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REVIEW

The human selenoproteome: recent insights into functions and regulation

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Abstract Selenium (Se) is a nutritional trace mineral essential for various aspects of human health that exerts its effects mainly through its incorporation into selenoproteins as the amino acid, selenocysteine. Twenty-five selenoprotein genes have been identified in humans and several selenoproteins are broadly classified as antioxidant enzymes. As progress is made on characterizing the individual members of this protein family, however, it is becoming clear that their properties and functions are quite diverse. This review summarizes recent insights into properties of individual selenoproteins such as tissue distribution, subcellular localization, and regulation of expression. Also discussed are potential roles the different selenoproteins play in human health and disease.

Keywords Selenium · Selenoprotein · Selenocysteine · Antioxidant · Redox

Introduction

Selenium (Se) is an essential nutritional trace element that is critical to the normal physiology of a wide range of species, including humans [1]. A striking example of its importance is the occurrence of Keshan disease, a cardiomyopathy endemic in certain Se-deficient areas of China that is completely preventable with Se supplementation [2, 3]. While Se deficiency in humans is rare, there is evidence that less overt changes in Se status may affect aspects of human health such as immune responses, neurodegeneration, cardiovascular disease, and cancer [1, 4–6]. The benefits of Se supplementation pertaining to cancer have been a focus of recent clinical studies, which have yielded varying results. One study conducted by the Nutritional Prevention of Cancer (NPC) study group indicated that Se supplementation significantly decreased the risk of lung, colorectal, and prostate cancers [7, 8]. This led to the largest, most comprehensive study on the effects of Se intake, alone and with vitamin E, on cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This randomized, placebo-controlled trial included 35,533 men from 427 participating sites in the United States, Canada, and Puerto Rico and was designed as a 12-year study. However, trial supplements were discontinued early (in year 7) predominantly based on a lack of evidence of benefit against cancer for either study agent [9]. It is likely that Se supplementation benefits certain populations only, such as Se-deficient or genetically predisposed groups, or that Se supplementation is particularly effective at lowering the risk of some health disorders and not others. Dissecting mechanisms by which dietary Se levels affect different aspects of human health is essential for understanding how altering levels of Se intake through Se supplementation may affect human health.

While small molecular weight selenocompounds influence human health, a crucial step in understanding the biological effects of dietary Se is determining the functions of the proteins into which Se is incorporated, i.e., selenoproteins. A total of 25 selenoproteins genes have been identified in humans, 24 of which exist in rodents [10]. The members of this family exhibit diverse patterns of tissue distribution, ranging from ubiquitous to tissue-specific expression. Subcellular localization is also varied with some selenoproteins exclusively expressed in certain

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organelles or as transmembrane proteins, while others are secreted to extracellular spaces or plasma. These and other properties have provided important information regarding physiological roles for selenoproteins.

The process of Sec incorporation into selenoproteins exists in different forms in the bacteria, archaea, and eukarya kingdoms. However, not all species within these kingdoms have the capacity for selenoprotein synthesis. Sec differs from cysteine by a single atom (Se vs. S), conferring a lower pKa (5.2 vs. 8.3) and higher reactivity. Certain selenoproteins that have cysteine in place of Sec at their active sites exhibit up to 100-fold lower in catalytic efficiency [11], but evolutionary selection for this increased efficiency has been counterbalanced by availability of Se, which has produced a complex distribution of Sec- and Cys-containing homologs throughout nature [12].

Selenoproteins are collectively essential for life, as demonstrated by the transgenic mouse model involving deletion of the gene encoding the tRNA dedicated to their synthesis, which results in embryonic lethality [13]. Certain model systems have shown that reduced selenoprotein activity is counterbalanced by a cytoprotective response mediated by the transcription factor Nrf2, which may represent a parallel, essential system involved in maintaining cellular redox homeostasis and viability [14]. Several selenoproteins have been characterized as antioxidant enzymes, serving to mitigate damage caused by reactive oxygen species (ROS). Three biological reactions catalyzed by selenoproteins are shown to illustrate important antioxidant or redox roles for these enzymes (Fig. 1). However, the emerging concept of ROS as secondary messengers of cell signaling has required closer examination of potential roles for selenoproteins as modulators of redox-regulated signal transduction (Fig. 2). Not all selenoproteins are enzymes involved in regulating cellular ROS, and the list of selenoprotein functions is expanding at an exciting pace [15]. Functions for several selenoproteins have yet to be determined, but much progress has been made recently in this rapidly evolving field. While selenoproteins are found in a range of prokaryotic and eukaryotic species, this review will focus on mammalian selenoproteins with an emphasis on recent insights into roles they play in various aspects of human health focusing on information derived from mouse studies, cell culture experiments, and some human studies.

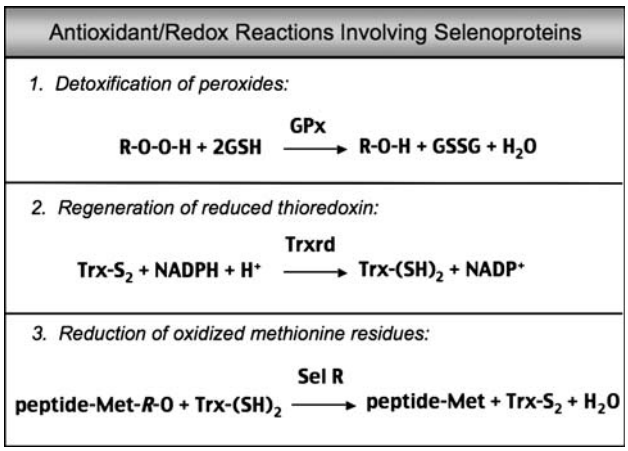

Fig. 1 Three examples of antioxidant or redox reactions catalyzed by selenoproteins. In the first reaction, different forms of peroxide (R–O–O–H) such as hydrogen peroxide or lipid peroxide are reduced by the GPx selenoenzymes using glutathione (GSH). In the second, oxidized thioredoxin (Trx-S_2) is converted to reduced thioredoxin (Trx-$(SH)_2$) by thioredoxin reductase (Trxrd) using nicotinamide adenine dinucleotide phosphate (NADPH). The third reaction involves reduction of the *R*-stereoisomer of methionine-sulfoxide (Met-*R*-O) within peptides to methionine (Met) by selenoprotein R (Sel R, also called MSRB1) using Trx

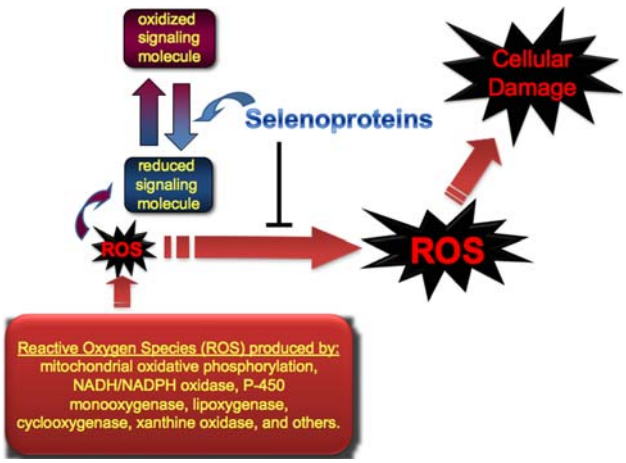

Fig. 2 Roles for selenoproteins in regulating oxidative stress and redox status of signaling molecules. Through antioxidant selenoenzymes such as glutathione peroxidases, thioredoxin reductases, or methionine sulfoxide reductase, cellular damage caused by reactive oxygen species (ROS) is mitigated. In addition, selenoproteins may directly or indirectly modulate redox-regulated signaling

