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Comprehensive Invited Review

From Selenium to Selenoproteins: Synthesis, Identity, and Their Role in Human Health

LAURA VANDA PAPP,[1,2] JUN LU,[3] ARNE HOLMGREN,[3] and KUM KUM KHANNA[1]

Reviewing Editors: John W. Finley, Helmut Sies, John F. Stolz, and Gary Williamson

[1]Queensland Institute of Medical Research, Cancer and Cell Biology Division, 300 Herston Rd, Herston 4006, QLD Australia.
[2]School of Biomolecular and Physical Sciences, Griffith University, Nathan campus Australia.
[3]Medical Nobel Institute for Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institute, SE-17177 Stockholm, Sweden.

ABSTRACT

The requirement of the trace element selenium for life and its beneficial role in human health has been known for several decades. This is attributed to low molecular weight selenium compounds, as well as to its presence within at least 25 proteins, named selenoproteins, in the form of the amino acid selenocysteine (Sec). Incorporation of Sec into selenoproteins employs a unique mechanism that involves decoding of the UGA codon. This process requires multiple features such as the selenocysteine insertion sequence (SECIS) element and several protein factors including a specific elongation factor EFSec and the SECIS binding protein 2, SBP2. The function of most selenoproteins is currently unknown; however, thioredoxin reductases (TrxR), glutathione peroxidases (GPx) and thyroid hormone deiodinases (DIO) are well characterised selenoproteins involved in redox regulation of intracellular signalling, redox homeostasis and thyroid hormone metabolism. Recent evidence points to a role for selenium compounds as well as selenoproteins in the prevention of some forms of cancer. A number of clinical trials are either underway or being planned to examine the effects of selenium on cancer incidence. In this review we describe some of the recent progress in our understanding of the mechanism of selenoprotein synthesis, the role of selenoproteins in human health and disease and the therapeutic potential of some of these proteins. *Antioxid. Redox Signal.* 9, 775–806.

I. INTRODUCTION

The trace element selenium (Se) was discovered in 1817 by the Swedish chemist Berzelius, who named it after the moon goddess, *Selene*, in Greek. Today, almost 200 years later, selenium is well established as an essential trace mineral of fundamental importance to human health. Selenium is known primarily for its antioxidant activity and, in therapeutic aspects, for its chemopreventive, anti-inflammatory, and antiviral properties (262). Much of its beneficial influence on human health is attributed to its presence within at least 25 proteins (184). Unlike other metal elements that interact with proteins in form of cofactors, selenium becomes cotranslationally incorporated into the polypeptide chain as part of the amino acid selenocysteine (Sec). Although well established as the 21st genetically encoded amino acid in the selenium research field, Sec is yet to be included in the educational textbooks. The remarkable aspect of Sec incorporation into proteins is its shared definition with the UGA codon (60), which in most circumstances signals translation termination. This codon duality is circumvented by the presence of evolutionary conserved *cis*- and *trans*-acting elements and protein factors dedicated to decoding of UGA as Sec.

The group of proteins that contain Sec as an integral part of their polypeptide chain are defined as selenoproteins. Selenoproteins are present in all lineages of life (*i.e.,* bacteria, archaea, and eukarya). Between the domains, 30 selenoprotein families have been identified (59, 184, 185, 348). Selenoproteomes among species are generally small; the largest repertoire exists in fish with 30 individual selenoproteins, followed by humans and rodents with 25 and 24 selenoproteins, respectively (59). Their small size can be explained by a limited selenium supply in nature and a rather energy-expensive synthesis process. Yeast and higher plants lack selenoproteins and the components required for their synthesis; however, they do express cysteine (Cys)-containing homologues (184). For most selenoprotein families, Sec/Cys interconversion is commonly observed across the species (59).

The human selenoproteome consists of 17 selenoprotein families, some with multiple genes with similar functions (184). These include glutathione peroxidases (GPx) (five genes), thioredoxin reductases (TrxR) (three genes), iodothyronine deiodinases (DIO; three genes), and selenophosphate synthetases 2 (SPS2). The remaining selenoproteins have been annotated in alphabetic order and include the 15-kDa selenoprotein/Sep15, SelH, SelI, SelK, SelM, SelN, SelO, SelP/SepP, SelR, SelS, SelT, SelV, and SelW. Only a few of these proteins have been functionally characterized. These include the GPxs, the TrxRs, SPS2, and DIOs, which all have oxidoreductase functions. Mapping the selenoproteomes in species across the domains has paved the way for the main challenge within the selenium field: the functional characterization of these proteins and their involvement in the etiology of disease.

II. FROM SELENIUM TO SELENOPROTEINS

A growing interest exists in understanding the biologic role of selenium, in particular its physiologic role in human health, in the prevention of diseases, and in its potential use as a therapeutic agent. The pathway of selenium into protein is a rather complex one. In this section, we briefly address the biology of selenium and emphasize in greater detail the molecular mechanisms that entail its incorporation into selenoproteins. A simplified overview of selenium metabolism in mammals is depicted in Fig. 1.

A. Selenium in biologic systems

The entry point of selenium in animals is *via* plants, which absorb the element in its inorganic form from the soil. On a global scale, selenium availability in the soil varies between areas. Low selenium content is observed in volcanic regions and in regions with "acid soil," such as the southeastern parts of the United States (239, 298). The presence of other elements, such as sulphur, aluminium, and iron, also negatively affects the uptake of selenium by plants (165, 305). Consequently, selenium deficiency–linked disorders in animals and humans have been documented in such areas, and where the food is produced mainly locally. In plants, selenium becomes converted to organic forms such as methylated low-molecular-weight selenium compounds and the amino acids selenomethionine (SeMet) and Sec. SeMet is the major selenocompound in cereal grains, legumes, and soybeans, and although it serves as a major precursor for Sec synthesis in animals, additional selenium metabolites also are available for this process (reviewed in 331).

In biologic systems, Sec, viewed as the analogue of Cys, is probably the most biologically active form of selenium. The difference between the two amino acids is that at physiologic pH, the selenol group of Sec exists in the more-reactive, ionized form, whereas the thiol group of Cys is protonated and less reactive (289). Importantly, selenium compounds have the ability to redox cycle and are metabolized to more-reduced states, whereas sulphur compounds become more oxidized. These differences are proposed to account for selenium compounds being more effective antioxidants and more potent cancer-preventive agents than their sulphur analogues (158, 329). For a comprehensive discussion of selenocompounds, their distribution, and their metabolism in plants and animals, the interested reader is recommended these recent reviews (44, 331).

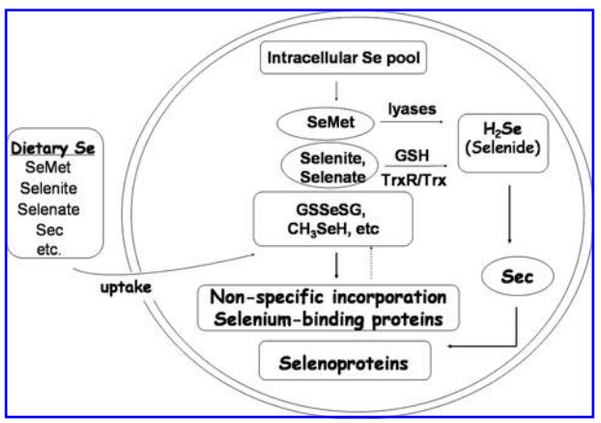

FIG. 1. Selenium metabolism in mammalian organisms. Dietary selenium metabolites are taken up into the cell, where, together with the existing intracellular pool, they become metabolized by different pathways, ultimately to yield selenide, which serves as the selenium source for Sec biosynthesis. (Se, selenium; GSSeSG, selenodiglutathione; CH_3SeH methylselenol; H_2Se selenide; SeMet, selenomethionine; Sec, selenocysteine; GSH, glutathione; TrxR, thioredoxin reductase; Trx, thioredoxin).

Selenium exerts its biologic functions largely through its presence in selenoproteins; however, some low-molecular-weight selenium compounds, such as methyl selenic acid, methyl-selenocysteine, and SeMet, have been found efficient as antitumorigenic agents in animal studies and *in vitro* models (115, 159, 329). In functionally characterized selenoenzymes, Sec is part of the catalytic group within their active site and is directly involved in redox reactions (354). Although the functions of many selenoproteins are not yet elucidated, at least three selenoproteins, TrxR1, TrxR2, and GPx4, are essential for life, as demonstrated in knockout mouse models.

The effects of selenium on the organism are concentration dependent, ranging from essential to antioxidant in the nanomolar-micromolar range to potentially prooxidant at concentrations above what is required for maximal selenoprotein synthesis (320). At even higher concentration, selenium compounds may accumulate and redox cycle with intracellular thiols, leading to oxidative stress and damage to cellular components, thus having toxic effects.

B. Selenium and health

Selenium is essential for life, and no doubt exists that adequate amounts of this element are required for optimal human health. Many of its physiologic roles are directly attributed to its presence within selenoproteins. For example, one of the most fundamental cellular processes, DNA synthesis, depends on the presence of selenium within the catalytic site of TrxR (10). Moderate selenium deficiency has been linked to many conditions, such as increased cancer and infection risk, male infertility, decrease in immune and thyroid function, and several neurologic conditions, including Alzheimer's and Parkinson's disease (262). However, for some of these conditions, the evidence is rather scant, lacks consensus, and must be further demonstrated. Keshan disease is a potentially fatal form of cardiomyopathy (disease of the heart muscle), prevalent in children and endemic in parts of China with extremely low levels of selenium in the soil (intake, $\leq$10 μg/day). Infection by Coxsackie B virus is believed to trigger the onset of this disease (203, 204). Remarkably, the condition is prevented or completely reversed by selenium supplementation (266, 338). How this protective effect is achieved is, however, currently unknown.

Myxedematous cretinism is a condition characterized by mental and growth retardation, which is attributed to a combined selenium and iodine deficiency (316). It is believed that

selenium deficiency causes a reduction in GPx and DIO enzymes activity, accumulation of hydrogen peroxide (H_2O_2) causing damage to the thyroid gland, and impaired thyroid hormone metabolism (78, 355). Selenium supplementation in this condition must be administered after iodide levels have been restored, as selenium increases the activity of DIO, leading to a further loss of iodide from the damaged thyroid (355).

According to recent studies, many countries in Europe and other parts of the world still have a dietary selenium intake below what is recommended by health regulatory bodies (75, 263). In the United States, where dietary intakes are higher than in many other countries, the current recommendation is 55 μg/day. In the United Kingdom, however, selenium intake is considerably lower, and the recommended dose is 75 μg/day for men and 60 μg/day for women (298). These recommendations were based on the plasma GPx optimal enzyme activity (94, 308); however, a recent study indicates that higher selenium intake is required to obtain full expression of selenoprotein P (338). It is thus suggested that SelP may be a better indicator of selenium nutritional status than GPx, and that the recommended dietary intake may need to be revised. The precise molecular mechanisms behind the effects of selenium in physiologic and in pathologic conditions remain unknown.

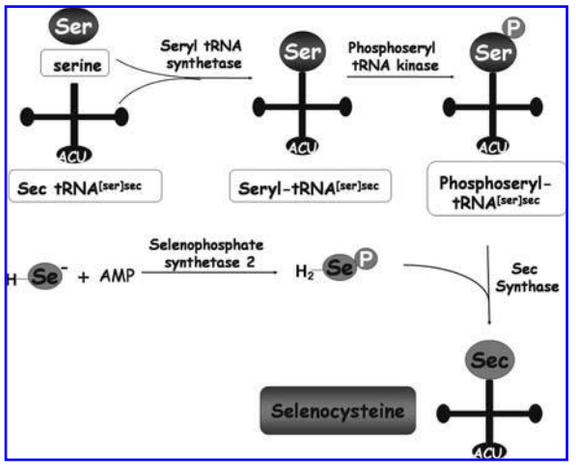

FIG. 2. Sec biosynthesis pathway in mammalian cells. Sec biosynthesis initiates with the attachment of serine to the Sec tRNA$^{[ser]sec}$ by seryl tRNA synthetase to yield Seryl-tRNA$^{[ser]sec}$. The phosphoseryl tRNA kinase phosphorylates the complex. The phosphate is then replaced by the selenium donor selenide (H_2Se-P), which is thought to be activated by selenophosphate synthetase. The resulting molecule is selenocysteyl-tRNA$^{[Ser]Sec}$, which delivers the Sec into the growing polypeptide chain.

C. From UGA to selenoproteins

Selenoprotein synthesis is an evolutionary conserved process. Nevertheless, some major differences are found in the mechanisms of selenoprotein synthesis between prokaryotes, eukaryotes, and archaea. The common feature to all organisms is the UGA-Sec codon, the specific tRNA, the SECIS element, and several protein factors. These factors, as well as the mechanism of Sec insertion in eukaryotes, are discussed next.

a. The UGA codon and selenocysteine biosynthesis. The genetic code is redundant, such that translational termination is coded for by UGA, UAA, and UAG (321). However, in mitochondria, UGA codes for tryptophan (249), and in the nuclear genome, UGA also codes for Sec. Thus, Sec is the 21st genetically encoded amino acid translated into proteins by reading of the UGA codon (194). GPx 1 was the first mammalian gene shown to contain UGA in its open reading frame, which corresponded to the site of Sec in the protein sequence (60, 356). Shortly after, it was indeed demonstrated that Sec is incorporated into protein by a tRNA molecule with an anti-codon complementary to UGA (200). Sec tRNA$^{[Ser]Sec}$ is unique in that it controls the expression of the entire selenoprotein family, a phenomenon that has not been reported for any other tRNA species.

Unlike the other 20 amino acids in the genetic code, Sec is synthesized universally on its own tRNA by using serine as an intermediate. Consequently, the tRNA was designated Sec tRNA$^{[Ser]Sec}$ (195, 199). The complete picture of the Sec biosynthesis pathway in eukaryotes was very recently defined (339). A remarkable aspect of Sec biosynthesis is that the process requires the enzyme SPS2, which itself is a selenoprotein in most organisms with selenoproteomes (some genomes have a cysteine-containing version of SPS2) (59). SPS2, but not SPS1, is directly involved in generating the active selenium donor, monoselenophosphate, for the biosynthesis of Sec (339). The phosphoseryl-tRNA$^{[Ser]Sec}$ kinase specifically phosphorylates the seryl-tRNA(Ser) molecule in the Sec biosynthesis reaction (58), which, in turn, serves as substrate of the Sec synthase ultimately to yield Sec (339). A schematic representation of the eukaryotic Sec biosynthesis pathway is presented in Fig. 2.

b. Sec tRNA$^{[Ser]Sec}$: role in selenoprotein synthesis and health. Mammalian genomes contain a single copy of the Sec tRNA$^{[Ser]Sec}$ gene (*trsp*), which produces two Sec tRNA$^{[Ser]Sec}$ isoforms: an unmethylated form and a methylated form, referred to as mcm^{5}U (5-methylcarboxymethyluridine) and mcm^{5}Um (5-methylcarboxymethyluridine-2'-*O*-methylribose) respectively (70, 89). The relative amounts and the distribution of the two isoforms vary in different tissues and cell lines. Selenium supplementation in cell culture as well as in animal models is known to modulate the relative ratios between the two isoforms by inducing the production of mcm^{5}Um (70, 129, 162). The synthesis, function, and regulation of Sec tRNA$^{[Ser]Sec}$ have been reviewed extensively (40, 55, 128, 131). Here we emphasize the physiologic role of Sec tRNA$^{[Ser]Sec}$ based on recently developed mouse models.

