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Regulation and function of selenoproteins in human disease

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Abstract

Selenoproteins are proteins containing selenium in the form of the 21st amino acid, selenocysteine. Members of this protein family have many diverse functions, but their synthesis is dependent on a common set of cofactors and on dietary selenium. Although the functions of many selenoproteins are unknown, several disorders involving changes in selenoprotein structure, activity or expression have been reported. Selenium deficiency and mutations or polymorphisms in selenoprotein genes and synthesis cofactors are implicated in a variety of diseases, including muscle and cardiovascular disorders, immune dysfunction, cancer, neurological disorders and endocrine function. Members of this unusual family of proteins have roles in a variety of cell processes and diseases.

Keywords

cancer; diabetes; Keshan disease; multiminicore disease; neurodegeneration; selenium; selenocysteine; selenoprotein; thyroid hormone

INTRODUCTION

The trace element selenium (Se), originally viewed as a toxin, is now understood to be an important micronutrient [1]. Selenium is incorporated into proteins not simply though ionic association, as most metals are, but is covalently bonded within the amino acid Sec (selenocysteine), the 21st amino acid [2]. Sec has a structure that is nearly identical with that of cysteine, except with selenium in place of sulfur. The presence of Sec in a protein, GPX (glutathione peroxidase) 1, was first reported in 1978 [3]. The cloning of GPX1 [4,5], as well as formate dehydrogenase [5,6], led to the surprising discovery that the codon for Sec was TGA, which acts as a stop codon in nonselenoprotein genes. An element in the 3′-UTR (untranslated region) of eukaryotic selenoprotein mRNAs, termed the Sec insertion sequence (SECIS), was discovered following the cloning of the selenoprotein DIO (iodothyronine deiodinase) 1 [7]. All eukaryotic selenoproteins require a form of the SECIS element for recoding UGA to the Sec codon [8].

Selenium was originally recognized as a toxic element. However, in 1957, studies investigating the requirements of nutrients in rodent diets revealed selenium (along with vitamin E) to be essential for prevention of liver necrosis [9]. This led to the realization that selenium deficiency was responsible for a number of disorders observed previously in animals, such as white muscle disease, as well as being a contributing factor to Keshan

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disease in humans [10]. Although toxicity at higher levels is still a serious problem, the importance of selenium as an essential micronutrient is now recognized.

Three classes of selenoproteins, the GPXs, TRXRs (thioredoxin reductases) and DIOs were among the first eukaryotic selenoproteins discovered and are the most extensively studied.

The GPXs are integral to antioxidant glutathione pathways, providing protection from ROS (reactive oxygen species). Five of the GPXs in humans (four in mice) are selenoenzymes [11]. GPXs are hydroperoxidases that use glutathione as a cofactor. The TRXRs use NADPH for reduction of TRX (thioredoxin) in cellular redox pathways [12]. The interactions of the GPX and TRXR selenoprotein families are shown in Figure 1. Another class of selenoproteins are the DIOs, which cleave iodine–carbon bonds in the metabolism of thyroid hormones [13].

Two additional selenoproteins that were identified early through biochemical studies are SelP (selenoprotein P), first reported in 1982 [14], and SelW (selenoprotein W), first described in 1993 [15]. SelP is an unusual selenoprotein, containing ten Sec residues in humans, 16–18 in amphibians and fish and 28 in sea urchins. SelP is primarily secreted from liver cells to deliver selenium to other body regions [16]. SelW is similar to the GPX family in that it shares the redox motif and binds glutathione [17]. The ‘W’ stands for ‘white muscle disease’, a disorder among grazing livestock found in regions with low selenium soil levels [15].

The completion of the human genome project led to the identification of many other selenoproteins though sequence homology and characteristic elements. SelH (selenoprotein H) is a nuclear-localized DNA-binding protein that may act as a transcription factor [18]. SelH increases glutathione levels and GPX activity, and may up-regulate other selenoproteins in response to stress. SelI (selenoprotein I) was found to be the mammalian form of the phospholipid-synthesizing enzyme ethanolamine phosphotransferase [19]. SelR (selenoprotein R)/SelX (selenoprotein X) is a member of the methionine sulfoxide reductase family, important for reduction of sulfoxymethyl groups. SelN (selenoprotein N) is found in the membrane of the ER (endoplasmic reticulum), and appears to be necessary for proper muscle development [20]. SelS (selenoprotein S) is also ER-localized, and is important for removal of misfolded proteins from the ER membrane [21]. The 15 kDa selenoprotein, Sep15, and SelK, SelM and SelT (selenoproteins K, M and T respectively) are small ER proteins with largely unknown functions [22]. SelO and SelV (selenoproteins O and V respectively) have perhaps the most elusive functions. SelO is widely distributed, whereas SelV expression is limited to testes [22].