Synthesis of selenoproteins

The mechanism by which selenoproteins are synthesized has been thoroughly described elsewhere [16–18], but a brief summary follows as this topic is essential for understanding the unique features and regulatory aspects of the selenoprotein family. All selenoproteins contain selenocysteine (Sec), the 21st amino acid, within their active sites. Translation of selenoproteins is similar to generalized protein translation in that it consists of three main steps: initiation, elongation, and termination. The special feature of selenoprotein translation lies in the recoding of the UGA codon, which is located in the coding region of selenoprotein mRNAs, from a stop codon to Sec-insertion codon. Most selenoprotein mRNAs, with the exception of

selenoprotein P (Sel P), contain a single Sec residue per polypeptide chain. Another unusual selenoprotein in this sense is selenoprotein L (Sel L), which uses a single selenocysteine insertion (SECIS) element for insertion of two Sec residues [19]. Sel L is absent in mammals, although distantly related Cys-containing homologs of Sel L are found in mammals. The translational machinery within the cell typically reads the UGA codon as a termination signal, releasing the nascent polypeptide from the ribosome. During translation of selenoproteins, *cis*- and *trans*-acting factors work in concert to redirect translational machinery to insert Sec at UGA codons instead of terminating polypeptide synthesis. These factors include specific secondary structure in the mRNA termed SECIS elements [20, 21], a unique tRNA ($tRNA^{[Ser]Sec}$) [22], the enzyme that synthesizes this tRNA termed Sec synthase (SecS) [22, 23], and the tRNA-modifying enzyme phosphoseryl-$tRNA^{[Ser]Sec}$ kinase (Pstk) [24]. The translation process also requires SecP43, which is required for methylation of the 2′-hydroxyl-ribosyl moiety in the wobble position of the Sec-$tRNA^{[Ser]Sec}$ and may regulate shuttling of the SecS-Sec-$tRNA^{[Ser]Sec}$ complex between the nucleus and cytoplasm [25, 26], an RNA binding protein (SBP2) [27, 28], and a specialized elongation factor (EFsec) [29, 30]. Recently, other proteins have been shown to be involved in the translation process including ribosomal protein L30, SECIS-interacting nucleolin, and Sec-tRNA gene transcription activating factor (STAF) [31–33]. A newly described *cis* element in the mRNA adjacent to the UGA codon has been implicated in Sec insertion efficiency [34], and the clinical importance of mutations in this element was recently demonstrated for selenoprotein N-related myopathies [35].

Under circumstances of low selenium, mRNA is degraded through nonsense-mediated decay (NMD) [36]. NMD is a pathway that targets mRNAs containing premature termination codons for degradation. The presence of both a UGA codon and an intron downstream of the UGA was shown to be required for selenium-dependent regulation of mRNA turnover [36, 37]. Interestingly, degradation of selenoprotein mRNAs under conditions of low Se is not uniform, with some transcripts clearly more sensitive to NMD than others [37, 38]. One factor that has been proposed to play a role in determining the hierarchy of sensitivity is the position of the UGA codon relative to the actual stop codon [39], though a recent study offers data inconsistent with this notion [38]. It is likely that several different factors contribute to sensitivity of selenoprotein mRNAs to NMD [40] and their influence may be exerted at different steps of the translation process [41]. The synthesis of individual selenoproteins, regulation of their transcription and translation, and how that relates to their function is addressed in more detail below.

Glutathione Peroxidases

The first identified selenoprotein was glutathione peroxidase 1 (GPx1) [42–44], and the GPx family subsequently became one of the more fully characterized groups of selenoproteins. In humans, GPx1 through 4 and 6 are Sec-containing enzymes, while in mice only GPx1 through 4 contain Sec in the active site [45]. In vitro activity assays suggest that all members of this group use glutathione (GSH) to catalyze the reduction of hydrogen peroxide and/or phospholipid peroxides, but the physiological localization and substrate specificity of each varies, collectively providing a wide spectrum of antioxidant protection. While GPx1 through 3 are 22- to 25-kDa proteins acting as homotetrameric enzymes, GPx4 is a 20-kDa protein that acts in a monomeric form. A more detailed description of each GPx follows.

GPx1

Also referred to as cellular GPx, GPx1 is one of the most abundant and ubiquitously expressed selenoproteins [46, 47]. GPx1 is also one of the most highly sensitive to changes in Se status, with levels of mRNA and protein dramatically reduced under low Se conditions [38]. In addition to Se status, other factors like oxidative stress influence the expression of GPx1. Somewhat counterintuitively, oxidative stress has been shown to reduce levels of GPx1 [48]. However, evidence suggests that global protein synthesis is reduced under conditions of stress as a means of reserving cellular resources [49] and that GPx1 recovers most rapidly compared to other selenoproteins [17]. Taken together, this suggests GPx1 plays a role in the overall recovery of the cells after oxidative stress. In vivo conditions of oxidative stress like asthma have been studied for effects on GPx1 expression. As mentioned above, GPx1 uses GSH to reduce ROS, producing GSSG in the process, which is converted back to GSH by the enzyme glutathione reductase. Under conditions of oxidative stress that accompany asthma, intracellular GSH/GSSG homeostasis is altered, resulting in impaired cellular signaling and increased susceptibility to lung injury [50, 51]. Regarding expression of GPx1 itself, some studies have shown that GPx1 levels increase in lung during asthma [52], while others failed to find significant changes in GPx1 [53]. The relationship between GPx1 and lung inflammation most likely is related not only to oxidative stress, but to Se status of the host as well [54].

A role of GPx1 in protecting against certain cancers has been supported by several lines of evidence. In a transgenic model in which mice lack a highly specialized methyl group in Sec-tRNA, GPx1 expression is strongly suppressed [41]. When these mice were treated with the

colonic genotoxic carcinogen, azoxymethane, significantly more aberrant crypts developed in the colon as compared with littermate controls. GPx1 expression has been found to be decreased or repressed in various in vitro and in vivo models of cancer [55, 56], and hypermethylation of the *GPx1* promoter in gastric cancer cell lines has recently been demonstrated [57]. In contrast, GPx1 activity was found to be increased in malignant human lung tissue compared to non-malignant tissue [58], raising the question of whether altered GPx1 levels directly contribute to development or progression of these cancers. There have been several studies demonstrating associations between *GPx1* genetic polymorphisms and cancer, though not all have consistently supported significant associations [47, 59]. In vitro, combining Se supplementation with GPx1 overexpression reduced UV-induced DNA damage [60]. More mechanistic studies are needed for better determining a potential role for GPx1 in cancer prevention.

GPx1 also plays an important role in protecting against neurodegenerative diseases. Studies in rodents have produced inconsistent results regarding the abundance and distribution of GPx1 in the regions and cells of the brain [61, 62]. In a recent study, the cellular distribution of GPx1 in human brain was mapped and found to be overall low in abundance, with highest levels detected in microglia and lower levels detected in neurons [63]. Comparing tissue from normal subjects to those with Parkinson's disease (PD) and dementia with Lewy bodies (DLB), GPx1-positive microglia were implicated in neuroprotection in PD and DLB.

Transgenic mouse models involving deletion or overexpression of GPx1 have provided important insights into functional significance of proper levels of GPx1 expression. In general, GPx1 knockout mice are healthy and fertile with no apparent increased sensitivity to hyperoxia [64]. When challenged with oxidative stress-inducing agents such as paraquat and hydrogen peroxide, GPx1 knockout mice were found to be more susceptible to morbidity and mortality [65, 66]. Also, GPx1 knockout mice were similar to Se-deficient mice in their susceptibility to coxsackievirus-induced cardiomyopathy similar to human Keshan disease [67].

Recently, GPx1 overexpressing mice were described showing spontaneous development of hyperglycemia, hyperinsulinaemia, insulin resistance, and obesity [68]. The effect of GPx1 overexpression on diabetes involves upregulated pancreatic duodenal homeobox 1 (PDX1) and downregulated uncoupling protein 2 (UCP2) in pancreatic islets [69], and emphasizes the requirement for some degree of ROS for maintaining proper cell function. These findings have particular relevance to human health given the SELECT findings of slightly higher risk of type 2 diabetes in Se-supplemented humans as described above as well as the strong correlation found between increased erythrocyte GPx1 activity and insulin resistance in gestational diabetic women [70].