Many important clues toward understanding the functions of Sec tRNA$^{[Ser]Sec}$ in selenoprotein synthesis, development, and health have come from genetically modified mice. The group of Hatfield and co-workers pioneered this work by establishing conditional and transgenic mice models, because complete deletion of the *trsp* gene in mouse is embryonic lethal (42). In the mammary epithelium, conditional removal

of *trsp* leads to a selective reduction in selenoproteins such as GPx1, GPx4, and Sep 15, whereas TrxR1 levels are barely affected (190). In addition, expression of the breast cancer-susceptibility gene product BRCA1 is decreased, whereas tumor-suppressor protein p53 is increased in these mice, suggesting a possible interplay between the DNA damage pathway and selenoproteins in breast cancer etiology. During the course of this study, these mice showed no phenotypical changes in the mammary gland. It would be interesting to know whether any breast tumors developed in aged animals, which would be expected as a result of loss of the BRCA1 protein. In liver, removal of *trsp* causes hepatocellular degeneration and necrosis, demonstrating that selenoproteins play a significant role in the proper functioning of this organ (56). In neuronal cells, a severe neurologic phenotype characterized by cerebellar hypoplasia, Purkinje cell and interneuron loss, reduced number of granule cells, impaired glial cell network, and loss of cerebellar interneurons is observed in the absence of Sec $tRNA^{[Ser]Sec}$ expression (130).

Transgenic animals overexpressing a mutant *trsp* gene that lacks the modified base isopentenyladenosine (i^6A^-) at position 37 display reduced expression of most, but not all selenoproteins (*e.g.*, TrxR3) (236). Despite this defect, these animals appear phenotypically normal, thus providing a unique model to study the direct role of selenoproteins in chemoprevention. These animals have recently been crossed with mice that express simian virus 40 (SV40) T-antigen targeted to the prostate and thus develop prostate cancer (91). The resulting selenoprotein-deficient mice exhibited accelerated development of lesions associated with prostate cancer progression compared with the control mice, providing evidence for a role of selenoproteins in prostate cancer development (91).

c. The SECIS element. Sec $tRNA^{[Ser]Sec}$ is necessary but not sufficient for decoding UGA codons as Sec. The universal determinant of Sec codon read-through is the secondary RNA stem-loop structure: the SECIS element. In eukaryotes, the SECIS element is located within the 3′-untranslated region (UTR) of the mRNAs, in some cases up to several kilobases away from the UGA codon (30, 31, 334). SECIS elements have overall low sequence similarities; however, their secondary structures are highly conserved and contain consensus sequences that are indispensable for Sec incorporation (183). Structure–function studies have determined the following defining features of a SECIS element required for Sec incorporation, also illustrated in Fig. 3: a conserved AAR motif with two consecutive unpaired AA residues, or CC residues as more recently identified for SelM (180) and Sel O (184), located within an apical loop; a stem structure containing a quartet of non–Watson-Crick G to A base-pairing referred to as the SECIS core, and an A or G residue preceding the SECIS core. SECIS elements fall under two categories according to their structure. The difference between the two forms lies in the existence of an additional internal loop (Fig. 3A and B).

A single SECIS element is sufficient to dictate Sec incorporation in all selenoproteins with the exception of SelP, which contains two SECIS elements that direct the decoding of 10 UGA-Sec codons in mammals and up to 17 in fish (59). The mechanism appears even more complicated, as SelP occurs in four different isoforms that arise from translation

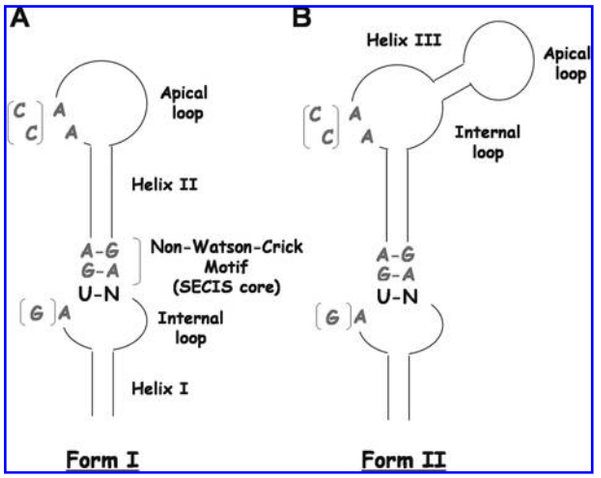

FIG. 3. Two forms of eukaryotic SECIS elements. Two SECIS element forms exist in eukaryotes, Form I (**A**) and Form II (**B**). The difference is the additional apical loop present in Form II. The conserved nucleotides required for function of SECIS elements include the AA (or CC) in the apical loop, the non–Watson-Crick motif or SECIS core, and the conserved A or G in the internal loop at the base of the stem.

termination at the second, third, and seventh UGA codons, depending on selenium levels (217). This raises the intriguing question of how the translation machinery decides between termination and translation at these UGA sites. A potential model was recently presented, suggesting that the two SECIS elements play different roles in the synthesis of SelP (292). It appears that SECIS 1 promotes the readthrough of the second and subsequent UGA codons directing synthesis of full-length SelP, whereas SECIS 2 plays a more substantial role in decoding the first UGA codon, potentially controlling translation of the truncated isoforms. Hence, the interplay between the SECIS elements and distinct UGA codons could serve both as a translational checkpoint to determine the fate of the mRNA, depending on intracellular selenium status, and a bottleneck for ribosome loading on the mRNA to decode multiple UGA codons (292).

d. The SECIS element and disease. It has been unequivocally proven that the integrity of the SECIS element is crucial for efficient Sec incorporation. Studies have shown that mutations to conserved SECIS residues totally abrogate UGA readthrough, whereas mutations of nonessential bases only partially do so in *in vitro* models (183). Mutations or single-nucleotide polymorphisms (SNPs) within SECIS elements in humans would most likely affect Sec incorporation efficiency *in vivo,* potentially contributing to the etiology of diseases. Of the many SNPs and mutations identified within selenoprotein genes, only very few are within SECIS elements. Nevertheless, their effects can be quite detrimental.

The SECIS element SNP at 1125G/A, identified within the Sep 15 gene, is not only differentially distributed among African-Americans and whites (31% *vs.* 7%), but also has a different frequency in cancer carriers compared with non–cancer carriers (150, 191). One of the studies found that

cancer carriers were twice as frequently homozygotes for the A than the G allele (150). Interestingly, when experimentally tested, the A variant was twice as efficient as the wild-type G variant at promoting UGA readthrough, but less responsive to increased levels of selenium in an *in vitro* reporter assay. A different study found that cells expressing the 1125G allele are more sensitive to selenite-induced apoptosis than is the 1125A allele (9). Although these findings are linked to the function of Sep 15, it can be hypothetically postulated that allelic variations within SECIS elements can influence Sec incorporation *in vivo* as well as the response to selenium supplementation. Thus differences in the chemopreventive effects of selenium may depend on polymorphic differences within the population, and individuals with such variations might have differences in predisposition to certain types of cancers. The roles of such allelic variations in pathology will naturally depend on the function of the selenoprotein they serve.

Another example of SECIS mutations was recently reported in the SelN gene (*SEPN1*), and in this case, the phenotype was far more dramatic (4). It has been well documented that mutations within the SelN gene (*SEPN1)* cause early-onset muscular disorders, in some cases leading to fatal respiratory failure (discussed in detail in the selenoprotein N section). This SECIS mutation led to an almost complete loss of protein expression because of failure in the SECIS element-SBP2 complex formation required for Sec incorporation.

e. The selenocysteine redefinition element. The selenocysteine redefinition element (SRE), a phylogenetically conserved stem–loop RNA structure different from the SECIS element, is the most recent addition to the factors involved in UGA-Sec decoding (146). By using bioinformatics approaches, SRE structures were predicted to exist within selenoproteins SelN, SPS2, SelH, SelO, and SelT. The SelN SRE was experimentally shown to be a positive modulator of Sec-insertion efficiency (146). Unlike the SECIS element that resides within the 3′UTR, the SRE is located within the coding sequence, six nucleotides downstream of the UGA-Sec codon. Remarkably, the SRE was sufficient to induce readthrough of the Sel N UGA-Sec codon when cloned into a luciferase construct, even in the absence of the SECIS element. The presence of a SECIS element in the same construct further enhanced the UGA-Sec codon readthrough, suggesting that SRE elements may help in fine-tuning the expression of some selenoproteins. This could be either a general or a tissue-specific effect. Although the discovery of the SRE element is an interesting new finding, further studies are required to understand its role in UGA-Sec decoding *in vivo*.

f. Sec-decoding protein factors. Apart from the *cis*-acting elements and the Sec-tRNA$^{[Ser]Sec}$ molecule, Sec decoding requires the cooperative action of several protein factors. In prokaryotes, this is achieved by the SelA, SelB, SelC, and SelD gene products, and the mechanism has been well delineated (39). In mammals, the mechanism of Sec decoding is more complex and less well understood. The SECIS-binding protein 2 (SBP2) (79, 80) and the Sec-specific elongation factor (mSelB/eEFSec) (101, 311) were, until recently, the only known Sec-decoding protein factors. However, three additional proteins that appear to function in the Sec-decoding machinery have been reported in the last year. These include the ribosomal protein L30 (63), the 43-kDa RNA-binding protein, Secp43, and the soluble liver antigen protein, SLA (340). A structural overview of these proteins is presented in Fig. 4. Moreover, new aspects of regulation of "old" factors, as well as novel molecular interactions between protein factors, have been delineated recently (175, 250, 285).

g. The SECIS-binding protein 2, SBP2. The best-characterized Sec incorporation factor is the SECIS-binding

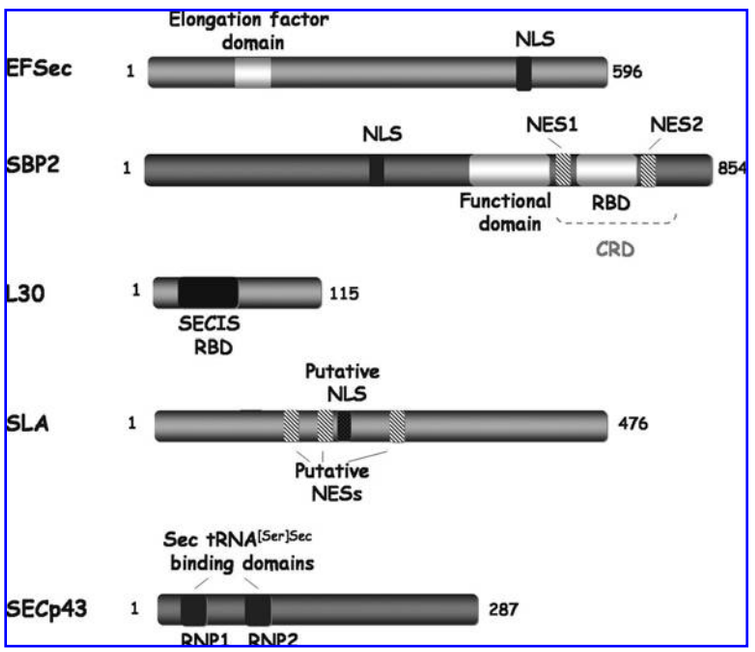

FIG. 4. Protein factors involved in selenoprotein synthesis. A schematic overview of the proteins involved in selenoprotein synthesis, also indicating functional motifs. NLS, nuclear localization signal; NES, nuclear export signal; RBD, RNA-binding domain; CRD, cysteine-rich domain; SBP2, SECIS binding protein 2; eEFSec, Sec-specific elongation factor; Secp43, 43-kDa RNA-binding protein; SLA, soluble liver antigen protein; L30, ribosomal protein L30.

protein SBP2. SBP2 was isolated and cloned from rat testicular extracts based on its high binding affinity to the GPx4 SECIS element (79). SBP2 binding activity was detected in a large molecular mass complex of ~500 kDa. Indeed, SBP2 was recently demonstrated, at least in some circumstances, to be part of a multiprotein complex consisting of Sec biosynthesis and incorporation factors EFSec, SECp43, SPS1, and SLA (discussed later) (284). SBP2 is ubiquitously expressed in tissues and may be encoded by several transcripts, some detected only in testis (80). Alternative splicing events lead to the expression of multiple SBP2 isoforms (our unpublished data), and their functional contribution to selenoprotein synthesis is currently under investigation.

At the sequence level, SBP2 is not homologous to any other known protein; however, it contains an L30-type RNA-binding domain (RBD) shared with several ribosomal proteins, a yeast suppressor of translation termination (SUP1), the eukaryotic translation termination release factor 1 (eRF-1), and the 15.5-kD/Snu13p protein (5, 52, 81). Rat SBP2 binds the AUGA consensus sequence within the SECIS element core *via* this RBD (107, 322) and interacts with the 28S ribosomal RNA (81). Human SBP2 has also been reported to have similar SECIS-binding activity *in vitro* (202).

In addition to the RBD, SBP2 contains several functional motifs: an N-terminal lysine rich nuclear localization signal (NLS) (250), a potential C-terminal NLS (86), two C-terminal leucine-rich nuclear export signals (NESs) (250), a functional domain dispensable for SECIS binding but required for Sec incorporation activity (81), and a ribosomal interaction domain that has not been precisely defined (81, 175). An overview of SBP2 structure and the location of these domains are presented in Fig. 4. SBP2 is a large protein of 854 amino acids, and intriguingly, the first N-terminal ~400 amino acids are dispensable for its Sec incorporation function *in vitro* (81) and *in vivo* (86).

The central role of SBP2 in selenoprotein synthesis was initially demonstrated *in vitro,* as cell lysates depleted of SBP2 lacked selenoprotein translation activity, and conversely, repletion with SBP2 restored translation of selenoproteins (80). Consistent with this, we recently demonstrated that siRNA-mediated depletion of SBP2 in cell lines leads to a global decrease in selenoprotein synthesis, further substantiating the vital role of SBP2 in Sec incorporation *in vivo* (250).

