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Selenium and selenocysteine: roles in cancer, health and development

Dolph L. Hatfield[1], **Petra A. Tsuji**[2], **Bradley A. Carlson**[1], and **Vadim N. Gladyshev**[3]

[1]Molecular Biology of Selenium Section, Mouse Cancer Genetics Program, Center for Cancer Research, National Institutes of Health, Bethesda, MD 20892

[2]Department of Biological Sciences, Towson University, Towson, MD 21252

[3]Division of Genetics, Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115

Abstract

The many biological and biomedical effects of selenium are relatively unknown outside the selenium field. This fascinating element, initially described as a toxin, was subsequently shown to be essential for health and development. By the mid 1990s, selenium emerged as one of the most promising cancer chemopreventive agents, but subsequent human clinical trials yielded contradictory results. However, basic research on selenium continued to move at a rapid pace elucidating its many roles in health, development, and cancer prevention and promotion. Dietary selenium acts principally through selenoproteins, most of which are oxidoreductases involved in diverse cellular functions.

Keywords

Cancer; selenium; selenocysteine; selenoproteins

Selenium in animal nutrition and human health

Selenium has been linked to many health benefits in humans and other mammals such as decreasing the incidence of cancer, protecting against cardiovascular diseases, treating certain muscle disorders, and delaying the onset of AIDS in HIV-positive patients [1]. It also has roles in mammalian development and boosting immune function. Although small molecular weight selenocompounds have been implicated as beneficial agents in several cases, this is mostly due to high levels of selenium used in chemotherapy, and most attention in recent years has been given to selenoproteins being the primary responsible agents [1].

Selenium was initially considered a toxin, because it was responsible for a disorder in livestock that grazed on the plains of the Nebraska and Dakota territories. This disorder was described in 1856 by army surgeon T.C. Madison, stationed at Fort Randall in northern Nebraska [2]. The army horses that grazed freely around the fort suffered from a necrotic hoof malady and excessive losses of long hair in the tail and mane. Franke reported in the

Corresponding author: Hatfield, D.L. (hatfield@mail.nih.gov).

mid 1930s that the disease resulted from livestock eating seleniferous plants, which accumulated high levels of selenium from the soil [3].

Selenium continued to be regarded as a toxin, and even a carcinogen, until 1957 when Schwartz and Foltz found that it prevented liver necrosis in rats [4]. Thus, it became apparent that selenium was toxic at high levels but was an essential dietary micronutrient at low levels. The beneficial side of selenium was rapidly recognized in the livestock industry: the deficiency of this element was implicated in a number of disorders including white muscle disease, a myopathy affecting calves and lambs; pancreatic degeneration and exudative diathesis in birds and other livestock; hepatosis dietetica in swine; and ill thrift and reduced male fertility in sheep and cattle [5]. Supplementing the diets of livestock around the world with selenium was estimated to save this industry in the hundreds of millions of dollars. In the human population, low selenium status has been associated with Keshan disease, a cardiomyopathy found in rural areas of China, and Kashin-Beck disease, a chronic, endemic osteochondropathy found primarily in northeastern to southwestern China ([6] and references therein).

Of all the health benefits attributed to selenium, the one that has received the most attention is its role as a cancer preventive agent. In fact, hundreds of millions of dollars have been spent on human clinical trials examining the role of selenium in cancer prevention (e.g., see [7–12]). While at least one trial has shown a decreased incidence in prostate, colon and lung cancers [7], others found no positive health benefits (e.g., see [8,9]), and the largest cancer prevention trial ever undertaken was terminated early [8]. Questions arose whether these clinical trials were being carried out with insufficient understanding of how selenium functions at the molecular level [13,14]. Little consideration was also given to the selenium status of the participants or the potential negative consequences of administering selenium to such large numbers of individuals. Another concern was the recent evidence that certain selenoproteins manifest a dual personality in that they not only prevent, but can promote cancer (discussed later and reviewed in [15,16]).

Occurrence of selenocysteine (Sec) in protein and selenoprotein functions

Sec, the 21st amino acid in the genetic code

Sec is a selenium-containing amino acid that occurs in proteins in organisms representing the three domains of life (Eukarya, Archaea and Bacteria) as well as in viruses. Selenium was originally detected as a covalently-bound component in mammalian glutathione peroxidase [17] and the selenium-containing amino acid was subsequently identified as Sec in bacterial selenoprotein A [18]. Sequencing selenoprotein genes revealed that the UGA codon corresponded to the location of Sec in proteins [19,20], suggesting that Sec was the 21st proteinogenic amino acid.

Selenoproteins and selenoproteomes

To date, approximately 100 selenoprotein families have been discovered. There is a great diversity in the use of selenoproteins by organisms. The largest set of selenoproteins (selenoproteome) has been observed in a unicellular brown alga that has 59 selenoprotein genes [21]. With regard to common model organisms, zebrafish has 37, mouse has 24, *Drosophila melanogaster* and *Escherichia coli* have three, and *Caenorhabditis elegans* has one, whereas *Saccharomyces cerevisiae* and *Arabidopsis* do not encode selenoprotein genes.

