus of one group of selenoproteins, such as TrxRs, SelS, SleR, SelO, Sell; The other group have Sec in the N-terminal and normally possess thioredoxin fold structure. In most of these selenoproteins, Sec is located in in the pocket thioredoxin fold $\beta\alpha\beta$ motif.

FIGURE 2. Putative catalytic mechanism of some mammalian selenoproteins. A. The proposed mechanism of TrxR-dependent reduction involves electron transfer from NADPH to FAD, via the N-terminal active site of one subunit to the Cys-Sec selenenylsulfide bond within the C-terminal active site of the opposite subunit, and finally to substrate, Trx. **B.** The catalytic redox cycle of GPxs involves the oxidation of Sec into selenenic acid by hydrogen peroxide and organic hydroperoxides and reduced into selenolate anion form by GSH system. **C.** The proposed deiodination mechanism of DIOs involved in the generation of oxidized DIO-SeI intermediate and thus the intermediate is reduced by thiol containing reductants and release iodide.

Figure 1

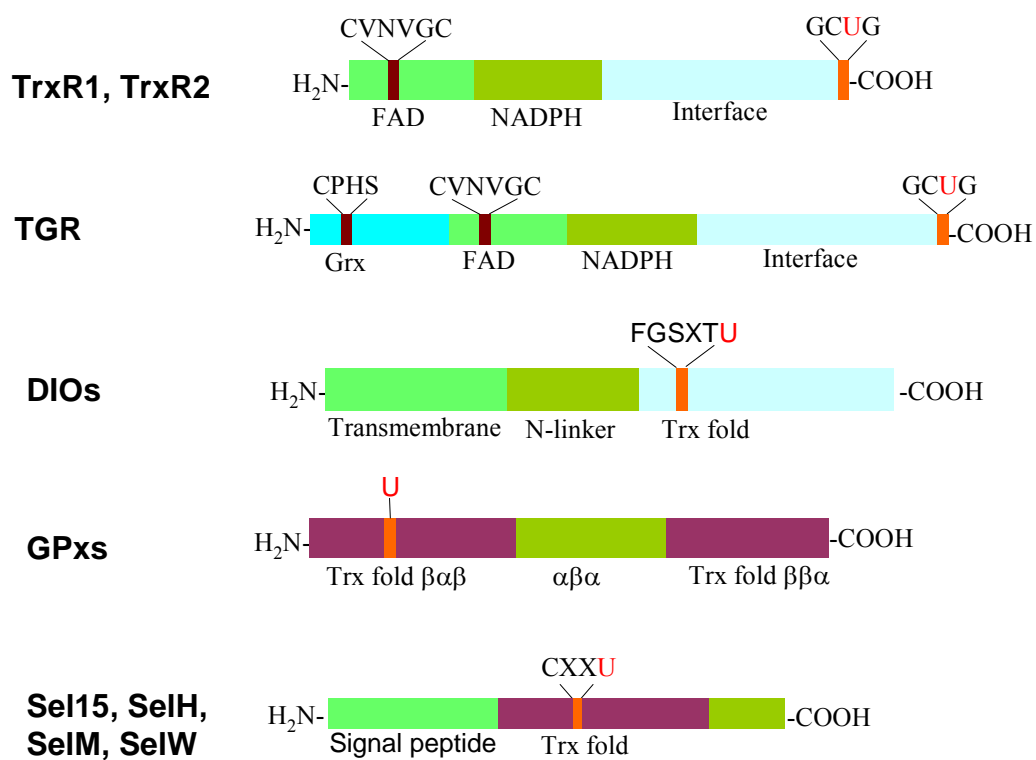


Figure 2