The subcellular localization of SBP2 has been a central question in the field and has been studied by several groups. Compelling evidence indicates that the steady-state localization of SBP2 is in the cytoplasm, in stable association with the ribosomes (81, 175, 250). Furthermore, we and others have reported that SBP2 is capable of shuttling between the nucleus and the cytoplasm, via intrinsic NLS and NES motifs (86, 250). However, some differences in the proposed location of the NLS and NES motifs were reported in the two studies. By using truncation constructs, site-directed mutagenesis, and *in vivo* nuclear-export assays, we found that the previously reported evolutionary conserved, N-terminal NLS is functional and identified two functional NESs in the C-terminal region of SBP2. These NESs mediate the nuclear export of SBP2 *via* the CRM1/Exportin1 nuclear-export pathway (250). Another study that used SBP2-deletion constructs identified an NLS in the C-terminal region and has proposed the existence of potential NES motifs in the N-terminal region of SBP2 (86); however, these motifs were not assayed specifically for their functionality. It is possible that SBP2 contains multiple NLS and NES motifs, and further studies are required to verify their function, and more important, their roles in the regulation of SBP2 Sec-incorporation function.

h. SBP2 mutations and thyroid metabolism. Recently, the first direct link between SBP2 and a human condition was reported. Mutations in the SBP2 gene were found to produce an abnormal thyroid phenotype associated with reduction in DIO2 enzyme activity and prepubertal growth retardation (95). Two different SBP2 mutations were identified in two unrelated families with similar thyroid phenotypes. A homozygous missense mutation resulting in amino acid substitution at R540Q was identified in three siblings belonging to a distantly related family. The second family had an affected child that carried a nonsense mutation leading to amino acid substitution K438X passed on from the father, as well as a mutation in an intron at IVS8ds+29G→A that creates an alternative donor splice site, and thus a partially mis-spliced transcript passed on from the mother. Both mutations result in a prematurely terminated protein lacking the RBD domain. In addition to DIO2 defects, GPx activity, as well as plasma Sel P levels, was significantly lower in affected individuals than in normal siblings, suggesting that the mutations caused a global reduction in selenoprotein synthesis. Given the central role played by SBP2 in selenoprotein synthesis, it is rather surprising that a relatively mild thyroid-specific phenotype is apparent in these children. However, none of the affected mutation carriers have a complete loss of SBP2, and it is possible that additional manifestations such as cancer predisposition due to impaired antioxidant protection, or decreased fertility in males due to reduced GPx4 will appear with increased age (95).

i. The Sec-specific elongation factor eEFSec. The mammalian EFSec protein has sequence and domain similarity to the general translation-elongation factor EF1A (101, 311). EFSec interacts with both isoforms of the Sec $tRNA^{[Ser]Sec}$ and co-immunoprecipitates in complex with SBP2 and Sec $tRNA^{[Ser]Sec}$ in cell lysates (101, 311). Sec $tRNA^{[Ser]Sec}$ is necessary for SBP2-EFSec complex formation and appears to have a stabilizing effect on EFSec protein levels (347). However, addition of SBP2 to preformed Sec $tRNA^{[Ser]Sec}$-EFSec complexes *in vitro* completely abrogates the interactions, suggesting that additional factors may participate in stabilization of this complex (284). Recently, a functional NLS was mapped within the C-terminal region of EFSec, and because the motif overlaps with the SBP2-binding region, it was suggested that the two interactions are mutually exclusive, and the NLS might be masked by SBP2 (86). If these complexes are formed in the nucleus, it is possible that SBP2 may help transport EFSec to the ribosomal sites in the cytoplasm. Alternatively, if complexes are formed at the ribosomes, where SBP2 usually resides, SBP2 binding may lead to sequestration of EFSec at the ribosomes, potentially to facilitate delivery of Sec $tRNA^{[Ser]Sec}$ at UGA-Sec codons. Interestingly, SBP2-EFSec complexes were identified in both the

nuclear and the cytoplasmic compartments (284), suggesting that both hypotheses may apply. The role of EFSec in Sec incorporation seems to be complex, as it is implicated in both the Sec-biosynthesis and Sec-incorporation pathways and appears to interact with most of the protein and RNA components of the selenoprotein-synthesis machinery (284). EFSec does not appear limiting for selenoprotein translation *in vitro*; however, it would be interesting to know whether its depletion in cell-culture models or *in vivo* shows similar effects. This would also clarify whether EFSec is indeed the factor required for delivery of the Sec $tRNA^{[Ser]Sec}$, as currently proposed. So far, no mutations or conditions that link to EFSec gene locus have been reported.

j. Ribosomal L30 protein. Ribosomal protein L30 belongs to the L7Ae family of ribosomal proteins, and like SBP2, it contains an L30-type of RNA binding motif (231). L30 is an essential component of the ribosome and functions in autoregulation of its own splicing and translation (319). Recent molecular and biochemical characterization of L30 reveal that it is a component of the UGA-Sec recoding machinery, and it binds specifically to SECIS elements (63). L30 is able to stimulate UGA codon readthrough in transfected cells, an effect that is further enhanced by co-transfection with SBP2. However, L30 and SBP2 do not seem to bind to the SECIS molecule simultaneously; rather, they bind SECIS in a competitive manner and are able to displace each other from the SECIS element (63). L30 appears to bind preferentially a conformational-altered SECIS element resembling a so-called kink-turn motif. In terms of its role in selenoprotein translation, a model has been proposed in which L30 binding to the SECIS element alters its structure, which would induce SBP2 release, promoting the delivery of $Sec\text{-}tRNA^{Sec}$ to the ribosomal A site.

k. The SECp43 and the SLA protein factors. The roles of SECp43 and SLA in selenoprotein synthesis were only recently characterized, although their identification as Sec $tRNA^{[Ser]Sec}$-binding partners was first reported several years ago. SLA was isolated by autoantibody precipitation in patients with a severe form of autoimmune chronic active hepatitis (117). The protein was then found associated with a tRNA molecule identified by sequencing as Sec $tRNA^{[Ser]Sec}$; however, the functional relevance of this interaction was not evaluated further in the study. Very recently, however, SLA was identified as the missing mammalian Sec synthase protein that functions in the final step of the Sec biosynthesis pathway (Fig. 2) (339). SECp43 was isolated independently, based on its ability specifically to precipitate Sec $tRNA^{[Ser]Sec}$ from mammalian cell lysates (90). SECp43 has two ribonucleoprotein-binding domains (RNPs) that constitute an RNA-recognition motif (RRM); however, binding to Sec $tRNA^{[Ser]Sec}$ *in vitro* could not be demonstrated. Interestingly, one of the SECp43 binding partners identified was a 48-kDa protein (90) now known as Sec synthase/SLA (339, 340). These two proteins have regained interest in the past year, and their roles in selenoprotein synthesis have recently been elucidated.

SECp43, SLA and Sec $tRNA^{[Ser]Sec}$ indeed form a complex in cell lysates, and depletion of either SECp43 or SLA decreased the binding of the remaining protein to the Sec $tRNA^{[Ser]Sec}$ (340). When coexpressed in cells, it appeared that SECp43 is able to sequester SLA from the cytoplasm to the nuclear compartment, where SECp43 normally resides. Combined depletion of both proteins causes a global decrease in selenoprotein synthesis, whereas SLA alone has no effect, and SECp43 appears to affect the expression of GPx1 only in a selenium-dependent manner (340). SECp43 also appears to regulate the levels of methylated Sec $tRNA^{[Ser]Sec}$, which in turn is known to control the synthesis of stress-related selenoproteins.

Another study has shown that SECp43 plays a role in the formation or stabilization of the EFSec–SBP2–Sec $tRNA^{[Ser]Sec}$ complex and promotes the formation and subcellular localization of the SPS1/SLA/SECp43 complex. SECp43 may also assist in the decoding of multiple UGA-Sec codons in selenoprotein P, and to prevent degradation of selenoprotein mRNAs by the nonsense-mediated-decay pathway (284). Collectively, these studies suggest that SECp43 and SLA are involved in both the mechanism of Sec biosynthesis and Sec incorporation and represent interesting candidates for future studies.

D. Selenoprotein synthesis

Despite the identification of several key components of the Sec-translation machinery, the mechanism by which the ribosome performs the incorporation of Sec at distinct UGA codons remains elusive. It is well established that this task is accomplished by the multiple protein and RNA factors described earlier, and it is likely that additional participants are yet to be discovered. It is reassuring to note that multiple events are happening at the ribosome to regulate the decoding of UGA into selenocysteine. The past 2 years have been particularly rewarding in terms of identification and characterization of novel protein factors, as well as a novel RNA structure involved in the regulation of this process.

Several models to describe the mechanism of Sec incorporation have been proposed in the past few years (52, 92, 285); however, a clear, detailed picture is still lacking. Recently, studies have provided new evidence that the Sec-biosynthesis pathway and the Sec-incorporation pathway are more closely linked than previously thought. Supramolecular protein complexes consisting of EFSec, Secp43, SLA, SPS1, SBP2, and L30 appear to form and dissociate dynamically in a nuclear, cytoplasmic, or ribosomal-specific manner. A simplified diagram illustrating the proposed complexes and their subcellular distribution is presented in Fig. 5. Many of these components have been detected in complexes differing in their constituents in the nuclear and the cytoplasmic compartments. Some of the components, such as SBP2 and EFSec, undergo nucleocytoplasmic shuttling via intrinsic NLS and NES sequences, either independently or in a complex with each other.

Several aspects of Sec incorporation remain unclear. One major question that has not been investigated involves the transport of the SECIS containing mRNA from the nucleus to the ribosomes. We and others have postulated that the nucleocytoplasmic shuttling of SBP2 could be linked to its binding to the SECIS element of selenoprotein mRNAs in the nucleus and transporting it to the ribosomes for translation; however,

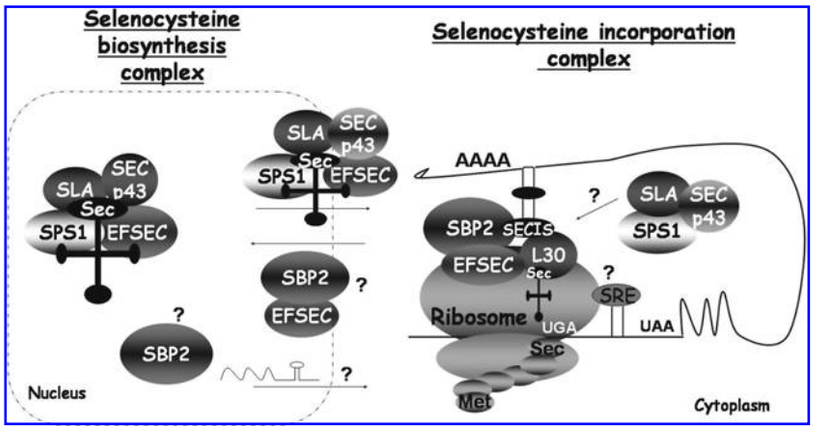

FIG. 5. Protein complexes involved in selenoprotein synthesis and their subcellular distribution. Multiprotein complexes that are involved in Sec biosynthesis and incorporation into protein shuttle between the nucleus and the cytoplasm. Question marks indicate unknown function of the component, or unknown function in the indicated subcellular compartment. Abbreviations are as in the legend of Fig. 4. Adapted from ref. 285.

this has not been experimentally proven. Similarly, the role of SBP2 in the nuclear compartment is still unclear. Because its N-terminal NLS-containing region appears to be dispensable for Sec incorporation not only *in vitro*, but also in cell-culture models (86), it is likely that the nuclear pool of SBP2 has additional nuclear functions that are independent of Sec incorporation. A better understanding of the molecular complexes formed in the two subcellular compartments is also in need of additional studies. In particular, the role of Secp43, SLA, and SPS1 complex in the cytoplasm is an intriguing aspect, as it appears from polysome separation studies that they are not part of the ribosomes.

Another aspect that requires further studies is the role of the newly identified RNA loop structure, SRE, in selenoprotein synthesis. Bioinformatics-based approaches predict SREs in a subset of selenoprotein mRNAs, and so far only the SRE of SelN was characterized and shown capable of driving UGA codon readthrough in the absence of the SECIS element *in vitro* (146). It is likely that the presence of such elements may fine-tune translation, potentially by impeding the ribosomal readthrough rate, allowing the Sec incorporation factors to interact at the UGA-Sec codon, or by modulating interactions with other RNA structures and proteins factors. However, the exact role of the SRE in UGA-Sec decoding remains to be further demonstrated. In light of recent findings that a single point mutation within the SECIS element of the *SEPN1* gene leads to a dramatic but not complete reduction in Sel N protein levels, it can be speculated that the SRE may allow some background level of UGA readthrough (4).

E. Regulation of mammalian selenoprotein synthesis

Selenium biology is a complex story in that its effects on the organism range from essential to toxic. Thus, highly controlled mechanisms must be in place to sustain optimal levels of selenium accumulation within cells, both in the form of free selenium compounds and, importantly, incorporated within selenoproteins. The regulation of selenoprotein synthesis is an important issue to understand in physiologic and pathologic aspects. It is not surprising to find that, as in the case of iron homeostasis, selenium is itself a key regulatory point of its incorporation into selenoproteins and acts predominantly at post-transcriptional levels, although a recent demonstration showed its action at the transcriptional level.

a. Transcriptional regulation. Transcriptional regulation of selenoprotein genes is less well characterized; nevertheless, it most certainly provides an important regulatory point. It was recently demonstrated that GPx2 is a target of the Nrf2/Keap1 system (19), which regulates the expression of phase 2 detoxification enzymes and redox active proteins, including TrxR1 (47). The Nrf2/Keap1 system is interesting from the point of view of its activation by electrophilic compounds, metals, thiol modifiers, and other potential anticarcinogenic compounds derived from dietary sources (47). Whether selenium or selenium metabolites also act as an activator of this system, thus controlling global or specific selenoprotein synthesis at a transcriptional level, remains an exciting area for future investigation. Transcriptional regulation of additional GPx family members extends beyond the Nrf2/Keap1 system and has been recently reviewed (45). A complex transcriptional regulation pattern involving interplay between several transcription factors, such as Oct-1, Sp1, and Sp3, and multiple transcription start sites in a cell- and stimuli-specific manner has been reported for the TrxR1 gene (reviewed in (270). Characterization of the promoter region and transcriptional regulation of the GPx4 gene also has been reported (157, 219). An interesting, speculative question is whether all or some selenoprotein genes contain potential selenium-response elements. Such elements would allow a more efficient regulation of their synthesis at the transcriptional level in response to alterations in selenium supplies, which could also account for the differences in their synthesis generally detected.

b. Post-transcriptional regulation. The post-transcriptional regulation of selenoprotein synthesis is an interesting subject that has been reviewed extensively (26, 52, 92, 131, 277). Animal studies as well as cell-culture models have demonstrated that a hierarchy in selenoprotein expression exists during selenium deprivation and repletion, and that some tissues and organs are better than others at maintaining not only selenium levels but also the production of certain selenoproteins during selenium deprivation (26, 46). This is indicative of

differences in the requirements and biologic roles of selenoproteins in different tissues. Thus selenium exerts a central regulatory point in selenoprotein production and acts at different levels, such as mRNA stability, by increasing susceptibility to the nonsense-mediated decay pathway (NMD) during selenium deficiency (220, 232, 326), by regulating the UGA-Sec codon-translation efficiency (106, 223), and by regulating total levels of Sec tRNA[Ser]Sec as well as the ratio between the methylated and unmethylated isoforms (57, 70, 129, 161, 162). Interestingly, different SECIS elements respond differently to changes in selenium levels, suggesting that selenium may also regulate selenoprotein translation through direct biochemical changes to SECIS elements (162).