Research is beginning to elucidate the functional importance of specific selenoproteins and their roles in human diseases [23]. The present review examines how genetic and expression level changes in selenoproteins adversely affect human health.

SELENOPROTEIN BIOSYNTHESIS

Sec is the most recently discovered eukaryotic amino acid encoded directly into proteins (as opposed to post-translational modification), making it the 21st amino acid. An overview of selenoprotein synthesis is shown in Figure 2. The tRNA for Sec ($tRNA^{Sec}$) recognizes the codon UGA, which functions in most mRNAs as one of three stop codons [1]. Serine is conjugated to $tRNA^{Sec}$ by seryl-tRNA synthetase, and then modified to phosphoserine by phosphoseryl-tRNA kinase. Dietary selenium is phosphorylated by SPS (selenophosphate synthetase) 2, and then added to phosphoserine by selenocysteine synthetase to produce Sec.

Eukaryotic selenoprotein genes require a SECIS element in the 3′-UTR of the mRNA in order to recode the UGA stop codon for Sec insertion. This unique stem–loop structure is the binding site for SBP2 (SECIS-binding protein 2), a complex protein with at least five isomers arising from alternative splicing of 17 possible exons [24]. The RNA-binding domain of SBP2 belongs to the L7Ae family of riboproteins, which includes some ribosomal proteins, snRNA (small nuclear RNA) and snoRNA (small nucleolar RNA)-binding proteins. Assembly of all of these riboproteins is dependent on both proper protein and RNA folding, and on a complex of proteins that includes the NUFIP [nuclear FMRP (Fragile X mental retardation protein)-interacting protein] adaptor protein, which mediates assembly of the R2TP co-chaperone complex and Hsp90 (heat-shock protein 90).

Biosynthesis of selenoproteins requires binding of SBP2 to the SECIS element and recruitment of the Sec tRNA-specific elongation factor, EFsec, bound to $tRNA^{Sec}$ [25]. The assembly of these factors on selenoprotein mRNAs in the nucleus sets the stage for decoding of UGA as Sec before export through the nuclear pore, and may also allow selenoprotein mRNAs to circumvent non-sense-mediated decay, a process that would normally lead to degradation of mRNAs with premature termination codons [26,27]. Oxidation of SBP2 leads to its import into the nucleus, where its reduction by nuclear-specific GPX and TRXR proteins is followed by CRM-1-dependent nuclear export [28].

Additional cofactors may contribute to selenoprotein synthesis. SECp43 was identified as a $tRNA^{Sec}$-binding protein [29], but its function has not been elucidated. The chaperone protein nucleolin binds to SECIS elements and may have a role in seleno-protein translation [27,30]. NSEP1 (nuclease-sensitive element-binding protein 1) is another SECIS-binding protein reported to function in selenoprotein synthesis [31,32]. As the selenoprotein family was discovered relatively recently, additional factors involved in the biosynthesis of these proteins may await discovery. The requirement of numerous specialized factors dedicated to incorporation of Sec into proteins suggests the evolutionary importance of selenoproteins.

SELENOPROTEINS AND MUSCLE DISORDERS

Severe selenium deficiency causes muscle disorders in humans and in animals. White muscle disease is a disorder associated with selenium deficiency in livestock raised on land with low selenium levels [10]. The muscles of affected animals appear paler than normal and may show distinct longitudinal striations or a pronounced chalky appearance owing to abnormal calcium deposition. White muscle disease can affect both skeletal and cardiac muscles where SelW is highly expressed. SelW is named after white muscle disease, and SelW levels are up-regulated in response to exogenous oxidants in muscle cells [17,33].

Selenium deficiency can lead to muscle disorders observed in humans in farmed regions with low selenium soil levels. Selenium deficiency is associated with myotonic dystrophy, causing weakness and muscle pain. Keshan disease, a potentially fatal cardiomyopathy, is discussed below. Kashin–Beck disease, an osteoarthropathy occurring in selenium-deficient regions of China and Tibet [34], and myxedematous endemic cretinism, a form of mental retardation occurring in regions of Africa [35], both involve concurrent selenium and iodine deficiency [36].