Functions of mammalian selenoproteins

The human selenoproteome is encoded by 25 genes. Approximately half of these genes code for proteins with known functions [22] (Fig. 1). Humans have five selenoprotein glutathione

peroxidases, which catalyze glutathione-dependent reduction of hydrogen peroxide or other peroxides; three thioredoxin reductases, which catalyze the reduction of thioredoxin or other proteins at the expense of NADPH; and three thyroid hormone deiodinases, which catalyze reductive deiodination of thyroid hormones, thereby activating or inactivating them [23]. There is also methionine-*R*-sulfoxide reductase 1 (MsrB1), which reduces oxidized methionine residues in proteins (repairing oxidatively damaged proteins and serving as a part of the redox regulation system involving reversible oxidation of particular methionine residues) [24]. In addition, human selenophosphate synthetase 2 is a selenoenzyme that catalyzes the ATP-dependent synthesis of selenophosphate, a selenium donor compound for Sec biosynthesis [25]. One human selenoprotein, Selenoprotein P, has 10 Sec residues. This plasma protein is synthesized primarily in the liver [26,27] and delivers selenium to other organs (see [28,29] and references therein).

The specific functions of several other human selenoproteins are unknown, although many details of their biology have been established [30]. Among these, Selenoproteins S and K are ER membrane proteins involved in retrotranslocation of misfolded proteins from the ER to cytosol for subsequent degradation by the proteasome. The 15 kDa selenoprotein, Sep15, is an ER-resident protein implicated in quality control of protein folding. There is also a distant Sep15 homolog of unknown function, designated Selenoprotein M. Characteristic features of other selenoproteins include the nucleolar subcellular localization of Selenoprotein H and testis-specific expression of SelV. Selenoproteins T, V, H and W form a subfamily characterized by a thioredoxin-like fold with the Sec located in the N-terminal region of this domain, whereas Sec is located in the C-terminal region (typically the second or third amino acid from the end) of SelS, SelK, SelI and SelO. The latter protein is also the largest mammalian selenoprotein, and it is located in mitochondria. The physiological and biochemical functions of SelN have been linked to muscle disorders and control of ryanodine receptor, respectively. However, none of the specific functions of these selenoproteins are known.

At least three mammalian selenoproteins, thioredoxin reductase (TR) 1, TR3 and glutathione peroxidase (GPx) 4, are essential for development in mice, whereas knockout mice deficient in GPx1, GPx2, GPx3, Sep15, MsrB1, and SelM are viable and have only mild phenotypes in the absence of stress [31]. SelP knockout mice are associated with systemic selenium deficiency, and this phenotype can be rescued by supplementation with dietary selenium [32,33].

Selenoproteins are oxidoreductases

Essentially all functionally-characterized selenoproteins are oxidoreductases [30] in which Sec is the catalytic residue. Clearly, the unique catalytic properties of Sec are the reason selenium is used in these proteins. However, there is no consensus as to what these properties are. Suggestions include the nucleophilicity of Sec, its low pKa (e.g., compared to Cys), its ability to be a leaving group and its resistance to inactivation by overoxidation [34]. These properties can be partially compensated for by Cys (e.g., Cys mutants of most selenoproteins preserve ~1% activity, and in addition, Cys homologs are known for most selenoproteins), but not by any other residue.

Recent studies revealed an interesting regulatory role for a selenoprotein. MsrB1 and two Mical proteins, were found to regulate actin through reversible stereo specific methionine oxidation [35]. Actin polymers can be disassembled by Mical-catalyzed oxidation of Met41 and Met44 to methionine-*R*-sulfoxide residues, whereas reduction of these residues back to Met by MsrB1 promotes actin repolymerization [35]. This study also established a new type of regulatory posttranslational modification.

Occurrence of selenoproteins

Approximately half of eukaryotes have selenoproteins, whereas only about 25% of bacteria and 15% of archaea preserved these proteins during evolution [36]. Biosynthesis and insertion of Sec into proteins require several genes; therefore, once this trait is lost, it cannot be restored. The only known exception is the rare event of lateral transfer of an operon responsible for the Sec trait in prokaryotes [37].

Overall, there is currently a very good understanding of which organisms utilize selenoproteins, and which do not. Information is also available with regard to identification of selenoproteins and location of their Sec residues. The principal function of selenoproteins is their participation in redox homeostasis, although the specific functions are diverse. Functions of about half of human selenoproteins remain unknown.