Another regulatory point of selenoprotein synthesis is provided through availability of essential *trans*-acting factors. Sec $tRNA^{[Ser]Sec}$ was found limiting for Sec incorporation in some cell-culture studies but not in animal studies (92). Evidence demonstrating that the two Sec $tRNA^{[Ser]Sec}$ isoforms control the expression of distinct selenoproteins was recently provided in transgenic mice rescued with either a wild-type *trsp*, or a methylation mutant *trsp* transgene (57). Interestingly, it was discovered that the methylated, mcm^5Um isoform controls the synthesis of selenoproteins involved in the oxidative stress response such as GPx1 and GPx3, whereas the unmethylated, mcm^5U form governs synthesis of housekeeping selenoproteins such as TrxR1 and TrxR3.

Among the protein factors, SBP2, EFSec, and SPS2 have been found limiting in some cell lines but not others (92). It is interesting to note that SBP2 appears to be limiting in human embryonic kidney (HEK293) cells, as its overexpression significantly increases selenoprotein synthesis (86), whereas in HEK293T cells, which are derived from HEK293 by SV40 T-antigen transformation, endogenous SBP2 levels appear to be sufficient for maximal selenoprotein synthesis (our unpublished observations). More recent studies using siRNA technology have demonstrated that depletion of SBP2 alone, or SECp43 and SLA in combination, leads to a general decrease in selenoprotein synthesis (250, 340). It is clear that the Sec biosynthesis and incorporation factors represent a main regulatory point for selenoprotein synthesis, at least in cell-culture models. Ultimately, the generation of knockout animal models for these factors will provide important clues to understanding their roles *in vivo,* during development, and in physiology and pathology.

c. Redox regulation. Redox regulation has emerged as an essential regulatory process of many pathways in cell biology (118, 207). However, disruption of the intracellular redox balance leads to a state of oxidative stress, during which proteins, nucleic acids, lipids, and other macromolecules can accumulate severe damage (282). Oxidative stress appears to be a major factor in aging and has been implicated in numerous diseases such as Alzheimer's, diabetes, and cancer (3, 29, 182). TrxRs and GPxs, through the action of Sec within their catalytic sites, serve housekeeping redox functions by controlling the activity of cellular proteins and reduction of hydroperoxides, respectively. Consequently, these enzymes are regulated in response to oxidative stress by induction of their gene expression and changes in activity and subcellular localization (132, 138, 168).

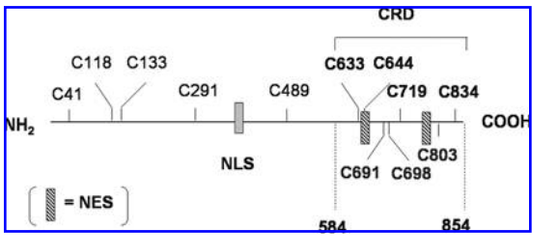

FIG. 6. SBP2 contains a cysteine-rich domain (CRD). Human SBP2 contains 12 cysteine residues, six of which are located within the C-terminal region, forming a redox-sensitive CRD domain. Cysteines within this domain form disulfide bonds and GSH-mixed disulfides, which regulate the Sec-incorporation function of SBP2.

Because SBP2 is central to selenoprotein synthesis, and none of the earlier studies had addressed the translational regulation of selenoproteins in response to oxidative stress, we explored these two aspects in cell-culture models. We demonstrated changes in subcellular localization of SBP2 after oxidative stress, but the protein levels of SBP2 remained unchanged (250). These findings further led to identification of a cysteine-rich domain (CRD) with redox-sensitive cysteine residues embedded within the RNA-binding domain and the two NESs (Fig. 6). During oxidative stress, this CRD formed inactivating disulfide bonds and glutathione-mixed disulfides, promoting SBP2 nuclear accumulation, most likely by masking the NES and inhibiting the binding by the nuclear export receptor CRM1. Interestingly, these modifications were efficiently reduced *in vitro* by the thioredoxin and glutaredoxin systems (250).

A well-characterized model of redox regulation with striking similarities to SBP2 has been demonstrated for the *Saccharomyces cerevisiae* transcription factor Yap-1. Yap-1 controls the activation of gene expression in response to oxidative stress (188), and its activity is controlled by nuclear sequestration mediated by a CRD that, on oxidation, forms disulfide bonds that mask the availability of an NES for CRM1 binding (88, 187, 337). In the case of Yap-1, its nuclear sequestration induces its activation of target gene expression to respond rapidly to stress conditions. As several selenoproteins are involved in the redox control and detoxification processes, we expected an increase in their expression in response to stress. Much to our surprise, we observed a general reduction in selenoprotein synthesis at several time points after stress. In addition, a hierarchy in their synthesis was observed, suggesting that some selenoproteins, such as TrxR and GPx, are preferentially translated over others during recovery after stress (Fig. 7). Analysis of data from previous reports revealed no changes in mRNA transcripts of 12 selenoprotein genes during similar oxidative-stress conditions, suggesting that the transcriptional response was not affected (238). Therefore, it is likely that reduced protein levels are due to the effect on translation. Accordingly, the growing body of evidence suggests that global protein translation is reduced in response to most types of cellular stresses, allowing the cells to conserve resources and to initiate a reconfiguration of gene expression to manage stress conditions effectively (140, 327). These events are regulated mainly through inhibitory phosphorylation of the

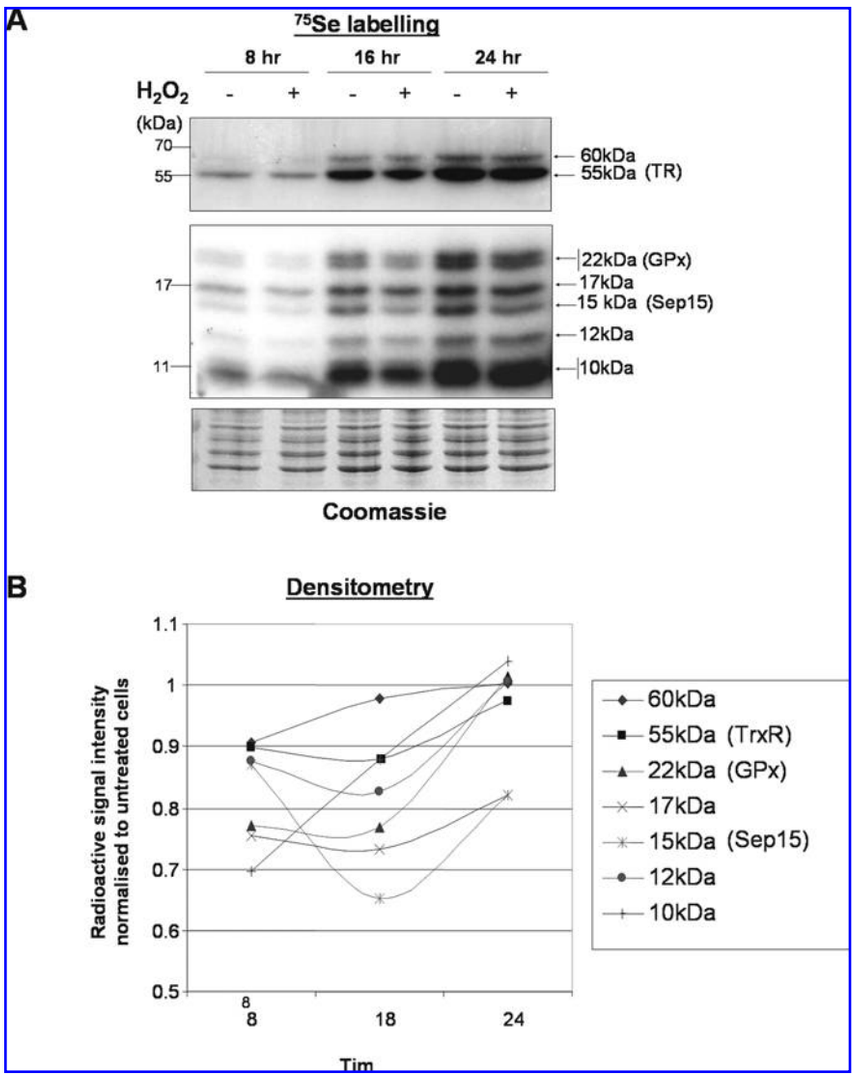

FIG. 7. Selenoprotein synthesis in response to oxidative stress. Sec incorporation was monitored by ^{75}Se labeling in HeLa cells, after treatment with H_2O_2 (600 μ*M*) for 1 h. ^{75}Se-containing complete media was added to untreated and treated cells (10 μCi/10-cm dish), and cells were harvested at 8, 16, and 24 h after ^{75}Se addition. (**A**) Autoradiographs show a general decrease in ^{75}Se signal within selenoproteins from H_2O_2-treated cells at all time points after treatment. Coomassie staining shows the loading of the gel. (**B**) Graphic representation of the fold decrease in radioactive signal intensity between untreated and treated samples analyzed by densitometry. The graph shows a hierarchy in selenoprotein synthesis in response to H_2O_2-induced oxidative stress.

global initiation factor 2-α (eIF2-α) (96, 104) and a simultaneous switch to the cap-independent, internal ribosomal entry site (IRES)–mediated translation to allow production of a selected set of proteins required for cell survival, proliferation, or death, depending on the severity of the stress (104, 243). Because SBP2 is limiting for selenoprotein synthesis, we proposed a model in which translational inhibition of selenoprotein synthesis during oxidative stress is mediated through sequestration of SBP2 from the ribosomes into the nuclear compartment through redox events (Fig. 8). The nuclear pool of SBP2 may therefore function to inhibit selenoprotein synthesis during unfavorable conditions of stress. During the cell-recovery phase, SBP2 is potentially reduced by the thioredoxin and glutaredoxin systems, facilitating its relocation to the ribosomes and reinitiation of selenoproteins translation. Interestingly, it was recently demonstrated that the *S. cerevisiae* thioredoxin system protects ribosomes against stress-induced aggregation of their components, thus maintaining translation integrity (260). In agreement with these data, we also detect thioredoxin in the ribosomal fraction of cells (our unpublished data), suggesting that the thioredoxin system may be keeping SBP2 in a reduced state within the ribosomes, which is required for efficient selenoprotein synthesis.

From these studies, it is evident that regulation of selenoprotein synthesis is even more complicated than previously thought, involving redox regulation of SBP2 through the thioredoxin and glutaredoxin systems. As a future goal, it would be interesting to elucidate the specific roles of glutathionylation and disulfide bonds on SBP2 function and ultimately how these pathways can be targeted to modulate expression of selenoprotein synthesis. This would be of particular interest in pathologic conditions with a redox imbalance such as cancers, Alzheimer's, and Parkinson's disease.

F. Selenium in mammalian proteins

The most common form of selenium in mammalian proteins is Sec, which becomes cotranslationally incorporated within the growing polypeptide chain. However, selenium-containing proteins exist also in other forms, such as proteins

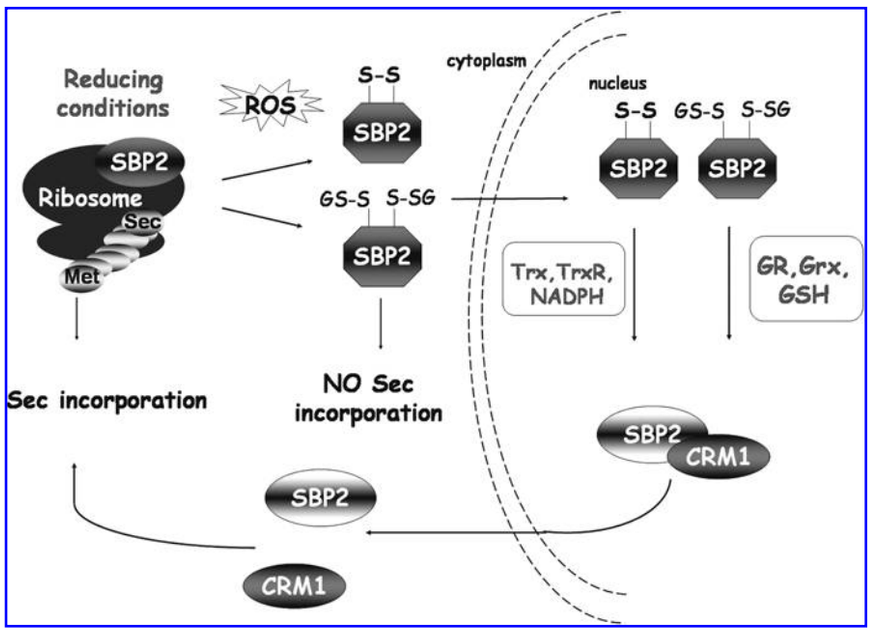

FIG. 8. Proposed model for the role of SBP2 in the regulation of selenoprotein synthesis during oxidative stress. In reducing conditions, SBP2 is localized at the ribosomes, and selenoprotein synthesis proceeds normally. On oxidative stress, cysteines within the SBP2 CRD become oxidized to form disulfide bonds (S-S) or glutathione-mixed disulfides (GSS), which may induce a conformational change within SBP2. This leads to the nuclear retention of SBP2 because of masking of the NES and inhibition in binding to the CRM1 exporter protein. The thioredoxin and glutaredoxin systems (Trx, TrxR, NADPH; GR, Grx , GSH) are required for reduction of SBP2 disulfides and glutathione-mixed disulfides in the nucleus. SBP2 interacts with CRM1, which facilitates its export to the cytoplasm, and selenoprotein synthesis can initiate. It is possible that the nuclear sequestration of SBP2 is a means of inhibiting selenoprotein synthesis during oxidizing conditions in the cytoplasm.

that nonspecifically incorporate selenium during translation, and selenium-binding proteins that bind selenium as a cofactor. The first group is believed to occur by nonspecific replacement of methionine with selenomethionine, at a high selenomethionine intake, when methionine levels are low, and when the intracellular S/Se ratio is low (26). It is not clear whether the nonspecific incorporation of selenium into proteins has any physiologic role. The selenium-binding proteins have not been given much attention over the years, so their biologic functions have not been elucidated; however, several recent reports indicate that this class of proteins may have a potential link to the development of cancer. An update on what is known about this family of proteins is therefore provided.

G. Selenium-binding proteins

Two selenium-binding proteins in which the selenium moiety is externally bound to the polypeptide have so far been identified in mammals: a 14-kDa protein (SLP-14) (20) and a 56-kDa protein (SLP-56, SBP56, hSP56, and selenium-binding protein 1 (SELENBP1 or SBP1) (21, 62). A second 56-kDa protein almost identical at both cDNA and protein level to SP56, but encoded by a different gene, was subsequently identified (193). This protein was shown to bind acetaminophen and was therefore initially named AP56, but it is now also referred to as SBP2. We suggest renaming of this protein as SELENBP2 to avoid confusion with SECIS-binding protein 2, SBP2.