GPx2

GPx2 is mainly expressed in the whole gastrointestinal tract including the squamous epithelium of the esophagus of healthy organisms and, in humans, is also detectable in liver [71]. It is not uniformly expressed in the intestine but is highest in the crypt grounds and decreases gradually toward the luminal surface, suggesting a role in proliferating cells [72]. The role of GPx2 is mainly to protect intestinal epithelium from oxidative stress given that GPx activity is retained in this location in GPx1 knockout mice and this activity was reduced with anti-GPx2 immunoprecipitation [73, 74]. GPx2 exhibits substrate specificity similar to that of GPx1, and they include hydrogen peroxide, *tert*-butyl hydroperoxide, cumene hydroperoxide, and linoleic acid hydroperoxide, but not phosphatidylcholine hydroperoxide [75]. The location of GPx2 expression suggests that this selenoprotein may serve as a first line of defense in exposure to oxidative stress induced by ingested prooxidants or gut microbiota. Expression of GPx2, along with GPx4, is much more resistant than GPx1 to dietary Se deficiency [37, 39, 76].

GPx2 is upregulated in cancers of gastrointestinal origin as well as other types of cancers [72, 77–79]. Its role in preventing tumorigenesis was supported by studies showing that GPx1/GPx2 double knockout mice progressively developed ileocolitis and subsequently intestinal cancer, but one intact *GPx2* allele was sufficient to prevent intestinal inflammation [80, 81]. However, the relationship between expression of GPx2, normal cell proliferation, and tumor progression is complex, making its role as a potential target of cancer therapy a controversial issue. A recent study used a siRNA approach to show that lower expression of GPx2 increased migration and invasion of cancer cell clones, but decreased their growth [82]. These data support the notion that manipulation of GPx2 might be either detrimental or beneficial, depending on the stage of tumor development.

GPx3

This GPx family member is the only secreted GPx enzyme and it constitutes approximately 20% of Se found in the plasma [83], though this number may change depending on Se status of the individual [84]. The main source of GPx3 in plasma is the kidney, produced by the cells of the proximal tubular epithelium and in the parietal cells of Bowman's capsule and released into the blood [85]. However, several different tissues appear to express

mRNA and protein, and GPx3 in this context most likely serves as a local source of extracellular antioxidant capacity. An example of this is in the heart, where GPx3 is the third most abundant selenoprotein mRNA detected [86], where levels of GPx3 in this tissue may reflect a role in protecting against oxidative damage to extracellular matrix under normal conditions or during stress. Also, GPx3 protein levels in the heart are high in the thyroid gland where it likely serves to reduce oxidative stress [87]. The reductant of GPx3 in vivo has not been clearly identified, though in vitro studies have shown that GPx3 may use GSH to reduce hydrogen peroxide or *tert*-butylhydroxide [88]. Results from other studies suggest that, in addition to GSH, thioredoxin or glutaredoxin may serve as reducing substrates [89], though others failed to confirm this finding [88]. More work is necessary to clearly characterize the in vivo reactions catalyzed by GPx3.

An important role was identified for GPx3 in early experiments showing a role in regulating the bioavailability of nitric oxide (NO) produced from platelets and vascular cells [90]. This was followed up with a study showing that decreased GPx3 activity led to platelet hyper-reactivity and an increased risk of thrombosis [91]. The clinical significance of this was supported with a study showing that impaired metabolism of ROS as a result of reduced GPx3 activity resulted in insufficient NO levels that affected normal platelet inhibitory mechanisms and predisposed study subjects to arterial thrombosis [92]. In vitro hypoxia is a strong transcriptional regulator of GPx3 expression [93]. This finding led to clinical studies demonstrating associations between polymorphisms in the *GPx3* promoter and the risk of ischemic stroke [94, 95]. However, a recent study was unable to confirm these findings [96]. The presence of GPx3 as one of two major plasma selenoproteins (along with Sel P) suggests a role for this selenoprotein in modulating NO concentration or other aspects of the vascular environment. Whether GPx3 affects susceptibility to stroke or other cardiovascular disorders may require more mechanistic studies.

GPx3 has been shown to be upregulated by peroxisome proliferator-activated receptor (PPAR)-induced antioxidant responses in human skeletal muscles [97], suggesting a role for this selenoenzyme in regulating extracellular oxidative stress that affects insulin resistance. Oxidative stress accompanies obesity and affects adipose tissue and, in several obese animal models, GPx3 expression was selectively reduced in this tissue accompanied by decreasing GPx3 in plasma [98]. Another obesity-related hormone is estrogen, which is linked to the maintenance and distribution of body fat. A recent study has demonstrated that *GPx3* gene expression is a direct target of estrogen receptor alpha stimulation in white adipose tissue [99]. GPx3 has been demonstrated to be lower in obesity and higher after weight loss, suggesting GPx3 is a mediator of effects of estrogen in relation to fat mass in humans.

GPx4

GPx4 is ubiquitously expressed in a variety of tissues, although the subcellular localization between cytosol, nuclear, and mitochondria differs between tissues [100]. GPx4 differs from the other GPx enzymes in several ways, including its requirement for life [101]. Its main substrate is phospholipid hydroperoxides in membranes [100], and, under conditions of low GSH, protein–thiol groups may be used as reducing substrates [102]. Reversing oxidation of lipid peroxides is a critical protective role for GPx4, but this selenoenzyme is also involved in metabolism of lipids such as arachidonic acid and linoleic acid [103]. Recent work has provided insight into a role for GPx4 as a sensor of oxidative stress and a transducer of cell death signals [104]. Specifically, a *loxp/cre* system was used to generate primary mouse embryonic fibroblasts with one or both *GPx4* alleles deleted, and disruption of *GPx4* was found to result in cell death signaling in a 12/15-lipoxygenase-dependent manner. These data link oxidative stress, GPx4, and lipid metabolism to pro-apoptotic signaling and most likely occur in most developing tissues as well as different adult tissues.

GPx4 knockout mice die in utero at midge station, and developmental retardation of the brain appears to play an important role in manifestation of this phenotype [101, 105, 106]. Similar to developing brain, adult brain is dependent on proper GPx4 function. Mutations or alterations of the antioxidant protein, DJ-1, have been suggested to play a role in the pathogenesis of human PD, and in PD tissue oxidative alterations to DJ-1 were associated with increases in GPx4 protein, but no changes in mRNA levels [107]. These data provide correlative evidence that DJ-1 participates in the cellular response to PD through oxidation-dependent translational regulation of oxidation responsive proteins like GPx4. This is consistent with the notion that depletion of GPx4 in hippocampus has been shown to result in neurodegeneration and GPx4 is directly involved in pro-apoptotic signaling [104]. In addition to PD, evidence for a role for GPx4 in protecting against Alzheimer's disease has recently been demonstrated. Brains of $GPx4^{+/-}$ mice were shown to have increased lipid peroxidation, which led to increased expression of β-Site amyloid precursor protein cleavage enzyme 1 (BACE1), a key rate-limiting enzyme identified in the production of β-Amyloid [108]. Altogether, whether low Se intake or insufficient GPx4 levels in brain contribute to the pathogenesis of PD or Alzheimer's disease warrant further investigation.