Sec tRNA and biosynthesis of Sec

Being the 21st amino acid in the genetic code, Sec has its own tRNA, which is one of the major players in the Sec insertion machinery. It is also the only known tRNA that controls the expression of an entire class of proteins. Because this tRNA is initially aminoacylated with serine, Sec tRNA is often designated as tRNA$^{[Ser]Sec}$. The tRNA$^{[Ser]Sec}$ population consists of two isoforms in mammals that differ from each other by a single 2'-*O*-methylribose at position 34 designated Um34 [38]. The synthesis of Um34 is dependent on selenium status and the resulting isoform, 5-methoxycarbonylmethyluracil-2'-*O*-methylribose (mcm^{5}Um), is enriched under conditions of selenium adequacy and poorly expressed under conditions of selenium deficiency. The isoform lacking Um34, 5-methoxycarbonylmethyluracil (mcm^{5}U), is less dependent on selenium status and is expressed under conditions of selenium deficiency [38].

These two Sec tRNA$^{[Ser]Sec}$ isoforms have different roles in mammalian selenoprotein synthesis [38], and are involved in the expression of different subclasses of selenoproteins. Mcm^{5}U is involved in the synthesis of housekeeping selenoproteins and mcm^{5}Um in the synthesis of stress-related selenoproteins (see section below "Roles of selenoproteins in health and development").

In all life forms that synthesize Sec on its tRNA, serine is initially attached to tRNA$^{[Ser]Sec}$ by seryl-tRNA synthetase (Fig. 2). In archaea and eukaryotes [39,40], seryl-tRNA$^{[Ser]Sec}$ is converted to phosphoseryl-tRNA$^{[Ser]Sec}$ by phosphoseryl-tRNA$^{[Ser]Sec}$ kinase (PSTK). This intermediate is then acted upon by selenocysteine synthase (SecS), wherein SecS converts the phosphoserine moiety to the acceptor molecule, likely aminoacrylyl-tRNA$^{[Ser]Sec}$, for receiving the activated selenium donor, selenophosphate, resulting in the final product of the pathway, selenocysteyl-tRNA$^{[Ser]Sec}$ (Fig. 2). Selenophosphate is synthesized from selenide and ATP by selenophosphate synthetase 2 (SPS2). Since SPS2 is a selenoprotein, it may be involved in the auto regulation of selenoprotein synthesis [25]. In bacteria, SecS (designated SelA in bacteria) acts directly upon Ser-tRNA$^{[Ser]Sec}$, converting the serine moiety to an intermediate, likely aminoacrylyl-tRNA$^{[Ser]Sec}$ as also occurs in eukaryotes, that in turn accepts selenophosphate, synthesized by selenophosphate synthetase SelD to yield Sec-tRNA$^{[Ser]Sec}$ [41].

Cys was also found to be incorporated into the selenoproteins TR1 and TR3, in place of Sec by a *de novo* pathway for Cys synthesis in mammalian cells and mouse liver [42]. The pathway involved replacing sulfide with selenide in the reaction with SPS2 to yield thiophosphate, which serves as a sulfur donor to yield Cys-tRNA$^{[Ser]Sec}$ that inserts Cys at UGA codons of selenoprotein mRNAs (Fig. 2).

Incorporation of Sec into protein

A specific cis-acting stem-loop structure, designated the Sec Insertion Sequence (SECIS) element, plays a major role in recoding UGA from stop to Sec [43]. The SECIS elements in archaea, bacteria and eukarya have completely different sequences, motifs and secondary structures [44]. Eukaryotic SECIS elements fall into two basic classes, designated Type I and II, and occur in the 3'-untranslated region of selenoprotein mRNAs. Archaeal SECIS elements have been found in both 3'-UTRs and 5'-UTRs of selenoprotein genes. In bacteria, SECIS elements are more simplified and occur within the coding regions immediately downstream of the UGA codon. They serve as the attachment site for the specific elongation factor, SelB, which is brought to the ribosome in a complex with Sec-tRNA$^{[Ser]Sec}$ [45]. The insertion of Sec in archaea and eukaryotes is more complex and involves additional factors. The specific elongation factor, EFsec, forms a complex with Sec-tRNA$^{[Ser]Sec}$ (EFsec-Sec-tRNA$^{[Ser]Sec}$) that binds to the SECIS binding protein 2 (SBP2)-SECIS complex and the ribosome [45]. In addition, there are at least three other factors, ribosomal protein L30 [46], nucleolin [47] and eukaryotic initiation factor (eIF4a3) [48], that have roles in Sec insertion into protein. Although their precise roles in the incorporation process remain unclear, ribosomal protein L30 serves as part of the basic machinery responsible for Sec insertion, whereas nucleolin and eIF4a3 likely have regulatory roles tempering selenoprotein synthesis. A plausible mechanism of Sec incorporation into protein and how these factors are involved is shown in Figure 3.