SELENBP1 is implicated to play a role in toxification/detoxification processes (257), cell-growth regulation (21, 119), intra-Golgi protein transport (255), aging (71), and lipid metabolism (251). Interestingly, several studies have reported decreased expression levels of both SELENBP1 and SELENBP2 in tumors compared with normal tissue. Early reports detected low SELENBP1 and SELENBP2 mRNA levels in skin and mammary carcinomas (193) and in prostate cancer cell lines (342). More recently, by using protein expression profiling of tumors, several groups have consistently reported significantly decreased SELENBP1 protein levels in lung cancers (64, 205), gastric cancers (133), ovarian cancers (151), colorectal carcinomas (172), and thyroid carcinomas (49) when compared with normal tissue. Two of the studies also found an association between low SELENBP1 expression levels and poor patient prognosis (64, 172). These observations, therefore, not only provide an additional link between selenium and its anticancer properties, but also suggest that SELENBP1 could be used as a potential marker for cancer development and patient outcome in several cancer models. Elucidation of the biologic function of SELENBP1 may aid in understanding the mechanisms by which selenium exerts its chemopreventive effects.

III. SELENOPROTEINS IN PHYSIOLOGY AND PATHOLOGY

Only a few of the 25 identified mammalian selenoproteins have so far been functionally characterized. Most of these selenoproteins exhibit enzymatic redox function *via* Sec, which confers their catalytic or antioxidant activities. Cellular processes so far demonstrated to require selenoproteins include biosynthesis of dNTPs for DNA, removal of damaging or signaling peroxides, reduction of oxidized proteins and membranes, regulation of redox signaling, thyroid hormone metabolism, selenium transport and storage and potentially protein folding. An overview of the human selenoproteins and their functions is presented in Fig. 9.

Based on the location of the Sec residue, selenoproteins can be divided into two groups. In one group, which includes

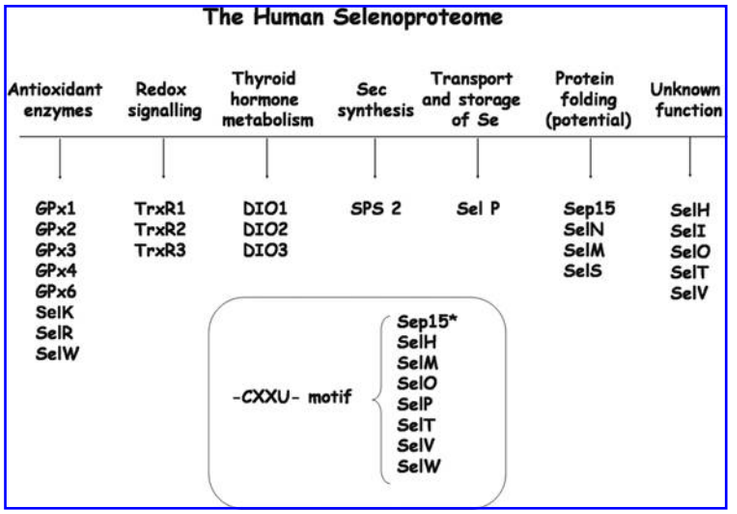

FIG. 9. The human selenoproteome. The 25 human selenoproteins are outlined and classified by their determined or potential function. These proteins are discussed in detail throughout this review. Selenoproteins with -CXXU- motifs are shown in the box. *-CXU- motif.

all thioredoxin reductases, Sel S, Sel R, Sel O, and Sel I, Sec is located in the C-terminal region, only a few amino acids from the stop UGA codon. The second group, including the rest of selenoproteins, are characterized by the presence of Sec in the N-terminal region, in between a β-strand and an α-helix, as part of a redox-active thioredoxin-like selenylsulfide/selenolthiol motif (110, 111, 164). Thus, human diseases associated with selenium deficiency may be attributed to increased oxidative stress and alterations in redox signaling. A summary of what is currently known about the human selenoproteins with emphasis on reported implications in pathology is presented in this section.

A. Thioredoxin reductases

TrxR, thioredoxin (Trx), and NADPH constitute the thioredoxin system, a major cellular redox system present in all living organisms (10). Two forms of TrxRs are known in nature: a small or bacterial-type nonselenium enzyme (70 kDa) present in all bacteria, archaea, and lower eukaryotes like yeast and plants (246). This ancient enzyme is a member of the pyridine nucleotide disulfide oxidoreductase class II family, which for substrate reduction uses a CxxC motif and extensive conformational changes and domain rearrangements during catalysis. The large or animal type of selenoenzymes (≥115 kDa) are present in higher eukaryotes including mammals. These enzymes are highly homologous to glutathinone reductase, rather than the small TrxRs, and the N-terminal active sites of large TrxRs are identical to that of glutathione reductase and use a CxxxxC motif in electron transfer to a C-terminal -Gly-Cys-Sec-Gly- active site without conformational changes (353, 354). The small and large TrxRs use different mechanisms in catalyzing the reduction of thioredoxin (Trx), which has a conserved Cys-Gly-Pro-Cys active site in all organisms (141, 164, 272). The mechanism of TrxR-dependent reduction of substrates involves electron transfer from NADPH to FAD, *via* the N-terminal active site to the Cys-Sec selenenylsulfide bond within the C-terminal active site of the opposite subunit (35). This is depicted in Fig. 10. Because of the low pKa of the selenol group, it becomes ionized at physiologic pH to the reactive selenolate form, giving rise to a cysteinyl-selenol. Therefore, TrxR is a highly reactive enzyme that can also be easily attacked by electrophilic agents (271). The structural and mechanistic differences between the mammalian and the bacterial TrxR should make it possible to use TrxR as a new drug-design target for antibacterial agents (14, 333).

Mammalian TrxRs are housekeeping yet inducible proteins with roles in many cellular processes. They act both by controlling the function of the central redox molecule thioredoxin, and

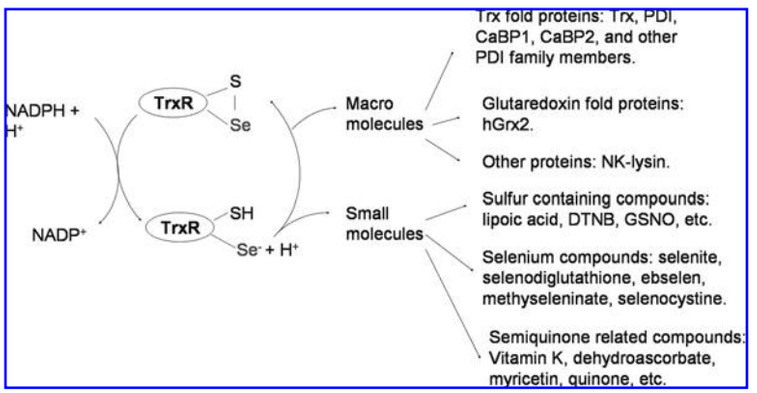

FIG. 10. Electron transfer from NADPH via mammalian thioredoxin reductases to different substrates. Mammalian TrxRs have a wide substrate range. The substrates include generally macromolecules in which disulfide bonds play critical roles in the regulation of their functions, but also low-molecular-weight compounds act as substrates for TrxRs.

by directly reducing numerous substrates. TrxRs contain an FAD domain, an NADPH-binding domain, an interphase domain, and a penultimate Sec residue in a 16-residue C-terminal extension, which is indispensable for their enzymatic activity (120, 216, 353, 354). Three mammalian TrxR selenoenzymes have been identified: the cytosolic enzyme TrxR1 (301), the mitochondrial enzyme TrxR2 (197, 228), and a testis-specific enzyme thioredoxin-glutathione reductase (TGR/TrxR3), the latter also possessing glutathione and glutaredoxin reductase activity (295, 296). In addition, alternative splicing events have been reported within these genes (61, 83, 229, 297), suggesting the existence of an even greater variety of TrxR species with different regulation and cellular functions.

Trx, which is a central factor in cellular redox regulation via its protein disulfide reducing capacity, is the best known protein substrate of TrxR. TrxR is the only enzyme known to catalyze the NADPH-dependent reduction of oxidized thioredoxin (Trx) (215). Many cellular processes are therefore reliant on the activity of these enzymes (Fig. 10). The Trx system catalyzes the reduction of protein disulfides such as in ribonucleotide reductase—an enzyme essential for DNA synthesis (141, 142), thioredoxin peroxidases (peroxiredoxins)—critical enzymes in the defense against oxidative stress (268), protein disulfide-isomerase (PDI)—the major enzyme that catalyzes protein disulfide formation within the endoplasmic reticulum (ER) (214). Additional substrates include two ER proteins with Trx-domains, calcium-binding protein 1 and 2 (CaBP1 and CaBP2) involved in calcium metabolism (213). Interestingly, NK-Lysin, an antibacterial polypeptide naturally produced by T lymphocytes, contains three disulfide bonds that can be reduced by TrxR. This reduction abolishes its cytolytic activity; thus TrxR is involved in protecting the cell against the cytotoxicity of NK-lysin (8).

The thioredoxin system plays a central role in the regulation of gene expression via redox control of transcription factors including NF-κB, Ref-1, AP-1, P53, glucocorticoid receptor, and apoptosis-regulating kinase (ASK1), thus indirectly regulating cellular activities such as cell proliferation, cell death, and immune-response activation (270). Conversely, several studies have now reported that TrxR is transcriptionally regulated via an antioxidant-response element (ARE) (137, 304). The redox sensitive Sec residue within TrxR has been suggested to act as a cellular redox sensor and regulator of cell signaling in response to elevated levels of reactive oxygen species (ROS) (296).

Beside macromolecules, a vast range of small molecules are efficient substrates of TrxRs. These include DTNB (5,5′-dithio(bis 2-nitrobenzoic acid), which is widely used to measure TrxR activity in *in vitro* assays, vitamin K, alloxan, dehydroascorbate, and lipoic acid (12, 13, 143, 216, 227). Nitric oxide (NO) is a molecule that plays many important roles in redox signaling and can form stable adducts with glutathione (GSH) to form S-nitrosoglutathione (GSNO) in physiologic systems. GSNO is reduced by TrxR and the resulting NO• molecule may, in turn, react with TrxR and inactivate its disulfide reductase activity (244).

Interestingly, many selenium compounds including selenite, selenodiglutathione, methyseleninate, selenocystine, and ebselen are substrates of TrxR (Fig. 10) (37, 38, 122, 189, 351, 352). Some of these compounds such as selenodiglutathione and selenite are metabolized to hydrogen selenide, the selenium donor for Sec biosynthesis. Thus, TrxR participates in selenium metabolism *via* selenium–selenium interactions (115) and plays an important role in controlling selenoprotein synthesis. In addition, TrxR can directly reduce lipid hydroperoxides and hydrogen peroxide, and the presence of selenium compounds such as selenocysteine or ebselen strongly increases this activity (37, 352). This was intriguing when originally observed in studies of selenite reduction by mammalian TrxRs, before it was known that the enzyme was a selenoenzyme. The fact that selenocystine and other selenium metabolites also redox cycle with oxygen and NADPH may explain why cells do not have a free pool of Sec. Furthermore, the extensive reactivity with TrxR may also explain the toxicity of selenite.

The central role played by the Trx system in development was highlighted by the embryonic lethal phenotype of the Trx gene (*Txn*) knockout mouse model (224). Although heterozygotes were viable, fertile, and appeared normal, homozygous mutants died shortly after implantation as a result of failure to proliferate, suggesting that *Txn* expression is essential for early differentiation and morphogenesis of the mouse embryo. Similarly, the *TrxR1* gene deletion resulted in early embryonic death around E10.5, because of severe growth retardation and widespread developmental abnormalities in most tissues, excluding the heart (160). A severe impairment in proliferation without obvious apoptotic cells also was observed in TrxR1-deficient mouse fibroblast grown in culture (160). The similar *Txn* and *TrxR1* knockout phenotypes are most likely explained by impaired DNA synthesis due to accumulation of oxidized, nonfunctional ribonucleotide reductase. These results confirm that the Trx/TrxR system is absolutely required for development and probably cell proliferation *in vivo*, and also emphasize the importance of the Sec residue for catalytic activity.

As observed for the *TrxR1*, complete removal of mitochondrial *TrxR2* causes embryonic death at around day 13 (76, 245). *TrxR2* homozygous mutant embryos showed decreased hematopoiesis, increased apoptosis in the liver, and cardiac defects (76). Interestingly, conditional deletion of *TrxR2* in heart resulted in cardiomyopathy, a condition reminiscent of that in the selenium-linked disease Keshan disease and Friedreich ataxia (76). The two selenoproteins, TrxR1 and TrxR2, both appear to be involved in embryogenesis; however, their functions are nonredundant during embryonic development. TrxR2 is essential for hematopoiesis, heart development, and heart function, whereas TrxR1 is essential for embryogenesis by controlling developmental aspects of embryogenesis.

Apart from its role during development, TrxR2 also is involved in control of mitochondrial redox processes and was shown to reduce cytochrome *c*, possibly playing a role in apoptosis signaling (241). A recent study also showed that induction of mutant TrxR2 affected the expression of several cell-cycle proteins and increased the progression rate of cells from G_1 to S phase, implicating TrxR2 in cell proliferation (174). Both Trx and TrxR1 are overexpressed in many malignant cells, including non–small cell lung carcinoma (167, 286), malignant pleural mesothelioma (166), T-cell acute lymphoblastic leukemia (281), breast carcinoma (225, 312),

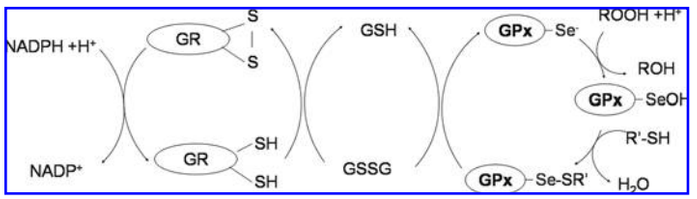

FIG. 11. Electron transfer from NADPH via glutathione reductase and GSH to mammalian glutathione peroxidases. GPxs obtain electrons from NADPH, *via* glutathione reductase (GR) and GSH to catalyze the reduction of hydrogen peroxide and organic hydroperoxides, thus protecting cells from oxidative damage.

colorectal cancer (258), hepatocellular carcinoma (169), gastric carcinoma (121), and cervical carcinomas (134). Overexpression of the thioredoxin system is associated with increased cell proliferation and decreased patient survival (258) and may also contribute to anticancer-drug resistance (256). A variety of potent TrxR1 inhibitors have been shown to alter the cancer-related properties of tumors and numerous malignant cells. Reduced TrxR1 expression in human hepatocellular carcinoma cell lines and mouse lung cancer cell lines leads to a reversal of the tumor phenotype, suggesting that TrxR may be an excellent potential target for anticancer therapy (114, 345).