Multiminicore disease

Muscular dystrophy is a collection of disorders involving slow degeneration of muscle tissue [37]. Several genetic causes have been identified. One form of congenital muscular dystrophy, termed multiminicore disease, is characterized by a distinct loss of organization of muscle fibres [38]. Mutations in ryanodine receptors and *SelN* have been identified as causing the disorder [39]. Severe mutiminicore myopathy, rigid spine muscular dystrophy-1

and desmin-related myopathy with Mallory bodies are part of the same disease spectrum and have been linked to *SelN* mutations [20,40–43].

Ryanodine receptors are channels in ER (sarcoplasmic reticulum in muscle tissue) that are responsible for calcium-stimulated release of calcium from intracellular stores [44]. Thus these receptors potentiate calcium signals that may be initiated from membrane calcium channels and receptors, or by other calcium store channels such as the InsP_3-sensitive channels. Mutations in the ryanodine receptor lead to an impairment of function that results in disorganization of muscle fibres [45].

The role of SelN in multiminicore disease has been elusive because the function of SelN is unknown. However, knocking down SelN in zebrafish led to a disorganization of muscle fibres that resembled multiminicore disease in humans [46]. One mutation causing multiminicore disease involves a loss of an SRE (selenium-response element), a *cis*-element found in some selenoproteins in addition to the SECIS element [47]. The SRE is found within the RNA-coding region following the UGA codon. The SRE mutation prevents read-through, leading to early termination of translation.

A recent study showed that SelN associates with ryanodine receptors, and this association is necessary for proper function of the receptors [48] (Figure 3). The mutations in SelN responsible for multiminicore disease thus impair calcium signalling by preventing proper function of ryanodine receptors.

Why is SelN needed for ryanodine receptor function? A role for SelN in calcium signalling has not been described previously. However, there is evidence that other selenoproteins may also regulate calcium signalling and calcium stores. Overexpression of SelT, another ER-localized selenoprotein, led to an increase in calcium levels, but inhibited calcium responses and endocrine release from PACAP (pituitary adenylate cyclase-activating polypeptide) [49]. We have recently presented evidence that SelM attenuates calcium increases in response to oxidative stress ([51] and M. A. Reeves, F. P. Bellinger and M. J. Berry, unpublished work) Thus selenoproteins may have important functions in calcium signalling.

CARDIOVASCULAR DISORDERS

Selenoprotein function in cardiovascular disease has been investigated primarily by analysis of oxidative stress under conditions of selenium supplementation and/or deficiency. Oxidative stress damages vascular endothelial cells and exacerbates cardiovascular diseases such as atherosclerosis, hypertension, and congestive heart failure [52]. Selenoproteins are crucially involved in the cellular antioxidant defence system, thus using selenium to prevent or treat cardiovascular disease has been under investigation for many years. However, clinical epidemiology studies often do not support data from experimental models, complicating interpretation of the results.

Selenium supplementation elevates expression and activity of GPX1, GPX4 and TRXR1 in vascular endothelial or smooth muscle cells and thus inhibits oxidative stress, cell damage and apoptosis from oxidized LDL (low-density lipoprotein) or triol, a cytotoxic hydroxylated cholesterol derivative found in blood, cells, tissues and atherosclerotic plaques in humans [53–56]. Similarly, long-term selenium deficiency in rodents severely decreases GPX activity and expression and increases both physiological and cholesterol oxide-induced damage to the heart and vasculature. These effects can be reversed by dietary supplementation of selenium [57,58]. Furthermore, selenium-supplemented animals and their offspring exhibit reduced ischaemia-induced oxidative damage to the heart and improved recovery of cardiac function [59,60].

Selenoproteins and cardiac function

The precise role of specific selenoproteins in cardiovascular disease has been partially elucidated, particularly with the GPX enzymes. GPX1 has been shown to inhibit ischaemia/reperfusion-induced apoptosis of cardiac myocytes in mice [61]. Genetic deletion of GPX1 in mice produces heart and vascular dysfunction and tissue irregularities [62]. Furthermore, GPX1-overexpressing mice are more resistant than wild-type to doxorubicin-induced cardiac dysfunction as measured by heart contractility, blood flow rate and heartbeat rate [63].

GPX3 is abundant in plasma and probably modulates redox-dependent aspects of vascular function. Excess ROS due to decreased GPX3 activity results in inadequate nitric oxide (NO) levels, which disrupts platelet inhibitory mechanisms and increases arterial thrombosis [64]. Additionally, hypoxia regulates GPX3 expression [65], and there are reports of an association between polymorphisms in the *GPX3* promoter and increased risk of ischaemic stroke [66,67].