Roles of selenoproteins in health and development

Mouse models involving Sec tRNA$^{[Ser]Sec}$ to elucidate the roles of selenoproteins in health and development

Various mouse models have been generated that use tRNA$^{[Ser]Sec}$ as a tool to providing a systems-level understanding of the roles of selenium and selenoproteins in health and development. These models encode: 1) transgenes carrying either wild type (designated *Trsp*^{t}) or mutant forms of tRNA$^{[Ser]Sec}$; 2) conditional knockout of the tRNA$^{[Ser]Sec}$ gene (*Trsp*$^{\Delta}$) targeting specific tissues and organs; and 3) *Trsp*$^{\Delta}$ complemented by *Trsp*^{t} or mutant tRNA$^{[Ser]Sec}$ transgenes, A37→G37 and T34→A34, designated *Trsp*^{tG37} and *Trsp*^{tA34}, respectively [38]. *Trsp*^{tG37} prevents N^6-isopentyladenosine formation at position 37 that in turn prevents Um34 synthesis [38]. The Um34 isoform of tRNA$^{[Ser]Sec}$, mcm^{5}Um, is required to synthesize a subclass of stress-related selenoproteins (e.g., GPx1), whereas the non-Um34 isoform, mcm^{5}U, synthesizes housekeeping selenoproteins (e.g., TR1) [49].

Trsp^{tA34} has A in its wobble position that is converted to inosine and the resulting anticodon, ICA, decodes UGA and the Cys codons, UGU and UGC. Twenty and 40 copies of *Trsp*^{t} and *Trsp*^{tG37}, respectively, were used in transgenic mice [50]. The more copies of the mutant *Trsp*^{tG37} transgene used, the less influence that the wild type Sec tRNA$^{[Ser]Sec}$ has on selenoprotein synthesis due to its dilution by the mutant transgene. However, in the case of *Trsp*^{tA34}, no more than 12 copies were tolerated by wild type mice, or two copies by liver-specific *Trsp* knockout, most likely, due to misreading Cys codons (inserting Sec in place of Cys) [49].

Mouse models involving Trsp^{tG37}

Trsp^{tG37} mice had dramatic reductions in stress-related selenoproteins and were used to demonstrate roles of these proteins in muscle function [51] and protection from DNA damage [52]. Ribosome profiling showed that selenoprotein synthesis in the liver of *Trsp*^{tG37} mice on selenium-adequate diets mimicked that of wild type mice maintained on selenium-deficient diets [53]. *Trsp*^{tG37} mice carrying a cancer driver gene or exposed to an

organ-specific carcinogen were used to elucidate the role of stress-related selenoproteins in various cancers. Results suggested that these selenoproteins reduce the incidence of colon [54] and prostate [55] cancers. Bi-transgenic mice carrying transforming growth factor α (*TGF*α) transgenes, which serves as a liver cancer driving gene when over-expressed, and $Trsp^{tG37}$ had a much higher incidence of liver tumors irrespective of whether they were maintained on a selenium-adequate or selenium-supplemented diet [56]. These mice, maintained on the selenium-deficient diet either with or without *TGF*α, developed a severe neurological disorder and widespread pyogranuloma. $Trsp^{tG37}$ mice were also targeted with a liver carcinogen when placed on selenium-deficient, -adequate and -supplemented diets [57].

Mouse models involving targeted removal of $Trsp^{\Delta}$

$Trsp^{\Delta}$ directed to specific organs in mice revealed roles of selenoproteins in endothelial cell [58], cartilage and bone [59] and skin development [60]; heart disease [58]; breast [61] and prostate cancer prevention [62]; and immune [63,64], thyroid [65] and neuronal function [66]. The observed phenotypes differed from relatively mild effects to lethality, exposing diverse roles of selenoproteins in different cell types.

Mouse models involving $Trsp^{\Delta}/Trsp^{t}$

Rescuing selenoprotein loss with $Trsp^{tG37}$ in conditional and standard $Trsp^{\Delta}$ provided alternative approaches in developing mouse models to elucidate selenoprotein roles in health and development. $Trsp^{tG37}/Trsp^{\Delta}$ mice expressed housekeeping selenoproteins and synthesized stress-related selenoproteins poorly, but exhibited an apparent normal phenotype [67]. These mice also expressed GPx4 poorly in testes which likely accounted for the reduced fertility found in males.

Roles of selenoproteins in cancer prevention and promotion

Although the above studies involving Sec $tRNA^{[Ser]Sec}$ led to many insights into the overall functions of selenoproteins in health and developmental issues, these approaches cannot assess the roles of individual selenoproteins in these processes. Focusing on specific selenoproteins has the advantage of addressing specific health and disease states. Interestingly, using both *in vivo* and *in vitro* approaches, three selenoproteins have been particularly instructive for understanding the role of selenoproteins in cancer. These proteins, TR1 [16], Sep15 [16] and GPx2 [15,68], were found to exhibit a split “Dr. Jekyll and Mr. Hyde” personality, both preventing and promoting cancer.

TR1, Sep15 and GPx2 are important cellular redox-regulators. Therefore, given that these oxidireductase functions would be needed by both normal and cancer cells, these very same processes most certainly result in anti- and pro-tumorigenic effects at a tissue-specific cellular level. For example, and as further discussed below, the high expression of Sep15 in colon cancer cell lines [69,70] may very well be a response of a tumor’s increased need for the associated redox function, without which proliferation and metastasis of tumor cells would be inhibited [69–71]. In contrast, since down-regulation of Sep15 mRNA expression has been found in 60% of malignant mesotheliomas [72], it remains to be elucidated whether these anti- and pro-tumorigenic effects are tumor stage or grade-dependent.