B. Glutathione peroxidases

Glutathione peroxidase (GPx) was the first mammalian protein shown to incorporate selenium in the form of Sec into its catalytic site and was assumed to be associated with the antioxidant activity of selenium (113). GPxs are well known for catalyzing the reduction of hydrogen peroxide and organic hydroperoxides, thus protecting cells from oxidative damage. In humans, seven GPxs are known, five of which are selenoenzymes and two that contain cysteine instead of Sec. The mechanism by which GPxs reduce their substrates is schematically presented in Fig. 11. The GPx family members include the following: the ubiquitously expressed cytosolic GPx (cGPx/GPx1) (108), a gastrointestinal-specific enzyme (GI-GPx/GPx2) (336), a secreted protein found in plasma (pGPx/GPx3) (299), a ubiquitously expressed enzyme that acts on oxidized lipids, phospholipid hydroperoxide glutathione peroxidase (PHGPx/GPx4) (307), including a sperm nuclei–specific enzyme (snGPx4) (41), and a newly discovered glutathione peroxidase (GPx6) located in olfactory epithelium and embryonic tissues (184). The cysteine variants include the GPx5 with restricted expression to the epididymis (318) and the ubiquitously expressed nonselenocysteine PHGPx named NPGPx/GPx7 (314). These enzymes differ in their tissue distributions and their substrate specificity for peroxide degradation (17, 45, 48). The common feature among selenium-dependent GPxs is the conserved catalytic triad containing Sec, Gln, and Trp, which acts by successive oxidation and reduction of Sec during the catalytic cycle. GPxs 1-3 are homotetrameric proteins with a subunit molecular mass of about 22–25 kDa, whereas GPx4 is a 20- to 22-kDa monomeric enzyme. GPxs are widely believed to be major components of the human antioxidant defense.

a. GPx1. GPx1 is a ubiquitous cytosolic enzyme and can metabolize only hydrogen peroxide and some organic hydroperoxides, but not fatty acid hydroperoxide in phospholipids. Studies from genetically modified mice suggest a complicated picture of the physiologic functions of GPx (198, 278). Mice deficient in the cellular GPx1 are healthy and fertile and show no increased oxidative stress or sensitivity to hyperoxia compared with wild-type mice. This suggests that GPx1 plays a limited role during normal development and under physiologic conditions (139). However, GPx1 was found to be the major mediator of the protective effects of selenium in mice subjected to paraquat- and H_2O_2-induced oxidative stress (67, 85). This is likely achieved by preventing the oxidation of NADPH, NADH, lipids, and proteins (66–68). GPx1 also is associated with protection against virus infection, as concluded from GPx1 knockout mice that developed a cardiomyopathy that resembles Keshan disease when infected with a benign Coxsackievirus (25). Interestingly, some retroviruses such as HIV have been found to encode viral GPx homologues in their genome (vGPx). When expressed in cells, the vGPx enzyme inhibited ROS-induced apoptosis and was thus proposed to promote viral replication, thus enhancing virulence (349). This is somewhat controversial, as selenium has widely been found to inhibit HIV disease progression by boosting the immune system, increasing cytokine production, and decreasing mortality in HIV-infected patients (263).

GPx1 has been implicated as a potential causal factor in the development of cancer. Loss of heterozygosity (LOH) of GPx1 locus has been observed in lung, breast, head and neck, and colon cancer (147–149). Genetic variants of the GPx1 have also been described, including a single polynucleotide polymorphism at the codon 198, which results in either a leucine or proline at that position (147). Case-control studies revealed that an allele with leucine at the codon 198 was associated with a greater risk of lung and bladder cancer (153, 261). However, it should be noted that most of these studies have been too small to have adequate power to derive valid conclusions. A functional difference in GPx-1 genotype at codon 198 was demonstrated by exclusively expressing each allele in breast cancer cells and showing that the leucine-containing allele is less responsive to selenium supplementation than the proline allele, suggesting a possible functional consequence for the allelic identity at the codon 198 (148). Furthermore, an additional common polymorphism exists in which a variable number of tandem alanine codons, 4, 5, or 6 repeats, are found in GPx1 exon 1 (235). A case–control study found an increased frequency of the polyalanine repeats in the prostate cancer cases compared with controls; however, the study found no significant association between Gpx1 genotype and the risk for prostate cancer (181). Nevertheless, reduced levels of GPx1 could conceivably influence the risk of some cancers through its role as an antioxidant or possibly through the modulation of DNA repair and cell-survival molecules (242). Conversely, GPx1-overexpressing transgenic mice had enhanced tumor incidence, probably because of a

decrease in ROS-mediated apoptosis and an increase in cell proliferation (17). Thus, levels of GPx1 must be maintained at a balanced level to obtain beneficial effects.

b. GPx2. GPx2 was initially identified as an epithelium-specific gastrointestinal glutathione peroxidase with the structure and substrate specificity similar to that of GPx1 (73, 336). However, elevated expression of GPx2 has been detected in several breast cancer cell lines (98), during neoplastic transformation of squamous epithelial cells (280), in colorectal adenomas (2, 109, 206, 233), and in the premalignant state of Barrett esophagus (234). GPx2 is thus potentially linked to malignant transformation; however, the regulatory mechanisms are not well understood.

As observed for GPx1, GPx2 knockout mice develop normally (99). However, combined disruption of *GPx1* and *GPx2* resulted in growth retardation and bacterial-induced intestinal inflammation, which led to ileal tumor formation (72, 97). This antitumorigenic involvement of GPx1 and GPx2 in intestinal cancer was attributed to their antioxidant ability to quench inflammation–related increases in hydroperoxide concentration in the gut. *Gpx2*, but not *Gpx1*, was efficient in rescuing these phenotypes, suggesting a specific role of the GPx2 selenoenzyme in protecting the gastrointestinal tract against inflammation and cancer development (100). A vital function of GPx2 can also be predicted from the high stability of its mRNA under selenium-limiting conditions and the rapid production of the GPx2 protein during selenium repletion compared with other selenoproteins (45).

c. GPx3. GPx3 (pGPx) is a glycosylated protein secreted to extracellular compartments. It uses a wide range of substrates including H_2O_2, fatty acid hydroperoxides, and phospholipid hydroperoxides and is an efficient antioxidant in the plasma (46). GPx3 is widely used as the marker of selenium status. GPx3 expression was found significantly increased in ovarian cancer tumors, and particularly high levels were seen in tumors with clear-cell histology. Thus GPx3 may represent a biomarker for this subtype of ovarian tumors (145). Other recent studies have found that the GPx3 promoter is frequently methylated, leading to loss of its expression in primary prostate cancers and in Barrett esophagus tumors, suggesting that epigenetic inactivation and regulation of the glutathione pathway may be critical in the development and progression of these types of cancers (196, 209).

d. GPx4. Unlike other GPxs, GPx4/PHGPx can reduce phospholipid- and cholesterol-hydroperoxides directly, by using electrons from protein thiols as well as from glutathione in mammalian cells (156). GPx4 is present in cytosolic, mitochondrial, and nuclear isoforms with differential tissue distribution. Targeted disruption of GPx4 is embryonic lethal. Cells from $GPx4^{+/-}$ mice are more sensitive to oxidative stress induced by γ-irradiation, paraquat, *tert*-butylhydroperoxide, and H_2O_2, demonstrating a unique and essential role of GPx4 in cellular differentiation during embryonic development, as well as being an essential antioxidant in mammalian cells (155, 343).

An additional fundamental role of GPx4 is its involvement in sperm maturation and male fertility. GPx4 exists as a soluble redox-active enzyme in spermatids and undergoes oxidative polymerization, forming a structural base of the sperm mitochondrial capsule in mature spermatozoa (313). More recent data suggest that the nuclear isoform of GPx4 has a role in chromatin condensation, contributing to the structural stability of sperm chromatin by acting as a protein thiol peroxidase (77). Selenium-depletion studies of rodents have clearly demonstrated the importance of this trace element in male fertility (248). Human studies have also linked male infertility to low levels of GPx4 activity and decreases in sperm motility and viability, suggesting that GPx4 is indispensable for structural integrity of spermatozoa (112).

C. Thyroid hormone deiodinases

The iodothyronine deiodinases (DIOs) connect selenium biology to thyroid hormone metabolism. Several extensive reviews on the topic are available (32, 34, 177, 178), but only brief aspects and recent updates are discussed herein. The family of DIOs consists of three differentially distributed, Sec-containing oxidoreductases (DIO1, DIO2, DIO3) that catalyze the activation (DIO1 and DIO2) and inactivation (DIO3) of the thyroid hormones thyroxine (T_4), 3,5,3′-triiodothyronine (T_3), and reverse-3,5,3′-triiodothyronine (rT_3) by removing distinct iodine moieties, as schematically indicated in Fig. 12. These hormones regulate various metabolic processes, such as thermogenesis, growth, and hearing, and are indispensable for the normal development of the fetal

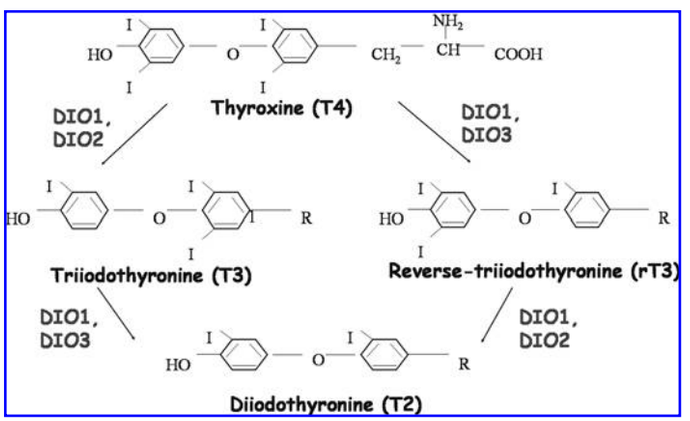

FIG. 12. Metabolism of thyroid hormone thyroxine (T_4) by the types 1, 2, and 3 deiodinases (DIO1, DIO2, DIO3). DIO1 and DIO2 catalyze the reduction of T_4 to yield the active form of hormone T_3, or, reverse T_3, rT_3, to yield T_2. DIO1 and DIO3 catalyze the deiodination of T_4 to rT_3, and of T_3 to T_2.

brain. They control gene expression in all vertebrate tissues via members of the thyroid hormone receptor (TR) family of transcription factors.

DIOs exhibit different patterns of expression during development and in adult tissues (287). For example, DIO1 is expressed mostly in the liver, kidney, thyroid, and pituitary; DIO2 in the thyroid, the central nervous system, the pituitary gland, and skeletal muscle; whereas DIO3 is most prominently expressed in the pregnant uterus, placenta, embryonic liver, embryonic and neonatal brain, and neonatal skin. The general belief is that DIO1 may play a role in T_3 production in the thyroid gland and controls the circulating T_3 levels, whereas DIO2 and DIO3 are proposed to function in the local deiodination processes, at a tissue- and organ-specific levels. However, recent evidence indicates that DIO2 may be a major source of circulating T_3 in euthyroid humans, whereas DIO1 may contribute more substantially at high, thyrotoxic T_4 levels, as seen in hyperthyroid patients (218). In addition, it has been shown that T_3 generated by intracellular DIO2 is much more effective in activating T_3-dependent gene transcription than that generated by DIO1, which further substantiates functional differences between DIO enzymes.

Despite differences in their amino acid sequence, all DIOs are structurally similar. They are integral membrane proteins that adopt a thioredoxin-foldlike structure with Sec present in the active site (33, 53). DIO1 and DIO3 are localized at the plasma membrane, whereas DIO2 resides in the ER membrane (22, 23). Presence of Sec appears to be absolutely required for their catalytic activity, as shown by *in vitro* expressed cysteine mutants that exhibit more than threefold reduced deiodinase activity (178). It is thus not surprising that selenium levels have a direct regulatory effect on the expression of DIOs. Among various selenoproteins, DIOs rank high in the hierarchy of selenium supply during selenium deficiency, DIO1 expression being maintained or slightly increased in the thyroid gland (24, 123, 135, 178). In brain and placenta, DIO2 and DIO3 expression is maintained during selenium restriction, whereas DIO1 expression decreases in other tissues. The mechanisms of DIOs regulation by selenium availability is not fully understood; nevertheless, it appears to be tissue or organ specific and also show hierarchy among the individual DIOs.

Additional regulators of DIOs expression are T_3 and thyrotropin (TSH), which act in a feedback loop, and cyclic adenosine monophosphate (cAMP) (177). T_3 induces transcription of the human *DIO1* gene via specific T_3 response elements (TREs) in the promoter, which are bound by TRs in response to nuclear accumulation of T_3 (309).

Knockout and transgenic mouse models have been generated for all DIOs, which have provided additional evidence about their physiologic roles (287). In brief, DIO1 and DIO2 knockout mice grow, develop, and reproduce normally in laboratory conditions, although they all showed aberrations in circulating thyroid hormones. However, some isoform-specific deficiencies were apparent. DIO2 knockout mice showed evidence of impaired auditory function and thermogenesis, as well as mild brain-function defects and temporary growth retardation. DIO1 mice had abnormal excretion patterns of thyroid-hormone metabolites including iodide, suggesting a role of DIO1 in conserving iodine stores within the organism, which could prove crucial during iodine deficiency. The DIO3 knockout model exhibited the most abnormal phenotype among the DIOs, having reduced viability, significant growth retardation, impaired fertility, and hypothyroid symptoms with significantly reduced T_3 and increased T_4 levels. The abnormal developmental pattern is likely attributed to DIO3 being a fetal enzyme. Continued phenotypic characterization of these mice, as well as cross-breeding among the different knockout mice, will provide important information regarding their roles in physiology (287). Interestingly, it also appears that DIO1 levels and activity are differentially expressed in male compared with female mice and also respond to selenium deficiency in a sex- and tissue- specific manner. Regulation of these effects appears to occur at both transcriptional and translational levels (269).

Well-documented pathologic conditions arising from primary DIO deficiency in humans have so far not been reported. However, the recent identification of SBP2 mutations in humans displaying a thyroid phenotype may provide a first such link (95). Apart from abnormal thyroid hormone levels, these rather young patients also manifested a transient growth retardation, which was, however, corrected at puberty. Interestingly, the transient growth retardation was similar to that observed in the DIO2 knockout mice (287). DIO2 activity was significantly decreased in skin fibroblasts and lymphocytes obtained from these patients, whereas DIO1 and DIO3 were not expressed and therefore not assessable. However, these enzymes are most likely also to contribute to the phenotype, because the loss of SBP2 appeared to cause a global selenoprotein synthesis defect (95). Altered expression and activity levels of DIOs have been reported in a number of tumors and cancer cell lines (7, 87, 170, 171, 324), suggesting a potential involvement of DIOs in cancer development, in particular in the thyroid.

Several diseases with disturbed thyroid hormone metabolism and expression of DIOs are known. Graves hyperthyroidism is an autoimmune disorder caused by the production of autoantibodies to the TSH receptor, present on the thyroid hormone, producing cells within the thyroid gland. The antibodies activate the cells in the same way as TSH itself, leading to an elevated production of thyroid hormone. The disease is diagnosed based on markedly elevated T_4 and T_3 levels, whereas TSH is suppressed. T_3 levels are known to induce DIO1 expression at the transcriptional level (34), which further contributes to the progression of the disease by elevating T_3 levels. The treatment for this condition uses antithyroid drugs such as propylthiouracil (PTU) which act predominantly by inhibiting the enzyme thyroid peroxidase; however, at higher concentrations, PTU also specifically inhibits DIO1 by binding to the Sec residue (201), which is advantageous in the treatment of severe hyperthyroidism (177). Interestingly, PTU does not seem to have a significant inhibitory effect on DIO2 and DIO3; the reason for this is not fully understood (32).