Overexpression of GPX4 reduces the atherogenic effects of lysophosphatidylcholine and 7-oxocholesterol, including necrosis and apoptosis of endothelial cells [68]. Additionally, overexpression of mitochondrial GPX4 *in vitro* protects against simulated ischaemia/reperfusion in neonatal cardiac myocytes [69]. Mice heterozygous for *GPX4* exhibit massive lipid peroxidation that produces cell death, which is dependent on 12/15-lipoxygenase and is mediated by apoptosis-inducing factor [70]. Collectively, these studies suggest that GPX4 inhibits atherosclerosis by reducing lipid and lipoprotein oxidation and downstream destructive processes.

Several reviews implicate the TRXR/TRX system in regulating processes of the cardiovascular system [71–73]. Changes in the intracellular redox environment alter inter- and intra-cellular signalling [74,75], including activation of hypertrophic and apoptotic pathways in cardiac myocytes [76–80]. Furthermore, the TRXR/TRX system contributes in regulating myocardial remodelling through the reversible oxidation of signalling molecules [71,73]. For example, adrenergic receptor activation-induced hypertrophy of adult rat cardiac myocytes is affected by the oxidation of cysteine thiols of Ras that can be reduced by TRXR1 [81]. It is important to note that TRXRs directly reduce substrates other than TRX [82], which may have relevant effects on heart and vascular function.

SelK is an ER protein that has an antioxidant function in cardiomyocytes and high mRNA expression in the heart [83]. Plasma SelP supplies selenium to cells [84], presumably supporting optimal expression of GPXs, TRXRs and other selenoenzymes. Additionally, SelP reduces peroxynitrite-induced protein oxidation and nitration, as well as lipid and LDL peroxidation [85], at the expense of oxidizing TRX [86]. Further studies on the functions of specific selenoproteins will help to elucidate the widespread effects of selenium on the cardiovascular system.

Selenium-related cardiomyopathies

Two cardiomyopathies associated with dietary selenium are Keshan disease and Chagas' disease. Keshan disease results in congestive heart failure and occurs because of low body selenium levels, attributed to the low-selenium soil in the Keshan region of China [87,88]. CVB3 (coxsackie virus B3) infection is also implicated as a contributing factor [89,90]. Oral selenium supplementation was found to virtually eliminate Keshan disease many years ago [91]. Subsequent studies in mice revealed that selenium deficiency increased the virulence of CVB3 [92,93]. Furthermore, in both selenium-deficient and GPX1-knockout mice, inoculation with non-pathogenic virus leads to pathological mutations and cardiomyopathy [94]. Specific mechanisms of how selenium affects CVB3 and Keshan disease remain

unclear [95]. Another disease involving selenium intake and a microbial parasite is Chagas' disease. Some patients infected with *Trypanosoma cruzi* develop a cardiomyopathy that is a common cause of heart failure in South America [96]. Patients with Chagas' disease and low selenium tend to have increased heart dysfunction, which suggests a protective function of selenoproteins [97]. As with Keshan disease, the mechanisms of selenoprotein protection of cardiovascular function lost during Chagas' disease have not been fully elucidated.

Clinical studies examining selenium status and cardiovascular disease mortality have provided contradictory data. For example, some studies have reported a 2–3-fold increase in cardiovascular mortality associated with low serum selenium concentrations (below 45 mg/l) [98], whereas others found no correlation with selenium concentrations, except for stroke mortality [99]. Several studies showed no clear association between cardiovascular mortality risk and low selenium [100–103], although a study of Danish men with low serum selenium (below 79 mg/l) have increased risk of ischaemic heart disease [104]. Additionally, low selenium levels correlate with risk of myocardial infarction [105]. Conflicting results between different clinical studies, and in comparison with experimental models, highlight the need for a mechanistic understanding of specific selenoprotein function in the cardiovascular system in order to determine the therapeutic benefits of selenium.