Similar to GPx1 and 3, GPx4 has been shown to play a protective role in cardiovascular disease. For example, overexpression of GPx4 inhibits the development of atherosclerosis in transgenic mice by decreasing lipid peroxidation and inhibiting the sensitivity of vascular cells to oxidized lipids [109]. The mitochondria of cardiomyocytes are particularly sensitive to oxidative damage. A novel transgenic mouse model was recently developed in which GPx4 was overexpressed exclusively in the mitochondria and the Langendorff model of ischemia/reperfusion (I/R) was used to demonstrate that increased GPx4 in this organelle reduced mitochondrial lipid peroxidation during (I/R) compared to littermate controls [110]. Higher levels of GPx4 in the mitochondria were sufficient to improve cardiac contractile function and preserve electron transport chain complex activities following I/R. In addition to protecting against I/R, overexpression of GPx4 inhibits the development of atherosclerosis in transgenic mice by decreasing lipid peroxidation and inhibiting the sensitivity of vascular cells to oxidized lipids.

Finally, a feature of GPx4 that separates it from other GPx family members involves its dual roles as both an enzyme and a structural protein. In particular, GPx4 is transformed in the later stages of spermatogenesis from an active Sec-containing glutathione peroxidase into a structural protein that becomes a constituent of the mitochondrial sheath of spermatozoa [111]. Similar to protection in cardiomyocytes described above, the mitochondrially expressed form of the GPx4 is most relevant in spermatogenesis, with the nuclear form being dispensable for fertility and the role of cytosolic GPx4 remaining unclear [112]. While Se deficiency does not appear to be a major cause of male infertility, there is evidence that low GPx4 content is associated with infertility. Early studies showed correlations between GPx4 content of human spermatozoa, measured as GPx activity, and parameters such as sperm count, motility, and morphological integrity [113]. Polymorphisms in the GPx4 gene may also contribute to male infertility, although a cause and effect relationship has not been clearly established [112].

GPx6

GPx6 is believed to be restricted in expression to the developing embryo and olfactory epithelium in adults [10]. However, tissue distribution is based on one published study and confirmation by others is needed. Since identification of GPx6, this protein has not been characterized in terms of function or disease. While it is reasonable to assume it plays an antioxidant role in physiological niches where its expression is highest, more definitive evidence this role is needed.

Thioredoxin reductases

Thioredoxin reductase (Txnrd) enzymes are oxidoreductases that use NADPH to catalyze the reduction of oxidized thioredoxin (Trx) [114, 115]. Trx is in turn used by several cellular enzymes as a cofactor in dithiol–disulfide exchange reactions, and this is a major mechanism by which a reduced environment is maintained within cells, particularly serving to maintain reduced cysteine groups [116]. Mammalian Txnrds contain a conserved N-terminal disulfide motif Cys-Val-Asn-Val-Gly-Cys and a C-terminal active site sequence Gly-Cys-Sec-Gly [117, 118]. The presence of the -Cys-Sec- in the active site, instead of Cys-Cys as is the case with *Drosophila melanogaster* and *Caenorhabditis elegans,* confers mechanistic advantages to the mammalian Txnrd enzymes including the ability to function at acidic pH [119]. Although it has long been believed that Txnrds are the only enzymes capable of reducing oxidized Trx [120, 121], a recent study has suggested that Txnrd1-indpendent mechanisms are important in the reduction of Trx under conditions of stress [122]. Trx is not the only substrate capable of being reduced by Txnrds, with several different macromolecules and small molecules identified as substrates for Txnrds including NK-lysin (a disulfide-containing effector peptide of T-lymphocytes) [123], alloxan [124], lipoic acid [125], selenite [126], and others.

There are three mammalian Txnrds: cytoplasmic/nuclear Txnrd1 (also called TR1 or TrxR1) that reduces Trx1, mitochondrial Txnrd2 (also called TR3 or TxnR2) that reduces Trx2, and testes-specific thioredoxin–glutathione reductase (also called Txnrd3, TR2, TxnR3, or TGR). Txnrd1 and 2 are both widely distributed throughout a variety of tissues, and several alternatively spliced forms have been described in humans and rodents, which may reflect complex regulation of expression and/or organelle- and cell type-specific location of animal Txnrds [127–130]. A splice variant of human Txnrd1 has recently been implicated in actin polymerization related to cell membrane restructuring [131]. Whether the different splice variants of Txnrd1 and 2 have different functions, and if they respond differently to stress or to Se intake, remains to be determined.

Txnrd1 and 2 are both housekeeping proteins expressed in cells under non-stressed conditions [132], and studies using radioisotope labeled Se (^{75}Se) have shown that Txnrd1 is detected at higher levels than Txnrd2 in most cases [133, 134]. Given the ubiquitous nature of the Trx/Txnrd systems, it is not surprising that Txnrds are required for numerous cellular processes. Their essential functions are evident by studies in mice demonstrating that genetic deletion of either results in embryonic lethality [135, 136]. When deletion is restricted to cardiomyocytes, only Txnrd2

is indispensable for viability, which may reflect a stricter requirement in developing heart tissue for Txnrd activity in the mitochondria. Alternatively, the different results may be related to the studies described above showing that at least two splice variants of Txnrd2 are localized outside the mitochondria and that deleting all three forms has a more dramatic effect on the developing heart compared to deletion of Txnrd1. In contrast to heart, Txnrd2 is not required for proper development of lymphocytes as demonstrated in transgenic mice with this selenoenzyme knocked out in $CD19^+$ B cells or $CD4^+$ T helper cells, neither of which exhibited detectable impairments [137].

Increasing Se intake results in increased expression of both Txnrd1 and 2 proteins [15]. However, Txnrd2 mRNA exhibits a higher resistance to degradation under Se-deficient conditions compared to Txnrd1 [133]. These findings were restricted to rat kidney and liver, and whether this hierarchy in sensitivity to Se status is true for other tissues is not clear. Levels of Se are not the only regulator of expression of Txnrds, both may be induced under certain conditions such as oxidative stress or response to growth factors [137–140]. With the emergence of ROS as secondary messengers of cell signaling, there has also emerged a role of the Trx/Txnrd system as modulators of cell signaling. For example, the Trx/Txnrd system has been shown to be involved in activation of the small G protein Ras in myocardiocytes through oxidation of thiol groups on Ras [141]. Undoubtedly, there is much more to be discovered regarding the role of Txnrd1 in regenerating Trx used in modulating redox-regulated signaling molecules.

There is increasing evidence that a variety of pathogens are dependent on Txnrd activity for viability and modulating levels or activity of Txnrds may prove effective targets for limiting certain infections. One example is HIV-1 infection, which is both affected by and affects Se status in infected individuals [4]. Txnrd1 expression was found to be lower in HIV-1-infected Jurkat T cells [142], and a recent study demonstrated that Txnrd1 acts as a negative regulator HIV-1-encoded transcriptional regulator, Tat [143]. In addition to infectious diseases, Txnrd1 has emerged as a potential target in cancer therapy, predominantly based on the notion that cancer cells exist in a stressed environment and rely on the Trx/Txnrd system for protection against stress-disregulated redox signaling [144]. Aggressive tumors in melanomas, thyroid, breast, and prostate and colorectal carcinomas significantly overexpress both Trx1 and Txnrd1 [145]. In vitro and in vivo reduction of Txnrd1 levels led to slower growth of tumor cells [146, 147]. Evidence is beginning to emerge regarding specific mechanisms by which Txnrd1 may affect tumor formation or progression. For example, Trx1/Txnrd1 has been implicated as a crucial electron donor system in DNA replication that occurs during S-phase growth such as that during tumor growth [148]. In addition, key cell signaling pathways including NFκ-B and MAPK's in colon cancer cells that are induced with anticancer drugs are modulated by the Trx1/Txnrd1 system [149]. The recent determination of the crystal structure of Txnrd1 [150] should facilitate specific targeting of this selenoenzyme with the goal of modulating its function.