Role of TR1 in cancer prevention and promotion

TR1 is one of key redox regulators in mammalian cells. Its principal function is to control the redox state of thioredoxin, which in turn keeps surface-exposed Cys residues in cytosolic and nuclear proteins in the reduced state [73]. An analogous system occurs in mitochondria, consisting of thioredoxin 2 (Trx2) and TR3 (interestingly, cytosolic and mitochondrial TRs

and Trxs are essential proteins). TR1 is also known to activate the tumor suppressor p53, and other cellular proteins, and it can be specifically targeted by carcinogenic electrophilic compounds [74]. Liver tumor incidence was dramatically enhanced by chemical carcinogenesis in mice lacking TR1 in hepatocytes compared to controls [75]. These and other properties of TR1 suggested that this selenoenzyme is an anticancer protein [76]. However, TR1 also has roles in cancer promotion. It is over-expressed in many cancers and cancer cell lines, and the cancer-related properties of these cells can be reversed (making them more like normal cells) by using specific inhibitors and anticancer drugs that target TR1 activity [77]. In addition, removal of TR1 in lung cancer cells changed morphology and anchorage-independent growth properties and led to a dramatic reduction in tumor progression and metastasis [78]. Thus, TR1 is also a pro-cancer protein and a prime candidate for cancer therapy.

Other studies have shown a role for TR1 in cancer that is independent of its major role of maintaining Trx in the reduced state [79]. For example, TR1-deficient cells were far more sensitive to selenium toxicity than Trx1-deficient cells [80]. Additionally, only TR1-deficient cells, and not Trx1-deficient cells, increased production and secretion of glutathione that was associated with enhanced selenite toxicity. All these studies involving TR1 elucidated the direct role of this selenoenzyme in governing malignancy and suggested alternative avenues for inhibiting the cancer processes.

Role of Sep15 in cancer prevention and promotion

Sep15 was first characterized in human T-cells [81], and like TR1, it was proposed to function as an oxidoreductase [82,83]. Sep15 is regulated by ER stress and forms a strong complex with UDP-glucose: glycoprotein glucosyltransferase (UGT), an enzyme that glucosylates misfolded proteins in the ER. Through this association, Sep15 is thought to contribute to quality control of protein folding and maturation, and this function may especially be important in the eye [84]. Reduced Sep15 expression was reported in lung cancer patients [85], in malignant lung, breast, prostate and liver tissues [86], as well as in cell lines derived from malignant mesothelioma cells [72]. Differences in polymorphic alleles of *sep15* were found to be associated with various cancers in different ethnic groups [87,88]. Many of these observations suggested a role for Sep15 in tumor suppression. However, studies on colon cancer *in vitro* [69,70] and *in vivo* [71] have revealed a role for this protein in cancer progression, possibly through effects on cell cycle regulation [69,70] and/or interferon-γ-regulated inflammation [71]. Therefore, even though much of its biological function remains unclear, Sep15 appears to be an important contributor to human health and disease and a plausible target for cancer therapy.

Role of GPx2 in cancer prevention and promotion

Among the five selenocysteine-containing human glutathione peroxidases (GPx), GPx2, termed the intestinal GPx, is, like other selenoprotein peroxidases, considered an antioxidant protein [89]. GPx2 has been found to affect apoptosis and regulate self-renewal of the intestinal epithelium [15], making GPx2 an important contributor to healthy intestinal epithelia. Its protective function is further seen in a model of chemically-induced colon carcinogenesis, where GPx2 protected mice from developing colon pre-cancerous lesions [90] and tumors [91]. Furthermore, GPx2 contributes to the detoxification of carcinogens through its up-regulation by Nrf2/Keap1 [68], which also can be considered beneficial in terms of cancer prevention. However, this role of GPx2 may depend on the stage of cancer, as up-regulation of Nrf2-targets also has been described to provide hepatic cancer cells with an anti-oxidative advantage [92]. Additionally, since GPx2 is a target for the Wnt-pathway [93], which is associated with cell proliferation, and is up-regulated by β-catenin [94], it may

also play a role in promoting tumor growth. Therefore, GPx2 appears to have roles in preventing and promoting cancer similar to TR1 and Sep15.