IMMUNE AND INFLAMMATORY DISORDERS

Selenoproteins and immune function

Selenoproteins are largely uncharacterized in the immune system, except with regards to inflammation. Although an initial acute inflammatory response is required for proper immune physiology, dysregulated chronic inflammation enhances the progression of several diseases including arthritis, cancer and viral infections, as well as autoimmune, cardiovascular, metabolic and neuro-degenerative disorders [106–112]. Levels of ROS influence inflammatory gene expression [113], thus selenoproteins affect inflammatory responses by regulating the oxidative state of immune cells. GPXs and TRXRs are necessary for optimal function of immune cells by controlling oxidative stress and redox regulation [114]. Specific selenoproteins also have ROS-independent roles in modulating inflammatory responses.

Mice with a T-cell-specific deletion in $tRNA^{Sec}$, resulting in knockout of all T-cell selenoproteins, have a large decrease in functional T-cells and exhibit moderate to severe atrophy of the thymus, spleen and lymph nodes. Furthermore, the mice have reduced antigen-specific production of immunoglobulins *in vivo*, implying a dysfunctional adaptive immune response. The deficits in selenoprotein-null T-cells are decreased TCR (T-cell receptor)-induced activation and proliferation of T-cells, and diminished TCR-induced IL-2R (interleukin-2 receptor) up-regulation and ERK (extracellular-signal-regulated kinase) phosphorylation [115]. Interestingly, IL-2R is increased in selenium-supplemented mice [116], emphasizing the importance of selenoproteins in regulation of IL-2R. Most of the defects in T-cells deprived of selenoproteins are reversed by application of the antioxidant *N*-acetylcysteine, which suggests that selenoproteins are required for proper regulation of ROS during T-cell activation and proliferation [115].

Dietary selenium and immune function

Selenium-deficient mice exhibit increased pathology from viral infection owing to an exaggerated pro-inflammatory immune response [95,117]. The iNOS (inducible nitric oxide synthase) and COX (cyclo-oxygenase) 2 pro-inflammatory genes are up-regulated in selenium-deficient cultured macrophages by a process dependent on the redox-sensitive transcription factor NF-κB (nuclear factor κB) [118]. Additionally, selenium supplementation suppresses pro-inflammatory gene expression in lipopolysaccharide-treated

macrophages by increasing the COX1-dependent formation of 15d-PGJ (15-deoxy-$\Delta^{12,14}$-prostaglandin J_2). 15d-PGJ_2 is an endogenous inhibitor of IKKβ [IκB (inhibitor of NF-κB) kinase β] that prevents phosphorylation of IκB by IKKβ and thus translocation and activation of NF-κB [119]. Interestingly, 15d-PGJ_2 can also repress NF-κB-mediated inflammatory responses by binding to and activating the nuclear hormone receptor PPARγ (peroxisome proliferator-activated receptor γ) [120–122]. Collectively, these data strongly suggest that inflammatory response termination, through increasing 15d-PGJ_2 and reducing NF-κB activity, is a selenium-dependent process.

Selenoproteins affect viruses in addition to host organism immune responses. Selenium deficiency or deletion of *GPX1* in mice increases CVB3 viral mutations and virulence [93]. Another RNA virus, influenza A/Bangkok/1/79, also becomes mutated and more virulent when inoculated into selenium-deficient mice compared with selenium-adequate mice [123]. Selenium supplementation inhibits TNFα (tumour necrosis factor α)-induced HIV replication [124]. This is at least partially due to TRXR1 reducing oxidized cysteine residues of Tat (transactivator of transcription), which inhibits efficient Tat transactivation and viral replication [125]. Finally, dietary selenium is reported to have a protective effect against hepatitis B virus infection in animal and epidemiological studies [126].

The therapeutic benefit of selenium for preventing excess inflammation has been investigated in clinical trials. Severely ill intensive care unit patients with SIRS (systemic inflammatory response syndrome) or sepsis have reduced plasma selenium levels that may cause a 3–4-fold increase in morbidity and mortality [127]. Despite the correlation of low plasma selenium with poor clinical outcome, one study reported that selenium supplementation in critical patients with sepsis or SIRS produces little clinical improvement, but is not toxic [128]. A more recent study showed that antioxidant supplementation, including selenium, significantly reduced the inflammatory response in major surgery or trauma patients, but failed to prevent organ dysfunction [129]. Many clinical studies involving selenium are ongoing, but large trials that examine specific selenoproteins in sepsis and SIRS are necessary to clarify the effects of selenium.