Deiodinases

The iodothyronine deiodinase family of selenoproteins consists of three enzymes: types 1, 2, and 3 (D1, 2, and 3; or DIO1, 2, and 3), which are membrane-anchored enzymes of 29–33 kDa that share substantial sequence homology and catalytic properties [151]. Thyroid hormone action is initiated by the activation of T4 prohormone to T3. This conversion is carried out by D1 or D2, which catalyze an outer ring monodeiodination reaction. T4 and T3 are irreversibly inactivated via inner ring monodeiodination catalyzed by D3, and D1 also catalyzes the inner ring deiodination of T3 to inactive T2. Thus, thyroid hormone metabolism is dependent upon the combined actions of the three deiodinases and is regulated mainly through D2 stability in response to changes in iodine supply, to cold exposure, and to changes in thyroid gland function [152–154]. All three deiodinases are expressed in a number of fetal and adult tissues. Their tissue and developmental expression patterns suggest that deiodinases may control the concentration of active thyroid hormone available to specific tissues or cell types at certain stages of development [155]. It is also important to note that considerable species- or sex-specific differences exist for deiodinases, which represents an active area of research and appears largely unresolved at present.

In general, D2 is believed to generate T3 from T4 for local use in specific tissues including pituitary, brown fat, and brain, whereas D1 generates T3 from T4 in the thyroid and peripheral tissues primarily for export to plasma. D1 and D2 knockout mice have been generated, which have facilitated in the functional characterization of these selenoenzymes. Given the importance of proper thyroid hormone levels in most tissues, it is somewhat surprising that D1 and D2 knockout mice were found to be relatively normal in terms of serum T3 level and their general health, growth, and reproductive capacity are seemingly unimpaired [156, 157]. The D2 knockout mouse confirmed the suspected role of this deidonase in regulating T3 to T4 hormone conversion in a local manner as these mice show significant deficits in thyroid stimulating hormone regulation [156], thermogenesis [158], and auditory function [159], and brain T3 content is significantly reduced even though the brain T4 content is elevated [160]. A recent study has described the D1/D2 double knockout, which

exhibits a phenotype that reflects the sum of the phenotypes of the D1 and D2 single knockout mice [161]. D1 and D2 do not appear to be essential for the maintenance of the serum T3 level, but they do serve important roles in thyroid hormone homeostasis with D2 playing an important role in local T3 production and D1 contributing to iodine conservation by serving as a scavenger enzyme in peripheral tissues and the thyroid. Interestingly, the thyroid gland has an exceptionally high number of selenoproteins expressed (at least 11), several of which may be involved in the protection of the gland against the high amounts of hydrogen peroxide produced during thyroid hormone biosynthesis [87].

Dietary Se levels may affect human thyroid hormone metabolism, but co-factors such as iodine deficiency and thiocyanate overload appear to be required for manifestation of diseases such as Kashin-Beck disease or endemic myxedematous cretinism [162]. A possible explanation is that optimal function of the deiodinases requires very little Se intake. However, mutations that result in defective expression and/or function of the key selenoprotein synthesis factor, SBP2, manifest in thyroid abnormalities associated with decreased D2 activity [163], suggesting that this selenoenzyme ranks high on the hierarchy of stability of selenoprotein mRNAs under low Se conditions.

Selenoprotein H

Selenoprotein H (Sel H) is a 14-kDa, thioredoxin fold-like protein that contains a conserved Cys-X-X-Sec motif (X is any amino acid). Its expression is widely distributed throughout a variety of tissues and relatively high in early stages of embryonic development [164]. Levels of Sel H mRNA are highly sensitive to adequate Se intake [38]. Sel H in *D. melanogaster* was found to be essential for viability and antioxidant defense [165]. Sel H is localized to the nucleus, and overexpression studies suggest it is a redox-responsive DNA-binding protein of the AT-hook family and that it functions in regulating expression levels of genes involved in de novo glutathione synthesis and phase II detoxification in response to redox status [166].

Selenoprotein I

Selenoprotein I (Sel I, hEPT1) was among several selenoproteins with no assigned function until a recent study found it to contain sequence homology to enzymes involved in phospholipid synthesis. Specifically, CDP-ethanolamine: diacylglycerol ethanolamine-phosphotransferase (EPT) catalyzes the transfer of phosphoethanolamine from CDP-ethanolamine to diacylglycerol to produce phosphatidylethanolamine, and Sel I was identified as possessing a CDP-alcohol phosphatidyltransferase motif, a common motif conserved in phospholipid synthases [167]. RT-PCR and Northern blot analysis revealed that human Sel I was ubiquitously expressed in multiple tissues, consistent with the notion that it is involved in a phospholipid biosynthesis pathway common to most tissues. The amino acid sequence for Sel I contains seven transmembrane helices, but no experimental data have yet verified that Sel I is a transmembrane protein or its subcellular localization. Further research is needed to address questions regarding this selenoenzyme in terms of its regulation during cell growth and activation and potential essential role in development or viability.

Selenoprotein K

Selenoprotein K (Sel K) is a small (16-kDa) protein and localized to the endoplasmic reticulum (ER) membrane [10, 168], and some evidence suggests it is associated with the plasma membrane [10]. Based on Northern blot analysis, expression of Sel K has been suggested to be relatively high in human heart [168]. However, a subsequent study demonstrated that mRNA levels are widely distributed throughout mouse tissues, with particularly high levels detected in spleen and testes [86]. This discrepancy may be due to differences in species, and tissue distribution in terms of protein expression has not yet been described. Like several other selenoproteins, the function of Sel K remains unclear. Overexpression of Sel K in cardiomyocytes was shown to decrease levels of ROS, although the mechanism by which this occurred was not determined [168]. The *D. melanogaster* ortholog of Sel K (dSel K) was not found to contribute to antioxidant activity [169]. The localization of Sel K to the ER may suggest a function relevant to this organelle, but evidence suggests that, in dSel K, the Sec-containing portion of the protein is located in the cytoplasm, not the ER lumen [169].

Selenoprotein M and Sep15

Selenoprotein M (Sel M) and Sep15 are 15-kDa proteins that share 31% sequence identity and localize to the ER [170]. Sel M and Sep15 have Cys-X-X-Sec and Cys-X-Sec motifs, respectively, and nuclear magnetic resonance (NMR)-based structural studies revealed that both have a two-layer α/β-fold with a central β-sheet surrounded by α-helices, typical of thioredoxin-like proteins [171]. The presence of thioredoxin-fold and conformational changes it undergoes after thiol-sulfide exchange, as well as sequence homology to protein disulfide isomerases [171], suggest these two selenoproteins function as thiol-disulfide oxidoreductases. Sep15 was shown to associate with UDP-glucose:glycoprotein glucosyltransferase (UGTR) in the ER, and this association was responsible for maintaining

the selenoprotein in the ER [172]. UGTR is involved in the quality control of protein folding, and both Sep15 and Sel M have been suggested to play a role in protein-folding in the ER [173], but direct evidence for this role in vivo is lacking. Recently, a transgenic rat model was developed involving overexpression of human Sel M, which produced altered levels of hydrogen peroxide, SOD, and GPx, and disrupted the relative levels of neutrophils to lymphocytes [174]. However, this study provided little insight into roles of endogenous Sel M.

A link between Sep15 and cancer has been made by several in vitro studies. For example, Sep15 was found to be downregulated in malignant mesotheliomas compared to normal mesothelial cells, and malignant mesothelioma cells with downregulated SEP15 or expressing a Sep15 polymorphic variant were less responsive to the growth inhibitory and apoptotic effects of Se supplementation than malignant mesothelioma cells expressing wild-type protein [175]. Other studies involving expression patterns of Sep15 have been inconsistent in providing evidence for a role for this selenoprotein in limiting the development of cancer [53, 176]. The relationship between Sep15 and lung cancer in humans may be particularly complicated by factors including smoking and Se status [177], and larger studies in humans may allow dissection of how these factors are related.