Hypothyroidism, conversely, is characterized by insufficient production of thyroid hormones, which can be caused by iodine deficiency, damage to the pituitary, or as a result of Hashimoto thyroiditis, an autoimmune disease caused by

antibodies against thyroid peroxidase, gradually destroying the thyroid gland. Also in these conditions, altered DIO levels are seen as a result of abnormal feedback regulation by thyroid hormones (34). Decreased DIO1 levels with a concomitant increased local DIO2 activity is observed, potentially to serve as a rescue mechanism to provide local levels of T_3. Recently, autoimmune antibodies to DIO2 in patients with Hashimoto thyroiditis and Graves disease have been reported, suggesting a direct pathophysiologic relation between DIO2 and autoimmune thyroid disease (240). Hypothyroidism during pregnancy can have detrimental effects, as even mild symptoms in the mother or the fetus can result in neonatal neurologic and cognitive deficiencies.

Combined selenium and iodine deficiency leads to the pathogenic condition named myxedematous cretinism (178). Decreased DIOs and GPx activity are both believed to be responsible for the development of this disease, acting through increased oxidative damage in the thyroid tissue due to insufficient GPx, as well as reduced thyroid hormone metabolism due to insufficient DIOs (178).

D. Selenoprotein P

Selenoprotein P (SePP, SelP) is the second major selenoprotein in plasma after GPx3 and is estimated to contain 50% of the plasma selenium (1, 264). SelP is secreted to the plasma by the liver in a glycosylated form; however, its expression is detected in all tissues (50). SelP is different from all other selenoproteins, as it incorporates multiple Sec residues per protein molecule (for example, 10 Sec residues in the human protein and 17 residues in the zebrafish homologue) (51, 184).

The main proposed role of SelP since its identification has been in the transport and delivery of selenium to remote tissues. This has been clearly confirmed in several studies by using the SelP knockout mouse models. Collectively, the studies demonstrate reduced selenium distribution to several tissues including the brain, testes, and the fetus, with consequential neurologic defects such as axon enlargement and degeneration, alteration in synaptic transmission in the hippocampus, impaired spatial learning, as well as growth defects and infertility in male mice (136, 253, 276, 277, 315). Interestingly, SelP knockout mice did not show any deficiencies in the thyroid hormone axis, and expression of DIOs was unaffected, suggesting that the thyroid system does not rely on SelP for its selenium supply (275). Conditional knockout of SelP in the liver, surprisingly, did not show a defect in selenium levels, selenoprotein expression, or a neurologic phenotype, as observed in the total SelP knockout, suggesting that locally expressed SelP plays an essential role in the brain (279). Collectively, it can be concluded that SelP does play a vital role in supplying selenium to various tissues, but locally expressed SelP may have additional functions, as demonstrated in the brain.

In addition to selenium transport, SelP may serve as a heavy-metal chelator (273), presumably by forming nontoxic Se–metal complexes, thus preventing neurotoxicity (330) and protecting against peroxinitrite-mediated oxidation and nitration (16). Because it can directly reduce phospholipid hydroperoxides *in vitro*, SelP may also have antioxidant functions (300). It has indeed been demonstrated that SelP protects endothelial cells (18, 291) and astrocytes (290) from oxidative damage and also inhibits oxidation of low-density lipoproteins (LDLs) (310).

Any clear link between SelP and disease has not yet been reported. Some evidence exists for decreased SelP levels in cirrhotic liver disease; however, this is as a consequence of impaired liver function rather than a causal effect (51). Downregulated SelP expression in prostate cancer tumors and colorectal carcinomas (2, 54) have been reported, whereas an oxidative stress–induced renal cancer model showed increased SelP levels (303). Low plasma SelPs were associated with a higher future risk of respiratory and digestive tract cancer in a case–control study of middle-aged men (252); however, the numbers are too small to derive any valid conclusions. In terms of selenium status assessment, a recent supplementation study found that plasma SelP is a more accurate marker for selenium saturation levels than the previously used GPx3 (338). SelP may also play a protective role against cardiovascular disease development by protecting vascular endothelial cells from oxidative damage (126). Based on the fact that SelP plays a major role in supplying the brain with selenium, as shown in mice models, and that a decrease in selenium content is found in brains from Alzheimer's disease patients (328), it is tempting to speculate that SelP may be directly involved in the etiology of this disease, and potentially other neurologic conditions (65). From the studies conducted so far, it is clear that SelP plays an important role in human health; however, future work will have to establish its involvement in specific pathologic conditions.

E. Sep 15

Sep 15 is among the first identified selenoproteins and was originally named the 15-kDa selenoprotein based on its molecular mass (27). Sep 15 is expressed in several tissues, with highest levels in brain, lung, testis, liver, thyroid, and kidney (191). Its expression is regulated in response to dietary selenium (103). The precise function of Sep 15 remains elusive. However, based on its localization to the ER, and interaction with the UDP-glucose:glycoprotein glucosyltransferases (GTs), a potential involvement in the quality control of glycoprotein folding within the ER has been proposed (179, 192). Recent structure-determination studies showed that Sep 15 is a member of the thioredoxin-like fold superfamily of proteins, highly homologous to the ER protein disulfide isomerase (PDI), and contains a surface-accessible, Sec-containing redox-active motif (-CXU-) (103). These data further strengthen the evidence that Sep15 may be a thiol-disulfide isomerase, involved in disulfide bond formation in the ER. Sep 15 may also play a role in regulation of apoptosis. In malignant mesothelioma cell lines, selenite-induced apoptosis was shown to depend on the presence of Sep 15 (9). Similar results were obtained in NIH3T3 cells (103); however, the mechanisms involved have not been characterized. So far, gene knockout mouse models have not been reported for Sep 15.

Sep 15 could be a potentially interesting candidate in pathologic aspects, particularly in cancers, although the evidence so far is scant. The effects of the SNPs within the

Sep 15 gene in cancer have already been discussed in the SECIS element section. In addition, the *Sep15* gene is located in a region of frequent loss of heterozygosity (LOH) (1p31) associated with malignancy, suggestive of a potential tumor-suppression function (69). Experimental proof for *Sep 15* LOH has so far only been provided from malignant mesothelioma (MM) cell lines (9) and in one patient with head and neck tumors (147). Sep 15 expression was also downregulated in liver tumors compared with normal livers from TGF-α/c-*myc* transgenic mice (191).

Because the evidence accumulated so far suggests that Sep 15 is required for apoptosis, and loss of Sep 15 is associated with malignancy, one can envisage a model (which also may apply to other selenoproteins) in which the loss of Sep 15 may be an early event in malignant transformation, allowing cells to escape death and proliferate into tumors. Clearly, continued functional characterization of Sep 15 and other selenoproteins is required to determine their involvement in cancer onset or predisposition, as well as its proposed role in mediating the chemopreventive effects of selenium.

F. Selenoprotein N

SelN is the only selenoprotein so far directly linked to a disease (230, 265), and unlike the other selenoproteins, its characterization started with a known loss-of-function phenotype. Several forms of early-onset myopathies characterized by hypotonia, weakness, axial muscle impairment, spinal rigidity and life-threatening respiratory failure have been linked to the SelN gene (*SEPN1*) locus (265). These include rigid-spine muscular dystrophy, multiminicore disease, and Mallory body–like desmin-related myopathy, and are collectively referred to as *SEPN*-related myopathies. Several pathologic *SEPN1* mutations within the coding region and the 5′UTR, and also within the SECIS element (discussed earlier), have been identified in patients with SEPN-related myopathies (105, 230). However, the underlying molecular mechanisms behind the SelN-dependent myopathies are poorly understood because the functional characterization of this protein is lagging behind. So far, it has been demonstrated that the SelN is ubiquitously expressed in tissues, and it generates a 65-kDa glycoprotein localized in the ER membrane. In mouse, its expression is particularly increased during embryonic development (254). Similarly, an early developmental expression pattern in somites and the notochord, which are the precursors to muscle and spinal cord, respectively, was observed in zebrafish embryos (306). Thus, although the biologic function of SelN is unknown, it is clear that it plays a vital role in muscle tissue.

G. Selenoprotein W

Selenoprotein W (SelW, Sepw1, SeW) is a small, 9.5-kDa protein, highly conserved among mammalian species, with the Sec residue present in the N-terminal region as part of the -CXXU- redox motif (124, 317). SelW is ubiquitously expressed in tissues, and its expression is regulated by selenium levels. Selenium deficiency causes reduction of SelW in skeletal muscles, heart, intestine, prostate, esophagus, and skin; however, its expression in the brain remains preserved during selenium deficiency (332). During embryonic development, Sel W is expressed as early as implantation and gastrulation, and subsequently, within the nervous system, limbs, and heart (210). Within the cell, SelW is localized predominantly in the cytoplasm, and a small fraction is bound to the cell membrane (344). SelW binds glutathione with very high affinity, which in early studies suggested a potential antioxidant function (28). Overexpression of SelW in cell cultures indeed protects cells against oxidative stress, and its levels are upregulated in response to exogenous oxidants in muscle cells. Both glutathione-binding and Sec residues were required for the antioxidant protection (163). However, the molecular pathways involved are not yet elucidated. The SelW promoter contains metal and glucocorticoid response elements (MREs and GREs) (6) as well as additional regulatory elements that differentially regulate its expression in muscle and glial cells (144). Metal-transcription factor-1 (MTF-1) was recently shown to regulate SelW expression in the liver (335).

SelW was originally identified as a selenoprotein lost in the muscle of selenium-deficient sheep with a condition called the white muscle disease. Although its function remains unknown, an involvement of SelW in muscle disease was proposed. Consistent with this, recent data show an early developmental expression pattern of SelW in muscle progenitor cells and high expression levels in proliferating myoblasts, suggesting a specific role of SelW in muscle. SelW is also one of the selenoproteins expressed in brain, where its expression levels are maintained during selenium deficiency. Moreover, SelW promoter activity and expression is specifically induced in response to metals in cultured glial cells (6), suggesting a potential specific function also in the brain. Genetic studies and animal models with tissue-specific targeted disruption of SelW are needed to provide ultimate proof for the role of SelW in muscle and brain development, as well as in muscle-related and neurologic diseases.

H. Selenophosphate synthetase 2

SPS2 is intriguingly a selenoprotein involved in the Sec biosynthesis that is required for its own synthesis. SPS2 catalyzes the conversion of selenide to selenophosphate, which is the selenium donor in the formation of Sec, as depicted in Fig. 2 (125). It has also been demonstrated that SPS2 has preferential substrate activity for selenide derived from selenite rather than Sec (302). Although not much else is known about the physiologic role of SPS2 and any implications in disease, it is clearly an essential component of the Sec biosynthesis machinery.

I. Selenoprotein R

SelR, also known as methionine-*R*-sulfoxide reductase (Msr) B1 (MsrB1), is a member of the Msr family of proteins, which catalyze the reduction of oxidized methionine (Met) residues (methionine sulfoxides). Oxidation of Met occurs in response to an increase in ROS, which can lead to protein damage, and if unrepaired, to abrogated protein function (288). Methionine sulfoxides occur in a mixture of *R* and *S* isomers *in vivo*, methionine-*S*-sulfoxides and methionine-*R*-sulfoxides. SelR was shown specifically to reduce the *R*-isomer, and the Sec residue is crucial for enzymatic activity (173, 186). SelR also binds zinc, via four cysteine residues, and

zinc binding is involved in the catalytic reduction of sulfoxides. SelR is predominantly localized in the nucleus and the cytoplasm of cells (173). Thus, SelR is a redox-active selenoprotein with a specific enzymatic function, required for the repair of oxidative damaged proteins. Recently, SelR and Cys-containing isoforms were shown to be required for lens cell viability, and their silencing in lens cells resulted in increased oxidative-stress–induced cell death, suggesting that they are important for lens cell function, resistance to oxidative stress, and may potentially play a role in cataract formation (221).

In general, studies have showed that mutations leading to a decrease in Msr activities are associated with a decrease in resistance to oxidative stress and to a shortening of the maximal lifespan. On the contrary, overexpression of Msr activities leads to an increase in resistance to oxidative stress and a significant increase in lifespan (288). Thus SelR may potentially be one of the selenoproteins through which selenium conveys its antiaging properties, and because its high levels of expression in brain, it may also play an important role in neurologic conditions.

J. Selenoprotein M

Selenoprotein M is a selenoprotein distantly related to Sep15, with the Sec residue present as part of a -CXXU- motif in its N-terminal region, which is suggestive of a redox function (180). In SelM, Sec is incorporated in response to the rare SECIS variant that contains the CC residues in the apical loop (Fig. 3). In mouse, SelM is moderately expressed in various tissues including the heart, lung, kidney, uterus, and placenta, and highly expressed in thyroid and brain (180). Interestingly, overexpression of the presenilin-2 (PS2) gene responsible for the early-onset Alzheimer's disease caused the suppression of SelM, but not SelP, in the brain of transgenic mice (152). Detailed studies of SelM in the brain are required to establish its function and potential involvement in disease.

K. Selenoprotein S

SelS (SEPS1) was initially cloned from diabetic rats, as it was observed that its expression was decreased in fasting diabetic animals. The protein was characterized under the name Tanis; however, the penultimate Sec residue was misinterpreted as a stop codon (323). The same study found that SelS expression is inhibited by glucose and that SelS interacts with serum amyloid A (SAA), an acute-phase inflammatory response protein. Based on these findings, it was proposed that SelS, through its interaction with SAA, may provide a mechanistic link between type 2 diabetes, inflammation, and cardiovascular disease.

SelS expression is induced in response to ER stress, via an ER stress-response element within the SelS promoter and via the nuclear factor (NF)-κB pathway (116). SNPs within the SelS promoter were found to significantly alter SelS expression after exposure to ER stress agents, and depletion of SelS by siRNA increased the release of inflammatory cytokines IL-6 and TNF-α, suggesting that SelS may regulate cytokine production in macrophages and may thus play a role in the control of the inflammatory response (82, 116).

L. Selenoprotein K

Human SelK is a 94-amino-acid protein with Sec residing at the penultimate position (184). SelK was only recently characterized (211). It was shown that SelK is expressed predominantly in the heart and skeletal muscle, but other tissues such as the pancreas, liver, and placenta also have detectable levels of SelK. The proposed localization of SelK is within the ER (211) and the plasma membrane (184). Overexpression of SelK decreased the levels of intracellular ROS and protected cardiomyocytes against exogenously imposed oxidative stress. These findings suggest that SelK may perform an antioxidant function in the heart (211).

M. Functionally uncharacterised selenoproteins

Selenoproteins that have not been characterized include SelH, SelO, SelI, SelT, and SelV. All proteins, apart from SelI, contain CXXU motifs that predict a redox-related function and will require experimental verification in the near future.