SelS polymorphisms and inflammation

One selenoprotein involved in immune responses is SelS, which is also named VIMP for VCP (valosin-containing protein)-interacting membrane protein [130]. VCP (also termed p97) is a cytosolic ATPase responsible for retrotranslocation of misfolded proteins from the ER, where they are tagged with ubiquitin and shuttled to the cell proteasome [21]. SelS is located in the ER membrane, and is believed to functionally link p97 to another ER membrane protein, derlin, thought to aid in removal of proteins from the ER lumen [21,130,131] (Figure 4). Secretion of *SelS* from liver cells and identification in human sera have also been reported [132]. Expression of SelS in liver cells is regulated by inflammatory cytokines as well as extracellular glucose concentrations [132,133]. SelS has an anti-apoptotic role and reduces ER stress in peripheral macrophages [134] and brain astrocytes [135].

Polymorphisms have been described that impair expression of SelS [136]. In particular, a change from G to A at position −105 in the SelS promoter was found to significantly decrease expression of SelS [136]. Individuals with this polymorphism had increased plasma levels of the inflammatory cytokines TNFα and IL-1β (interleukin 1β), possibly increasing the risk of several inflammatory diseases. The −105 polymorphism correlates with increased incidence of stroke in women [137], pre-eclampsia [138], coronary heart disease [139] and gastric cancer [140]. The polymorphism also exhibits epistasis with a −511 polymorphism of *IL-1β*, greatly increasing the risk of rheumatoid arthritis in individuals with both polymorphisms, although there was no correlation of polymorphisms with rheumatoid

arthritis alone [141]. However, it should be noted that other studies did not find correlations of *SelS* polymorphisms with stroke [142], autoimmune disorders [143] or inflammatory bowel disease [144]. Although the *SelS* polymorphisms are not known to be directly responsible for any particular disorder, they demonstrate how altered expression of one specific selenoprotein can increase the risk of multiple disorders. Further study on specific selenoprotein functions in immune responses will help clarify the effects of selenium on the immune system, and increase its therapeutic potential.

SELENIUM AND CANCER

There is a wealth of information on selenium and selenoproteins in cancer [145–148], and thus we only provide a brief overview within the present review. Much has been written about selenium as a cancer-preventing agent [147–149]. Early studies suggested that selenium could help reduce the risk of different forms of cancer [148]. However, secondary analysis of the NPC (Nutritional Prevention of Cancer) study [150] and the recently reported SELECT (Selenium and Vitamin E Cancer Prevention Trial) study [151] also raised the possibility that selenium increased the risk of Type 2 diabetes.

Many selenoprotein gene polymorphisms have been linked to risk of cancer. Polymorphisms of *GPX1* have been linked to various forms of cancer, including breast, prostate, lung, head and neck cancer [152–154]. Polymorphisms in *GPX2*, *GPX4* and *SelP* have been implicated in colorectal cancer [155,156], whereas *Sep15* polymorphisms may increase lung cancer risk [157]. As mentioned above, *SelS* promoter polymophisms have been linked to gastric cancer [140]. Recently, epistasis between polymorphisms of *SelP* and mitochondrial superoxide dismutase were shown to confer risk of prostate cancer [159]. Additionally, changes in expression of GPX1, GPX2, Sep15, SelP and TRXR1 have been observed in different forms of cancer [148,149].

The NPC trials originally sought to determine whether selenium supplementation could reduce the risk of skin carcinomas. Although skin cancer incidence did not differ between groups, the original study found decreases in total incidence of cancer and of prostate, lung and colorectal cancers [160]. Follow-up studies confirmed the protective effect of selenium in preventing prostate cancer [161]. Thus it is surprising that the SELECT study found no significant reduction in prostate cancer with selenium supplementation [151]. However, the supplementation of trial participants was terminated early because of concerns about diabetes and increased prostate cancer from vitamin E, although the subjects in the study are still being monitored for possible health benefits. It is possible that the trial was terminated too early to observe changes similar to those seen with the NPC trial. The SELECT study had several design differences from the earlier NPC trial, including the use of purified selenomethionine in supplements as opposed to selenized yeast used in the earlier trial [151]. Interestingly, the combination of selenium and vitamin E did not seem to increase either diabetes or prostate cancer; the incidences of these disorders with the dual-supplement group was notably lower than the increases found with either supplement alone.

As not all selenoproteins change equally with selenium supplementation [162,163], we need to examine the direct roles of selenoproteins to assess whether supplementation is advisable for treatment or prevention of a specific disease. Selenium may be more desirable for some health benefits. In some cases, alternative methods to regulate the expression and function of specific selenoproteins may have more health benefits.