Selenoprotein N

Similar to Sel K and Sel S, selenoprotein N (Sel N, SEPN1, SepN) is a transmembrane protein localized to the ER membrane, but much larger in size (70 kDa) [178]. There are two known isoforms of the Sel N gene product, with isoform 1 corresponding to the full-length transcript and isoform 2 excluding exon 3 from splicing. Both transcripts are detected in skeletal muscle, brain, lung and placenta, with isoform 2 being the predominant transcript [179]. Several independent studies have linked mutations in the Sel N gene to muscular disorders, including rigid spine muscular dystrophy [180], the classical form of multi-minicore disease [181], desmin-related myopathy with Mallory body-like inclusions [182], and congenital fiber-type disproportion [183]. All these disorders, collectively termed SEPN1-related myopathies, are clinically characterized by poor axial muscle strength, scoliosis, and neck weakness, and a variable degree of spinal rigidity. Data showing high expression of Sel N in fetal tissue and proliferating cells are suggestive of a role in early muscle formation, which is consistent with the clinical features of Sel N-related mutations. Recently, it was shown that efficient insertion of Sec into Sel N requires a Sec redefinition element (SRE) located adjacent to the UGA codon, and mutations in this region have been shown to have negligible levels of Sel N protein in patients [35] and this may explain associations between these point mutations and SEPN1-related myopathies [184].

The location of Sel N in the ER membrane raises questions regarding its biological role in muscle cells and this was recently addressed in a study demonstrating protein–protein interactions between Sel N and the ryanodine receptor (RyR), which is a major component of the RyR intracellular calcium release pathway [185]. Interestingly, RyR channels are exquisitely sensitive to redox regulation. Sel N presumably associates and/or regulates this channel through redox-based chemistry as suggested by the presence in Sel N of a Cys-X-X-Ser domain, which together with a conserved alpha-helix structure corresponds to thiol-dependent redox sites in proteins [186]. Using Sel N-depletion in zebrafish embryos, neither expression patterns nor the overall levels of RyR proteins altered by loss of Sel N, but RyR-related calcium release was reduced. Overall, evidence suggests that Sel N serves to regulate RyR-mediated calcium mobilization required for normal muscle development and differentiation. It remains to be seen whether Sel N regulates calcium mobilization in other tissues or under particular conditions, or if its role in the ER membrane is different in muscle versus other tissues.

Selenoprotein O

Selenoprotein O (Sel O) is one of the selenoproteins that has remained enigmatic since identification of its sequence in the human genome several years ago [10]. While human Sel O is predicted to consist of 669 amino acids with a calculated M.W. of 73.4 kDa (NCBI accession no. NP_113642), there is no information regarding its tissue distribution, subcellular location, or physiological role. The presence of a Cys-X-X-Sec motif is suggestive of a redox function [10], though experimental data are lacking.

Selenoprotein P

Selenoprotein P (Sel P) is a unique member of the selenoprotein family in that it contains multiple Sec residues per protein molecule. Specifically, human and mouse Sel P both contain 10 Sec residues. Although Sel P cDNA contains 10 UGA codons in the reading frame, the translated product appears to include less than 10 Sec residues per peptide chain in the circulation in both rodents and humans [84]. The high molar quantities of Se in Sel P suggests a role in Se transport, and one of the first clues regarding this role came with studies showing that culturing cells in Sel P-depleted media was found to reduce activity of the glutathione peroxidase (GPx) family of selenoproteins, and activity was restored following reconstitution of the media

with Sel P [187]. Indeed, Sel P contains 40–50% of the total Se in plasma, suggesting this protein may act as a Se transporter and knockout mouse models of Sel P definitively characterized the essential role of Sel P of transporting dietary Se [188, 189]. Hill et al. found that, in terms of Se content, the tissues most affected by Sel P deficiency were testes and brain, while kidney and heart were less affected. The phenotype of the knockout mice was consistent with these findings and included neurological problems and male sterility. Sel P knockout mice injected with ^{75}Se had lower levels of isotope in brain and testis, but higher accumulation in liver compared to controls. These findings suggested that the liver is a tissue that readily takes up Se and incorporates it into Sel P, which is then secreted into the plasma for transport of Se to other tissues. This was supported by studies of Schweitzer et al. demonstrating that liver-specific inactivation of the gene encoding Sec tRNA (*trsp*) resulted in decreased plasma and kidney GPx activity [190]. Expression of nearly all selenoproteins at both mRNA and protein levels is reduced in Sel P knockout mice, while expression in other tissues like heart and lung is unaffected [86].

The role of Sel P in the transport of Se throughout an organism has been further defined with results from recent studies. In one study, ^{82}Se was injected into mice intravenously and amounts of isotope determined over time for several different tissues [191]. While levels of Se-albumin and GPx3 increased in the period shortly after injection (1–6 h), Sel P was found to be the predominant form of Se in blood from 6 to 72 h after injection. Although i.v. injection does not perfectly replicate dietary intake, these results support the notion that Sel P is the predominant means of Se transport between tissues. The transport component of Sel P is contained within the last nine Sec residues, as replacement of Sel P with a shortened form containing only the first Sec residue results in neurological disorders similar to the full knockout [192]. The fact that Sel P is a Se-transport protein suggests existence of receptors for its uptake, and apolipoprotein E receptor-2 (ApoER2) was recently demonstrated to be required for Sel P uptake by the testis and that deletion of ApoER2 reduces testis and brain, but not kidney, Se levels and produces neurodegeneration [192, 193]. These data reflect utilization by kidney of a Sel P receptor distinct from ApoER2, and a recent study showed that megalin, a lipoprotein receptor localized to the proximal tubule epithelium, was responsible for Sel P uptake in kidney [194].

Se transport is not the only function carried out by Sel P as is evident by the presence of several different domains exhibiting interesting functions, including glutathione peroxidase activity, heparin binding, and heavy metal ion complexation [84]. The first Sec residue toward the N-terminus has long been suggested as providing antioxidant capacity to cells [195, 196]. A recent study provided direct evidence of the importance of this Sec residue in infection with the intracellular parasite, *Trypanosoma congolense,* in experiments using transgenic mice expressing a version of Sel P ($Sepp^{\Delta 240–361}$) including the antioxidant motif but lacking the Se transporter domain [197]. Expression of Sel P retaining the first Sec residue was sufficient to protect the host cells from oxidative damage, to confer parasite-clearing capabilities to liver macrophages, and increase host survival after infection. This function may have implications for the human disease African trypanosomiasis or other parasitic diseases in which production of high levels of oxidative stress in phagocytes is crucial for effective clearance of the pathogen and viability of these phagocytes relies on host Se status and Sel P expression [4].

Another human disease recently associated with Sel P is Alzheimer's disease. For example, analysis of postmortem tissue from patients with hallmark lesions of this disease demonstrated colocalization of Sel P with amyloid plaques [198]. This observation coupled with lower circulating Sel P during inflammatory conditions like sepsis and Crohn's disease [198–202] may have important implications for potential links between Se status, inflammation, and neurological disorders. In addition to neurological disease, single nucleotide polymorphism (SNP) analysis has revealed a link between lowered Sel P expression and prostate cancer risk [203]. Consistent with these results, Sel P mRNA was found to be significantly reduced in lung tissue samples from non-small cell lung cancer (NSCLC) patients compared to healthy tissue [58] as well as a number of different human and mouse tumor tissues compared to controls [204]. This decreased Sel P mRNA was also associated with lower GPx activity and higher level of thiobarbituric acid-reactive species (TBARS) in the malignant tissue, suggesting that local sources of Sel P are important in mitigating oxidative stress during cancer and may be related to the first Sec residue implicated in lowering oxidative stress during parasitic infection as described above. The relatively large levels of Sel P in plasma and brain may also serve as an important defense against heavy metals such as mercury and others [205].

Selenoprotein R

Selenoprotein R (Sel R, MsrB1) is part of the methionine sulfoxide reductase (Msr) family of proteins, which also includes MsrA, MsrB2, and MsrB3 [206]. ROS can oxidize methionine residues in proteins to produce a mixture of S- and R-forms of methionine sulfoxide (Met-O), which are reduced by MsrA and MsrB enzymes, respectively.