Concluding remarks

The biological functions of the micronutrient selenium are mediated in large part by selenoproteins: proteins containing Sec in the active site. Among the human selenoproteins encoded by 25 selenoprotein genes, about half are oxidoreductases, whereas the specific functions of the remaining selenoproteins are unknown. Human selenoproteins are involved in glutathione-dependent hydroperoxide removal, reduction of thioredoxins, selenophosphate synthesis, activation and inactivation of thyroid hormones, thioredoxin-dependent repair of oxidized methionine residues, and ERassociated protein degradation. These and other functions are responsible for the role of selenium in human health, including its pro- and anticancer activities, roles in the immune system, and other functions. There are many aspects of selenium and selenoprotein metabolism that remain to be explored. Although many of the factors involved in the insertion of Sec into protein have been defined, the overall mechanism is poorly understood. Furthermore, despite extensive efforts to evaluate the beneficial and detrimental effects of selenium in human clinical trials, critical barriers remain, including significant gaps in our knowledge of how selenium and selenoproteins act metabolically to prevent and, in some cases, promote cancer. A better understanding of these basic mechanisms will facilitate the design and interpretation of safe and effective human trials and lead to new strategies for therapeutic intervention. Several of the major unresolved questions in the selenium field are given in Box 1.

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Box 1. Outstanding Questions

- Other than their presumed redox-regulating activity, what are the biological roles of the approximately one-half of the human selenoproteins whose functions are unknown?
- What is the identity of the Um34 methylase responsible for converting mcm^5U to mcm^5Um?
- What are the specific functions of the orphan selenium and selenoprotein machinery such as SPS1, SBP2L, ribosomal protein L30, nucleolin and eukaryotic initiation factor, eIF4a3?
- How does dietary selenium function in terms of being protective against disease other than through selenoproteins?
- What are the cellular uptake mechanisms for the various chemical forms of selenium?
- What other selenoproteins manifest split personalities in preventing and promoting cancer?
- How does selenoprotein expression affect disease states, *e.g.*, diabetes, different cancers, cardiovascular disease, neurological disorders; and how do disease states affect selenoprotein expression?
- What are the effects of selenoprotein SNPs in the human population?
- What is the contribution of dietary selenium to healthy aging?

Highlights

1. Selenocysteine is the 21st amino acid in the genetic code.
2. Selenoproteins are largely responsible for the many health benefits of selenium.
3. Some selenoproteins exhibit a split personality in preventing and promoting cancer.

Selenoprotein	Abbreviation	Function	Sec location	Protein size
Glutathione peroxidase 1	GPx1	Cytosolic glutathione peroxidase	47	201
Glutathione peroxidase 2	GPx2	Gastrointestinal glutathione peroxidase	40	190
Glutathione peroxidase 3	GPx3	Plasma glutathione peroxidase	73	226
Glutathione peroxidase 4	GPx4	Phospholipid hydroperoxide glutathione peroxidase	73	197
Glutathione peroxidase 6	GPx6	Olfactory glutathione peroxidase	73	221
Thioredoxin reductase 1	TR1, TrxR1, TxnRd1	Reduction of cytosolic thioredoxin	498	499
Thioredoxin/ glutathione reductase	TGR, TR2, TrxR3, TxnRd3	Testis-specific thioredoxin reductase	655	656
Thioredoxin reductase 3	TR3, TrxR2, TxnRd2	Reduction of mitochondrial thioredoxin and glutaredoxin	522	523
Methionine-R-sulfoxide reductase	MsrB1, SelR, SelX	Reduction of oxidized methionine residues	95	116
Selenophosphate synthetase 2	SPS2	Synthesis of selenophosphate	60	448
Iodothyronine deodinase 1	DI1, D1, Dio1	Thyroid hormone-activating iodothyronine deodinase	126	249
Iodothyronine deodinase 2	DI2, D2, Dio2	Tissue specific thyroid hormone-activating iodothyronine deodinase	133, 266	273
Iodothyronine deodinase 3	DI3, D3, Dio3	Tissue specific thyroid hormone-deactivating iodothyronine deodinase	144	278
Selenoprotein N	SelN, SEPN1, SepN	Putative role during muscle development	428	556
Selenoprotein P	SelP	Selenium transport	59, 300, 318, 330, 345, 352, 367, 369, 376, 378	381
15 kDa selenoprotein	Sep15	Putative role in quality control of protein folding in the ER	93	162
Selenoprotein M	SelM	Unknown	48	145
Selenoprotein K	SelK	Putative role in ER-associated degradation	92	94
Selenoprotein S	SelS, SEPS1, VIMP	Putative role in ER-associated degradation	188	189
Selenoprotein O	SelO	Unknown	667	669
Selenoprotein W	SelW, SEPW1	Unknown	13	87
Selenoprotein T	SelT	Unknown	36	182
Selenoprotein H	SelH	Unknown	38	116
Selenoprotein V	SelV	Unknown. Testis-specific expression	273	346
Selenoprotein I	SelI	Unknown	387	397