NEUROLOGICAL DISORDERS

Selenium is retained within the brain even under conditions of dietary selenium deficiency, implying the potential importance of the trace element in neurological disorders [164,165].

Damage from ROS takes place in neurodegenerative disorders such as AD (Alzheimer's disease), PD (Parkinson's disease), ischaemic damage, exposure to environmental toxins and drugs of abuse, and brain tumours [166].

Alzheimer's disease

Oxidative damage to macromolecules is an early indication of AD that can appear before clinical symptoms [167]. AD patients suffer memory loss, impaired cognitive function and changes in behaviour and personality [168]. The brains of AD patients can be identified by their characteristic extracellular plaques consisting of the protein, amyloid β, as well as by intracellular neurofibrillary tangles. Most cases of AD are 'late-onset', progressing with age, and the causes are unclear. However, several autosomal dominant mutations have been identified that can result in 'early-onset' AD. One of these is a mutation in presenilin-2, an enzyme involved in processing amyloid precursor protein [169]. A mouse model overexpressing the human mutation has reduced levels of brain SelM, an ER-specific selenoprotein of unknown function [170]. Thus SelM may have a protective role in AD.

Although originally identified as a plasma protein, SelP is abundant in neurons and ependymal cells in the human brain [171]. Expression of SelP in brain increases with aging, suggesting it may play a role in ameliorating oxidative stress [172]. Genetic deletion of *SelP* impairs synaptic function in the hippo-campus, a region involved in memory, and reduces spatial learning as well as long-term potentiation, a cellular model for learning and memory [173]. A recent analysis of expression data indicated that SelP was also increased in AD beyond that found in aging [174]. We investigated the expression of SelP in postmortem human brain. We found a unique expression pattern of SelP within the centre of neuritic (dense-core) plaques [175]. We also found co-localization of SelP with plaques and neurofibrillary tangles. Although a specific role for SelP in AD is uncertain, the location of SelP suggests that it could play a role in mitigating the oxidation accompanying plaques.

Serum SelP is greatly influenced by dietary selenium, and thus selenium supplementation may have a direct neuroprotective role by increasing SelP expression [16]. Recent studies have suggested that selenium supplementation can decrease amyloid toxicity in cell culture and animal models [176,177]. An ancillary study of the SELECT study, PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium), is currently in progress to examine the possible benefits of increased dietary selenium on preventing AD [178]. Although participants of the SELECT study have been advised to discontinue their supplements because of the possibility that selenium may increase the risk of Type 2 diabetes or that vitamin E may increase the risk of prostate cancer, the cohort is still being monitored [151]. A decrease in the risk of AD could possibly justify any increase in the risk of diabetes with selenium supplementation for individuals with family history or early signs of the disease.

Parkinson's disease

The neurotransmitter dopamine controls many important brain functions despite being released from only 2 % of neurons in the brain [179]. Severe loss of dopamine-releasing neurons in the substantia nigra is central to the neurodegenerative disorder, PD [180]. Symptoms of PD include rigidity, tremor and loss of movement control, with mood changes and cognitive impairments found in later stages of the disease [181]. PD is characterized by loss of dopamine terminals in putamen and caudate within the striatum from neurons projecting from the substantia nigra (the nigrostriatal pathway). The dopaminergic neurons in substantia nigra exhibit lesions termed 'Lewy bodies', made up of aggregates of ubiquitinated α-synuclein [182]. Several findings suggest an involvement of selenoproteins in preserving the nigrostriatal pathway. The substantia nigra and putamen have higher

concentrations of selenium than other brain regions [183]. Selenium deficiency increases pathology in mouse models of the disease [184–187]. PD patients have an approx. 50 % decrease in glutathione, suggesting impaired GPX function [188]. Chemical lesions of dopaminergic terminals and neurons are greatly exacerbated in selenium-deficient animals [184,189], whereas selenium supplementation was protective to dopamine neurons and up-regulated GPX activity [190,191]. A recent report demonstrated that GPX1 is associated with microglia in PD pathology [192]. Knockout of *GPX1* in mice greatly potentiates dopamine loss and pathology in a rodent PD model [193], whereas overexpression of GPX1 has a protective role [194,195]. Thus GPXs and other selenoproteins may play important roles in protecting dopaminergic transmission and preventing PD. However, to date, no changes in selenoprotein expression or function have been reported to correlate directly with this disease.