While the other family members contain Cys at their active sites, Sel R is the only member of the Msr family that is a selenoprotein. The presence of Sec instead of Cys at the active site of Sel R has been suggested to have certain catalytic advantages and disadvantages [207, 208], though Se bioavailability must also be considered when contemplating evolutionary pressure for the emergence of Sec-containing enzymes. Sel R is widely distributed throughout different tissues, though highest levels are found in liver and kidney, and the Sel R knockout mouse model was recently described demonstrating these tissues to be most affected in knockouts in terms of susceptibility to oxidative damage of proteins [209]. The phenotype of the Sel R knockout appears to be milder than MsrA knockout in terms of oxidative stress and aging, although the Sel R-deficient mice have not yet been fully characterized. Suggested roles for Sel R in humans include protection from neurodegeneration [210], lens cell viability [206], and oxidative damage during aging [211]. Closer scrutiny of the Sel R knockout mice may shed light on these functions. A recent study uncovered a cell signaling role for MsrA in the modulation of calcium/calmodulin kinase II (CaMKII), which contains two tandem Met residues that upon oxidation to Met-O activate this important signaling molecule [212]. Future studies involving Sel R may include its role not only in the mitigation of oxidative damage to methionine residues on proteins, but a role in regulating certain cell signaling molecules through alteration of redox status of specific methionine residues.

Selenoprotein S

Selenoprotein S (Sel S, SEPS1, SELENOS, Tanis, VIMP) is a transmembrane protein located in the ER and plasma membranes and is widely expressed in a variety of tissues [213]. It has been suggested to participate in the removal of misfolded proteins from the ER lumen for degradation [214] and to protect cells from oxidative damage [215] and ER stress-induced apoptosis [216]. SNPs in the Sel S promoter have been shown to regulate levels of inflammatory cytokines IL-1, TNFα, and IL-6 [216], and expression of Sel S has been shown to be modulated by glucose metabolism and ER stress [214, 217]. Several diseases have been associated with genetic variations in Sel S, including cardiovascular disease and stroke [218, 219], preeclampsia [220], rheumatoid arthritis [221], and gastric cancer [222]. However, other case-control results failed to confirm association between Sel S polymorphisms and type 1 diabetes, rheumatoid arthritis, or inflammatory bowel disease [223]. Further investigation of Sel S should provide important information regarding its role in the plasma membrane and ER and how that relates to the disorders attributed genetic variations of its gene.

Selenoprotein T

Selenoprotein T (Sel T) is ubiquitously expressed throughout embryonic development and adulthood in rat, and most likely localized to ER through a hydrophobic domain [224]. Sel T is a member of a subfamily of selenoproteins (also including Sel W, Sel H, and Sel V) that share sequence similarity containing a thioredoxin-like fold and a conserved Cys-X-X-Sec motif [225]. Based on a transgenic mouse model involving isoforms of Sec-tRNA for selenoprotein synthesis, the expression of Sel T is proposed to be similar to those selenoproteins involved in stress-related phenomena [41]. However, increased expression of Sel T under conditions of stress has yet to be demonstrated. A recent study has shed some light on Sel T expression and a biological role for Sel T in calcium mobilization. Specifically, Sel T expression was increased in a neuroendocrine cell line, PC12, during differentiation stimulated by the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) [224]. Overexpression of Sel T increased calcium mobilization and this was dependent on the Sec residue in Sel T. Conversely, Sel T shRNA decreased PACAP-induced secretion of growth hormone, suggesting that Sel T is involved in the signaling pathways activated by PACAP, perhaps through calcium regulation. However, data have yet to be presented for an in vivo role for Sel T in calcium mobilization or any other biological function.

Selenoprotein V

Selenoprotein V (Sel V) was originally identified with other selenoproteins from analyses of the human genome [10]. Expression of this selenoprotein appears to be restricted to testes [10, 86], but its function in this tissue is unknown. Sel V shares sequence homology with other selenoproteins, including Sel H, Sel T, and Sel W, and these selenoproteins all possess a thioredoxin-like fold and a conserved Cys-X-X-Sec motif, suggesting redox functions [225]. Given the importance of Se status on the testes, investigation into potential roles of Sel V in male reproductive biology is warranted.

Selenoprotein W

Selenoprotein W (Sel W, SEPW1) is a small selenoprotein (9.5 kDa) that contains a Cys-X-X-Sec motif. Protein and mRNA expression correlate in humans and are widely distributed throughout a variety of tissues [226]. In mice, Sel W is also expressed in several different tissues, although the heart appears to exhibit high levels of mRNA but lacks expressed protein [86, 227]. Levels of Sel W mRNA are highly dependent on adequate dietary Se levels

Table 1 Summary of functions of selenoproteins and regulation of their expression by Se status

Selenoprotein	Abbreviation	Important insights into function and significance	Dietary selenium effects	Subcellular localization
Cytosolic glutathione peroxidase	GPX1	GPX1 knockout is more suseptible to oxidative challenge. Overexpression of GPX1 increases risk of diabetes	Very sensitive to Se status, following insufficient Se, or oxidative stress rapid GPx1 recovery. Se deficiency leads to nonsense mediated decay of GPx1 mRNA	Cytoplasmic
Gastrointestinal glutathione peroxidase	GPX2	GPX1/GPX2 double knockout mice progressively develop intestinal cancer, one allele of GPX2 added back confers protection	Relatively resistant to dietary Se changes	Cytoplasmic
Plasma glutathione peroxidase	GPX3	Important for cardiovascular protection, perhaps through modulation of Nitrous Oxide levels; antioxidant in thyroid gland	Sensitive to Se status	Secreted
Phosholipid hydroperoxide glutathione peroxidase	GPX4	Genetic deletion is embyronic lethal; GPX4 acts as crucial antioxidant, structural protein in sperm, and sensor of oxidative stress and pro-apototic signals	Relatively resistant to dietary Se changes	Cytoplasmic
Olfactory glutathione peroxidase	GPX6	Importance unknown		
Thioredoxin reductase Type I	TrxR1, TR1	Localized to cytoplasm and nucleus. Genetic deletion is embyronic lethal	Increased Se increases activity. Se deficiency decreases activity, but does not change mRNA levels	Cytoplasmic, nuclear
Thioredoxin reductase Type II	TrxR2, TR3	Localized to mitochondria. Genetic deletion is embyronic lethal	Subject to dietary Se changes (i.e., increased Se increases expression)	Mitochondria
Thioredoxin reductase Type III	TRxR3, TR2, TGR	Testes-specific expression		
Deiodinase Type I	D1, DIO1	Important for systemic active tyroid hormone levels		Membrane-associated
Deiodinase Type II	D2, DIO2	Important for local active tyroid hormone levels	Expression levels are stable under low Se conditions	Membrane-associated
Deiodinase Type III	D3, DIO3	Inactivates thyroid hormone		Membrane-associated
Selenoprotein H	Sel H	Nuclear localization, involved in transcription. Essential for viability and antioxidant defense in *Drosophila*	Highly dependent on adequate dietary Se levels	Nuclear
Selenoprotein I	Sel I, hEPT1	Possibly involved in phospholipid biosynthesis		Transmembrane
Selenoprotein K	Sel K	Transmembrane protein localized to endoplasmic reticulum		ER, plasma membrane
Selenoprotein M, Selenoprotein 15	Sel M, Sep 15	Thiol-disulfide oxidoreductases localized to endoplasmic reticulum		ER
Selenoprotein N	Sel N, SEPN1, SepN	Potential role in early muscle formation; involved in RyR-related calcium mobiliation from ER; mutations lead to multiminicore disease and other myopathies		ER
Selenoprotein O	Sel O	Contains a Cys-X-X-Sec motif suggestive of redox function, but importance remains unknown		