IV. ORGANOSELENIUM COMPOUNDS AND SELENOPROTEINS AS POTENTIAL CHEMOPREVENTIVE AND THERAPEUTIC TARGETS

Selenium compounds have shown protective effects against various cancers. Both organic and inorganic forms of selenium have been used. The prototypes most commonly used are sodium selenite and selenomethionine. The majority of the epidemiologic and prospective studies conducted in different worldwide regions have shown an inverse relation between selenium status and risk of cancer and cancer mortality (298). Several case–control studies also confirmed that selenium levels in blood, serum, hair, and toenails are lower in cancer patients than in control subjects (298). A significant inverse correlation between baseline selenium and death of esophageal and gastric cancer (325), as well as lung cancer risk (267), have been found. These findings suggest that selenium supplementation may have protective effects against some types of cancer in individuals with lower dietary selenium intake.

The epidemiologic data stimulated interest in testing selenium as a chemopreventive agent in human clinical trials. Chemoprevention trials have been carried out in regions of China with a high incidence of hepatocellular carcinoma due to high incidence of hepatitis B combined with high aflatoxin contamination of food. The incidence of cancer was decreased by 35% in selenium-salt–supplemented group (346). However, because the health and environmental insults are radically different in China compared with those in the westernized world, the conclusions from this trial cannot be interpreted as universal. The first double-blind study of selenium as a chemopreventive agent was the Nutritional Prevention of Cancer initiated by Clark and colleagues (74). Although selenium treatment did not significantly affect the incidence of nonmelanoma skin cancer, patients receiving the supplement showed a significantly lower risk of cancer developing at

other sites: lung, prostate, colon, or rectum (74, 93). Prostate cancer incidence decreased by a striking 65%. The main conclusion from this trial was that the protective effect of selenium against cancer was strongest in those participants who had comparatively low baseline selenium concentration in the blood at the time of entering the study.

These data have provided impetus for additional human trials, including a multicenter trial designated Prevention of Cancer by Intervention with Selenium (PRECISE) with Denmark, the U.K., and Sweden as key participants. Two 5-year pilot studies in the U.K. and in Denmark have been completed. The Danish pilot trial, which involved 500 elderly, aged 60–74 years, was a placebo-controlled dose–response trial using supplementation with yeast selenium at 100, 200, or 300 μg Se/day or placebo. The selenium concentrations in whole blood, plasma, and in toenails, which were used as biomarkers of selenium intake, ranked the subjects in the same way according to dosage group and demonstrated good compliance. It was concluded that toenail selenium could be used as a noninvasive biomarker of compliance. Furthermore, the results showed that glutathione reductase activity was increased in erythrocytes in the highest-dosage group but not in plasma, and that the GPx activity was increased in thrombocytes among women receiving the middle and the highest selenium dosages. Currently, funding is being sought for continued studies (E. H. Larsen and K. Overvad, personal communication). A prospective, randomized and double-blind, placebo-controlled multicenter trial, designated as SELECT, is also under way to determine the protective effect of selenium and vitamin E on the risk of prostate cancer (208). Another trial will evaluate the ability of selenium to halt or slow the preclinical progress of prostate cancer (293). This trial is applicable for men with persistent elevated prostate-specific antigen (PSA) but who have negative biopsies. Another trial is under way that will evaluate the ability of selenium to prevent the transformation of neoplasia into invasive cancer. This trial is applicable for men with high-grade prostatic intraepithelial neoplasia with a negative biopsy for invasive prostate cancer (222). Finally, a trial is under way to study the effect of selenium on the progression of prostate cancer. Participants in this trial are men who have biopsy-proven prostate cancer who have elected to forego therapy and have instead opted for watchful waiting (294). Outcomes from these trials will provide further clues toward understanding the chemopreventive and chemotherapeutic effects of selenium in different cancer models.

Animal studies have also shown protective effect of various forms of selenium against many types of cancers, including liver, skin, mammary gland, and colon. In particular, development of 7,12-dimethylbenz[a]anthracene (DMBA)–induced breast cancer and UV-induced skin cancer were significantly reduced in selenium-fed animals (176, 259). In rat models, selenium supplementation also significantly reduced the carcinogenetic process in chemically induced liver cancer when administered both during the promotion and the progression phases (36).

The protective effects of selenium are postulated to be due to its metabolism into low-molecular-weight selenocompounds and because of its role in the regulation and activity of selenium-containing proteins or selenoproteins. A number of potential mechanisms are proposed for the chemopreventive effects of selenium, including stimulation of apoptosis, induction of cell-cycle arrest, activation of the tumor-suppressor p53, induction of DNA-repair genes, enhancement of immune functions, and influence on estrogen- and androgen-receptor expression (298). Transgenic and knockout mouse models have clearly implicated direct roles of selenoproteins in some cancer models. However, despite the data that have been gathered so far, the connection between selenium and cancer remains intriguing and elusive.

A. Selenium compounds and selenoproteins as therapeutic targets

Selenoproteins play a critical role in many vital cellular functions and are therefore essential for disease prevention, including heart disease, neurodegeneration, liver disease, and cancer, as discussed earlier. However, because the functions of most mammalian selenoproteins discovered are not known, their potential as therapeutic targets so far has only limited applications. Many of the stable organoselenium compounds that have been developed are being tested as antioxidants, immunomodulators, and anticancer and antihypertension agents. Of particular interest is ebselen, which originally was shown to mimic the action of GPx (237). Many diseases are associated with overproduction of hydroperoxides that inflict cell damage, and ebselen is effective against H_2O_2 and smaller organic hydroperoxides. Ebselen has a potent anti-inflammatory activity in various animal models (274, 283). Because of these properties, ebselen has been used in the treatment of patients with acute ischemic stroke (15, 247, 341). Recent animal studies also show neuroprotective, antioxidant, and anti-inflammatory actions of ebselen in a rodent model of transient cerebral artery occlusion (84, 154). Recently, ebselen was shown to be an excellent substrate for mammalian TrxR and a superfast oxidant of reduced Trx (352). Therefore, ebselen is mainly a peroxiredoxin mimic, and its target is the thioredoxin system (351, 352). Ebselen is reduced to the selenol by TrxR or Trx and reoxidized by peroxides, including hydrogen peroxides. Ebselen also stimulates the reduction of dehydroascorbic acid (vitamin C) (350).

Several features of TrxR make it a suitable target for anticancer therapies. These include its requirement for cancer cell proliferation, its high levels of expression in cancer cells, and the accessibility of its active site for reaction with reactive compounds. Many of the clinical anticancer drugs such as nitrosourea, cisplatin (11), diaziquone, doxorubicin (226), and potential cancer therapeutic agent motexafin gadolinium (127) have been shown to be excellent inhibitors of TrxR, and therefore could gain wider applications in cancer treatment in the future. TrxR as a proposed anticancer drug target is shown in Fig. 13.

Natural polyphenols are distributed in the plant kingdom and prokaryotes and have been assumed to possess biologic properties such as antioxidant, antiproliferative, or anti-inflammatory activity and are proposed to be preventive in cancer and cardiovascular disease. We have found that curcumin (102) and flavonoids such as quercetin, myricetin (212) have strong, specific, inhibitory effects on mammalian TrxRs. The inhibition involves an attack by these compounds

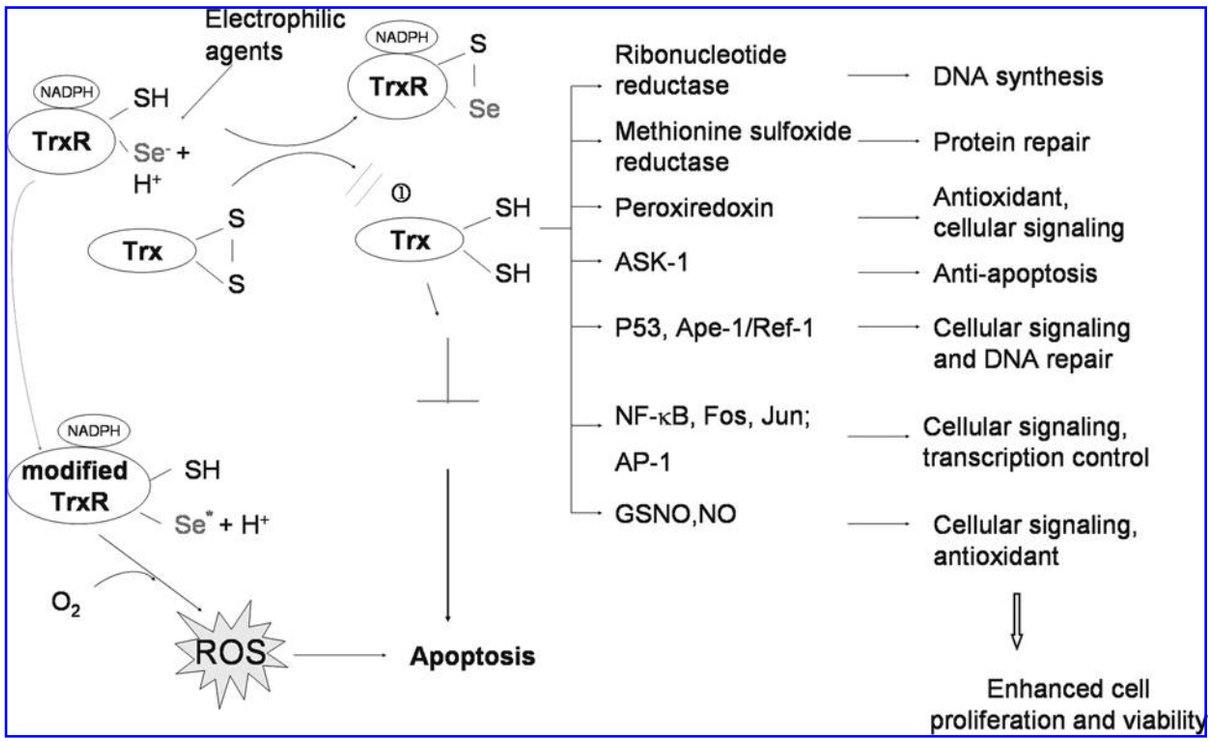

FIG. 13. Thioredoxin reductase in normal physiology and as an anticancer target. TrxR is the only enzyme known to catalyze the NADPH-dependent reduction of oxidized thioredoxin. Together with NADPH, TrxR and Trx comprise a thioredoxin system that catalyzes the reduction of protein disulfides within substrates as listed, which control several signaling pathways. Inhibition of TrxR emerges as a novel cancer-therapy strategy. TrxR inhibition induces the accumulation of oxidized Trx, leading to inhibition of Trx-controlled cellular activities such as cell proliferation, antioxidant defense, and apoptosis induction. TrxR inhibition by some agents may also result in Sec-modified TrxR and increase of ROS promoting apoptosis.

on the reduced C-terminal Cys-Sec-Gly active site of TrxR (212). Furthermore, flavonols with large numbers of heteroaromatic quinols have been reported to possess anticancer activity because of inhibition of TrxR (43). Taken together, it appears that TrxR is an effective target for cancer therapeutics that deserves more attention.

V. CONCLUDING REMARKS

The past 10 years have been an exciting time in selenium research. A considerable increase has occurred in our knowledge about the roles played by selenium compounds and selenoproteins in human health. Several selenium compounds such as sodium selenite, SeMet, or organo-selenium compounds have been shown to have promising cancer-preventive activity in model systems, animal studies, and clinical trials. Conversely, selenium has a very low therapeutic window, as in high doses, selenium compounds have a negative effect on DNA integrity and repair and might possibly increase cancer risk. Therefore, further studies are urgently required to evaluate the safety of both the dietary and pharmacologic application of selenium and to establish valid biomarkers in terms of adequacy of intake and functional requirements. With regard to mechanistic issues, a better understanding is needed for the molecular aspects of selenium-dependent chemoprevention, in particular, the possible roles of selenoproteins. The application of gene knockout technology for selenoproteins in carcinogenesis models will help to determine whether the chemopreventive effects of selenium are seen in models that preclude selenoprotein synthesis. Knowledge of selenoprotein synthesis has increased considerably, but at the same time, a number of questions remain unresolved, such as the dynamics of the supramolecular protein–RNA–ribosome complex that controls Sec biosynthesis and its subsequent incorporation into selenoproteins.

Selenoproteomes in species from all domains of life have been recently characterized, not only providing an evolutionary insight into how this family of proteins may have evolved, but also laying the foundation for the functional characterization of these proteins and elucidating their potential involvement in the etiology of disease. TrxR and GPx are well characterized as major components of the antioxidant defense, with roles in many cellular processes. DIOs are enzymes involved in thyroid hormone metabolism. Other selenoproteins are involved in transport, metabolism, and storage of selenium. Strikingly, only one selenoprotein, SelN, has been directly linked to some forms of myopathy, which might help in development of therapeutic strategies. At least nine selenoprotein families exist for which a definite function

has not yet been attributed. Alhough possible roles in redox functions are predicted, functional characterization of these newly discovered members might reveal novel functions.

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ABBREVIATIONS

ARE, antioxidant response element; BRCA1, breast cancer susceptibility gene 1; Cys, Cysteine; CRM1, chromosomal region maintenance protein 1; CRD, cysteine-rich domain; DIO, thyroid hormone deiodinase; ER, endoplasmic reticulum; eEFSec, sec-specific elongation factor; GSH, glutathione; GR, glutathione reductase; GSNO, *S*-nitrosoglutathione; GPx, glutathione peroxidase; IRES, internal ribosomal entry site; L30, the ribosomal protein L30; LOH, loss of heterozygosity; mcm^5U, 5-methylcarboxymethyluridine; mcm^5Um, 5-methylcarboxymethyluridine-2'-*O*-methylribose; NADPH, nicotinamide adenine dinucleotide phosphate; NMD, nonsense-mediated decay; NLS, nuclear localization signal; NES, nuclear export signal; NO, nitric oxide; PTU, propylthiouracil; RBD, RNA-binding domain; RNP, ribonucleoprotein-binding domains; ROS, reactive oxygen species; RRM, RNA recognition motif; SBP2, SECIS-binding protein 2; Se, selenium; Sec, selenocysteine; SeMet, selenomethionine; SECIS, selenocysteine insertion sequence; Secp43, 43-kDa RNA-binding protein; SELENBP, selenium-binding protein; *SEPN1*, Sel N gene; SPS, selenophosphate synthetase; SLA, soluble liver antigen protein; SNPs, single-nucleotide polymorphisms; SRE, selenocysteine redefinition element; SV40, simian virus 40; Trx, thioredoxin; T_4, thyroxine; T_3, 3,5,3′-triiodothyronine; rT_3, reverse-3,5,3′-triiodothyronine; TSH, thyroid-stimulating hormone/thyrotropin; TrxR, thioredoxin reductase; *trsp*, Sec $tRNA^{[Ser]Sec}$ gene; Yap-1, yeast-activator protein 1.

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Address reprint requests to:
Kum Kum Khanna and Laura Papp
Cancer and Cell Biology Division
Queensland Institute of Medical Research
300 Herston Rd, Herston 4006, QLD
Australia

E-mail: kumkumK@qimr.edu.au
lauraP@qimr.edu.au

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