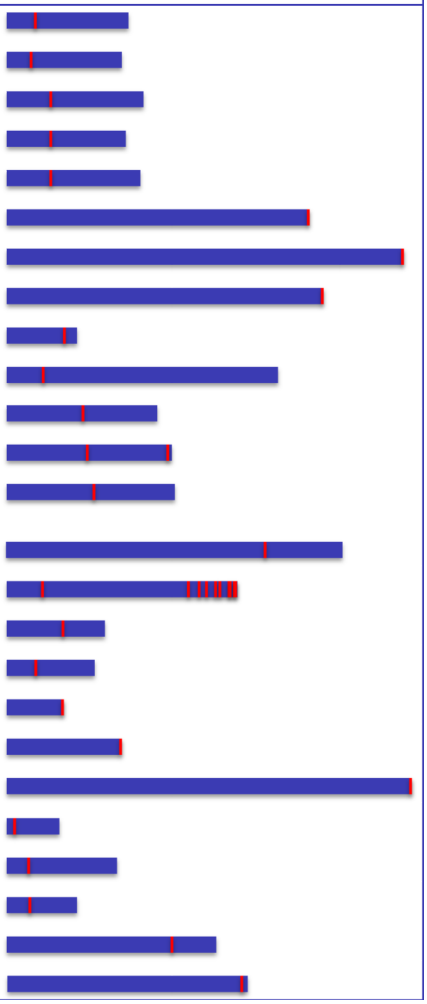

Figure 1.

Human selenoproteome. The names, designations, protein size and location of Sec in human selenoproteins are shown. The length (blue panels) and location of Sec (red mark) in proteins are shown schematically on the right.

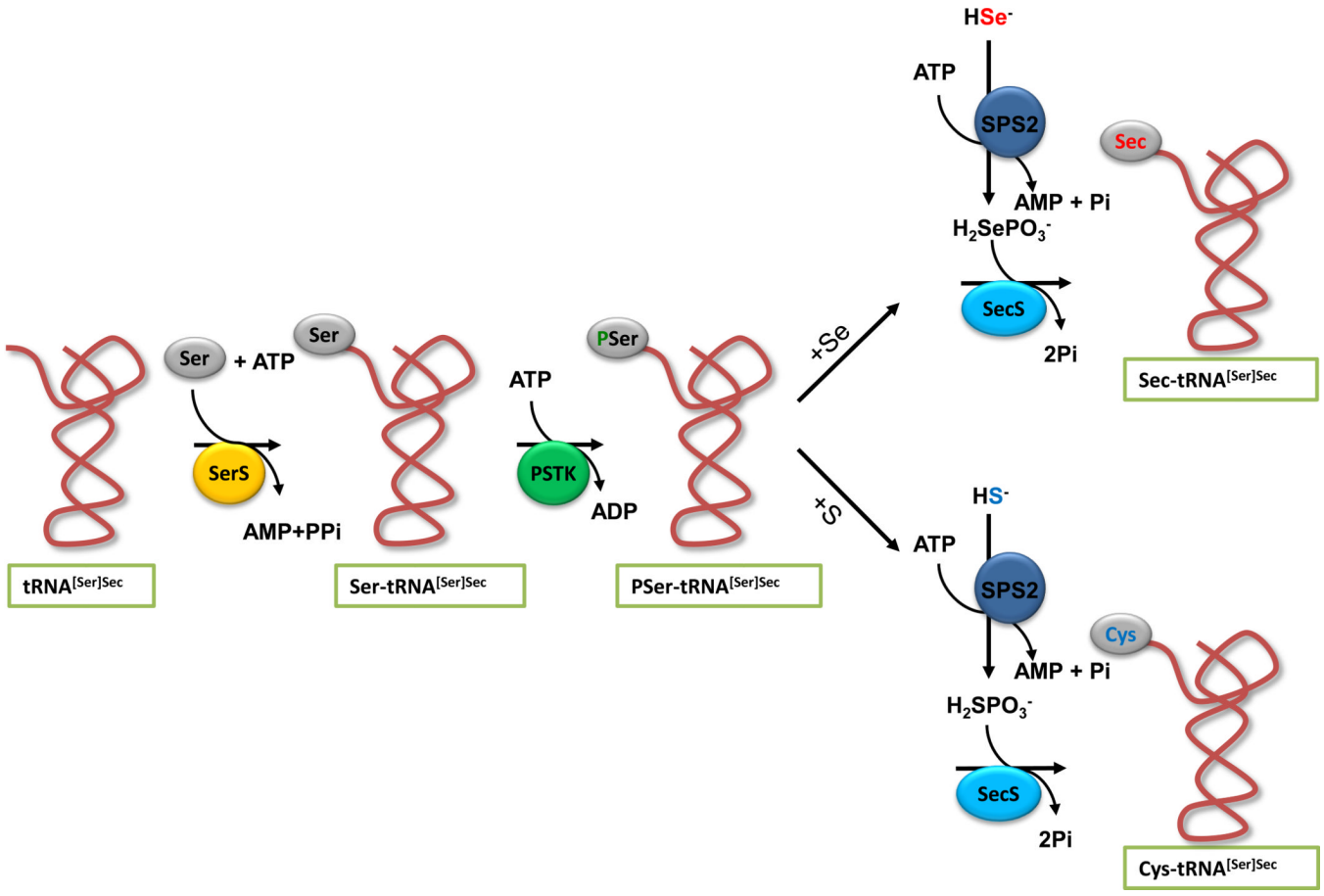

Figure 2.