Table 1 continued

Selenoprotein	Abbreviation	Important insights into function and significance	Dietary selenium effects	Subcellular localization
Selenoprotein P	Sel P	Selenium transport to brain and testes; Sel P knockout leads to neurological problems and male sterility. Sel P also functions as intracellular antioxidant in phagocytes	Serves as a biomarker for Se status, and is moderately sensitive to Se status	Secreted, cytoplasmic
Selenoprotein R	Sel R, MsrB1	Functions as a methionine sulfoxide reductase and Sel R knockouts show mild damage to oxidative insult		Cytoplasmic
Selenoprotein S	Sel S, SEPS1, SELENOS, VIMP	Transmembrane protein found in plasma membrane and endoplasmic reticulum. May be involved in ER stress		ER
Selenoprotein T	Sel T	Endoplasmic reticulum protein involved in calcium mobilization		ER
Selenoprotein V	Sel V	Testes-specific expression		
Selenoprotein W	Sel W, SEPW1	Putative antioxidant role, perhaps important in muscle growth	Highly dependent on adequate dietary Se levels as well as levels of Sel P	Cytoplasmic
Selenophosphate synthetase	SPS2	Involved in sythesis of all selenoproteins, including itself		Cytoplasmic

as well as levels of Sel P [38, 86, 228]. Sel W interacts with glutathione and evidence suggests it plays an antioxidant role in cells [229]. Due to high expression found in proliferating myoblasts, it has been suggested that Sel W functions in muscle growth and differentiation by protecting the developing myoblasts from oxidative stress [230]. One target of Sel W recently identified in immunoprecipitation experiments was the protein 14-3-3 [225], and high resolution NMR spectroscopy confirmed these interactions depend on the thioredoxin-like fold of Sel W [231]. However, the biological role for this interaction is unknown and the role of Sel W in vivo remains unclear.

Selenophosphate-synthetase 2

Selenophosphate-synthetase 2 (SPS2) is an enzyme involved in the biosynthesis of selenoproteins. Specifically, selenocysteyl-tRNA$^{[Ser]Sec}$ is aminoacylated by seryl-tRNA synthase and the seryl moiety is phosphorylated by Pstk as mentioned above to form *O*-Phosphoseryl-tRNA$^{[Ser]Sec}$. The latter is a substrate for SecS, which replaces the phosphoryl moiety of phosphoserine, derived from the selenium donor, selenophosphate, to yield Sec [14]. Selenophosphate is the active form of selenium, which is transferred to the selenocysteyl-tRNA$^{[Ser]Sec}$. In eukaryotes, this reaction is carried out by SPS2 [232, 233], a homologue of bacterial SelD. In this sense, SPS2 is a selenoprotein that autoregulates its own production along with the production of other selenoproteins [234]. SPS1 is a related protein that contains a Cys residue in place of Sec, but its role in selenoprotein synthesis or any other biological process is unknown [25, 235, 236]. SPS2, but not SPS1, is essential for selenoprotein synthesis in the mouse fibroblast cell line NIH3T3 [237], though whether this holds true in vivo has not been determined. It is also interesting to note that bovine SPS2 lacks Sec [238]. Mice in which Sel P was deleted have reduced mRNA levels for all selenoproteins in brain and testes, except for SPS2, which showed increased mRNA levels in both tissues in the Sel P knockout mice [86]. This may reflect a compensatory mechanism during low Se status in these tissues. A recent study showed that lipopolysaccharide-injected mice had lower levels of SPS2 mRNA and protein in the liver, as well as lower levels of other selenoprotein synthesis factors [199]. The authors note that this decrease in selenoprotein synthesis factors during sepsis may contribute decisively to the decline of serum Se concentrations in critical illness and represents a promising therapeutic target to improve health and reduce morbidity of patients. The possibility remains that lowered serum Se may represent a defense mechanism triggered to deny host-derived Se to certain gram-negative bacteria to slow growth, in which case the opposing effects of Se supplementation and high doses of antibiotics must both be

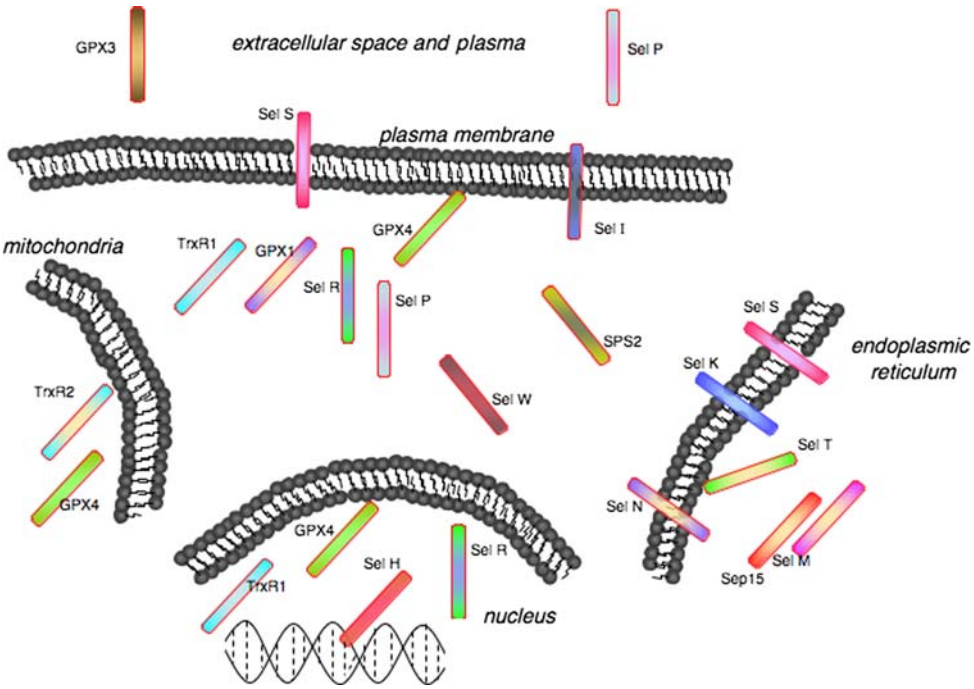

Fig. 3 Selenoproteins exhibit varied subcellular localization, which may offer insights into their functions and regulation. Note that some selenoproteins have been omitted due to restricted tissue distribution or unknown subcellular localization

considered. The relationship between Se, selenoprotein synthesis, and host–pathogen interactions is an important issue and warrants further investigation.

Conclusions

Many recent studies have provided insight into functional roles and significance of individual selenoproteins (Table 1). As this table indicates, however, there are many functional and regulatory aspects of selenoproteins that remain unknown. Another way to regard selenoproteins is in terms of subcellular localization (Fig. 3), and this perspective gives rise to several questions. In several cases, identifiable localization signals are not present, so how is compartmentalization of selenoproteins in these cases regulated? Also, do the secreted selenoproteins, GPx3 and Sel P, serve as antioxidants in local extracellular spaces as well as plasma? What is the significance of localization of so many selenoproteins (at least six) to the endoplasmic reticulum? Do they serve protein-folding/chaperone roles for certain groups of proteins or do they add reducing capacity to maintain redox balance in this organelle? Do selenoproteins in the nucleus other than Sel H participate in transcriptional regulation either directly or indirectly? These and other questions will require further basic science investigation, which will eventually provide crucial insight into how dietary Se and selenoproteins affect human health.

Overall, there has been substantial progress made in the field of selenoprotein biology. A major step was the identification of the 25 selenoprotein genes in the human genome [10], which opened up the field of selenoprotein research, and new functions for many selenoproteins have since been elucidated. In addition, identification and characterization of splice variants or post-translationally modified versions of the products of these genes have expanded the number of functional selenoproteins as well as the range of biological roles for individual selenoproteins. Advances in proteomics, mouse models, and polymorphism analyses are certain to assist in further characterization of selenoproteins, and emerging new technologies and novel approaches are certain to lead to a more complete understanding of the human selenoproteome.

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