Biosynthesis of Sec and *de novo* biosynthesis of cysteine. The biosynthesis of Sec occurs on its tRNA and the pathway begins with the attachment of serine to Sec $tRNA^{[Ser]Sec}$ by seryl-tRNA synthetase (SerS) in the presence of ATP. Phosphoseryl-tRNA kinase (PSTK) phosphorylates the serine moiety to form an intermediate, phosphoseryl-$tRNA^{[Ser]Sec}$, that in turn is acted upon by Sec synthase (SecS), converting the phosphoserine moiety to an intermediate, likely aminoacrylyl-$tRNA^{[Ser]Sec}$. SecS accepts selenophosphate ($H_2SePO_3^-$; upper pathway), converting the intermediate to Sec-$tRNA^{[Ser]Sec}$. Selenophosphate synthetase 2 (SPS2) synthesizes selenophosphate from selenide in the presence of ATP. In the lower pathway, sulfide can replace selenide in the reaction with SPS2, generating thiophosphate ($H_2SPO_3^-$) that in turn can interact with SecS and PSer-$tRNA^{[Ser]Sec}$ to yield Cys-$tRNA^{[Ser]Sec}$.

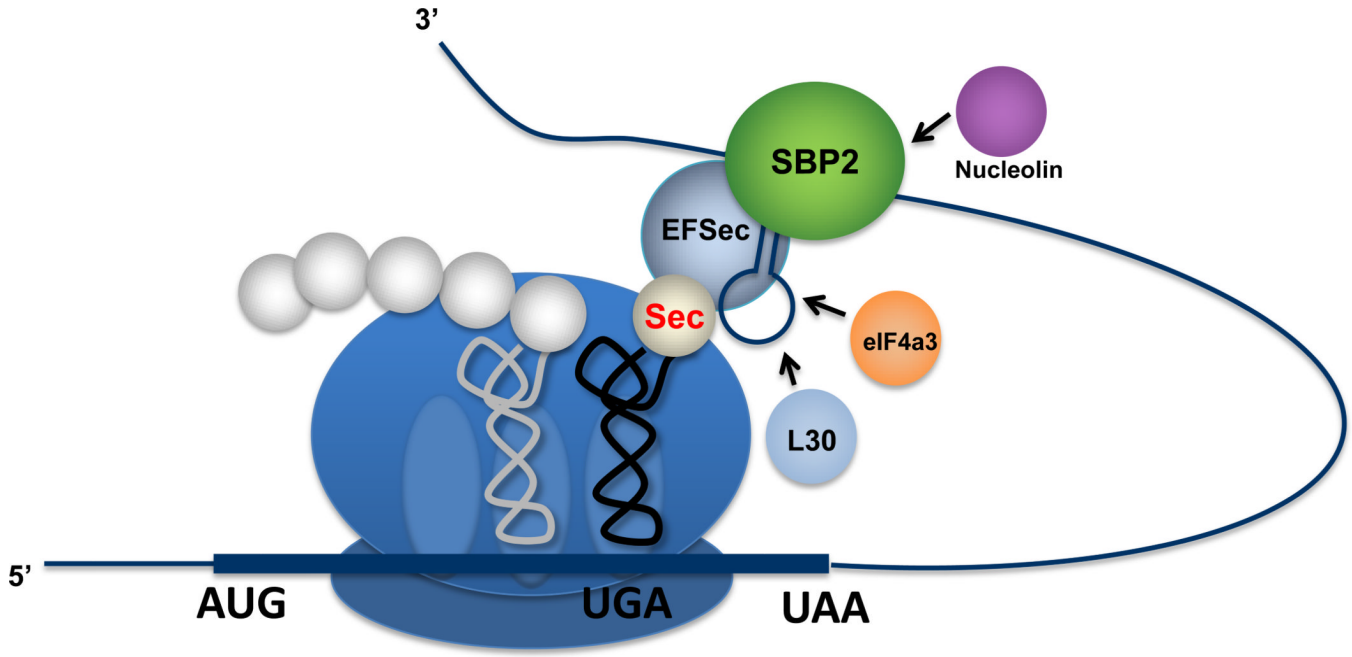

Figure 3.

Incorporation of Sec into protein in mammals. The incorporation of Sec into protein involves a multifarious complex containing the Sec insertion sequence (SECIS) binding protein 2, SBP2, bound to the SECIS element that occurs in the selenoprotein mRNA 3’-untranslated region and the Sec elongation factor, EFsec, bound with Sect-RNA$^{[Ser]Sec}$ that is decoded at the ribosomal acceptor site. The other factors, L30, eIF4a3 and nucleolin, have regulatory roles in governing the insertion process. The decoded Sec-tRNA$^{[Ser]Sec}$ will be transferred to the peptidyl site, wherein the growing polypeptide will be covalently bound to Sec-tRNA$^{[Ser]Sec}$.