Epilepsy

Epilepsy is a chronic neurological disorder characterized by seizures which cause interruptions in normal brain function [196]. There are many classifications of epilepsy syndromes, with each seizure type presenting unique problems, and thus treatment options. Owing to the variations within this disorder, additional treatments for epilepsy are being explored. A clinical study performed in infants showed that low levels of selenium in the blood lead to infant seizures and neurological conditions [197]. Epilepsy, ischaemia and brain trauma cause a signal cascade of free radicals and activation of pro-apoptotic transcription factors, resulting in neuronal loss [198]. Rats on selenium-deficient diets had increased susceptibility to kainate-induced seizures and cell loss [198]. Another study combining selenium and TPM (topiramate), a new anti-epileptic drug which inhibits voltage-gated sodium and calcium channels, showed protective effects following PTZ (pentylentetrazol)-induced seizures [199]. GPX and plasma membrane calcium ATPase activity were increased following PTZ challenge in rats treated with selenium and TPM, thus inhibiting free radical production and regulating calcium-dependent processes [200]. SelP-knockout mice develop neurological seizures and movement disorders when raised on restricted selenium diets [201,202], providing further evidence for a possible role for selenoproteins in preventing epilepsy.

SELENOPROTEINS AND ENDOCRINE DISORDERS

Selenoproteins play important roles in the production of hormones and growth factors, particularly for thyroid hormone production. The energy demands of endocrine tissue as well as redox reactions involved in the production and release of factors require selenoproteins such as GPXs and TRXRs to prevent accumulation of ROS. As discussed above, SelT may be involved in the control of calcium-dependent release of PACAP hormonal peptide from pituitary.

Thyroid hormone

Activation of thyroid hormone is dependent upon the DIO class of selenoproteins. These enzymes catalyse deiodination of the pro-hormone thyroxine, or T_4 (tetra-iodo-L-thyronine), to the active hormone T_3 (tri-iodothyronine), and to the inactive metabolites rT_3 (reverse tri-iodothyronine) and T_2 (di-iodothyronine) [203,204].

Mutations in *SBP2* were found to be responsible for deficiencies in thyroid function in two families, one from Saudi Arabia and one from Ireland [205]. One of these mutations impaired exon splicing, leading to an intron retention that changed the reading frame, producing a truncated SBP2. The altered SBP2 resulted in decreased levels of DIO2 [13].

Thus mutations in the machinery necessary for the production of selenoproteins can result in specific health impairments [10].

It is curious that the mutations in *SBP2* do not have greater consequences. Selenium deficiency in humans, notably in Keshan disease described above, can lead to severe cardiomyopathy [10]. Targeted disruption of the genes encoding several selenoproteins, including TRXR1 and TRXR2, and GPX4, or of the gene encoding $tRNA^{Sec}$, leads to embryonic or early postnatal lethality [206]. Thus impairing the selenoprotein synthesis machinery could be expected to have more severe consequences than those seen with *SBP2* mutations.

Part of the answer may be in the complexity of SBP2 and its varying affinities for different selenoprotein mRNAs. The RNA-binding domain is intact in the *SBP2* mutations, but selectivity for differing SECIS elements is impaired [27]. Two major forms of SECIS elements, forms 1 and 2 (numbered in order of discovery), have been described, although unique elements exist in some selenoprotein messages [1]. The wild-type form of SBP2 has greater affinity for form 2, but the Saudi mutation discussed above renders SBP2 less selective as well as reducing overall affinity [27]. Of course, it is likely that mutations in *SBP2* that completely prevented its function would be lethal and never detected in adults and families. The mutations in *SBP2* present an interesting study of how synthesis of selenoproteins can be selectively impaired to cause a specific disorder.

Diabetes

Diabetes mellitus is a disorder resulting in impaired control of blood glucose levels by either impaired insulin release (Type 1) or impaired insulin function or insulin resistance (Type 2) [207]. The resulting hyperglycaemia increases ROS production, which may contribute to the progression of this disorder [208]. Some studies have suggested that selenium may be beneficial in treating diabetes [209–212]. However, recent clinical trials such as the SELECT study have suggested a possible risk of developing Type 2 diabetes resulting from selenium supplementation [150,151,213]. Selenium has insulin-mimetic properties *in vitro* and *in vivo* that appear to be independent of insulin release [13,214,215], which could potentially accelerate development of insulin resistance.

SelS is glucose-regulated, and was originally discovered in a rodent model for diabetes [216,217]. Mice overexpressing GPX1 develop insulin-resistance, a hallmark of Type 2 diabetes [218]. GPX1 is increased by selenium supplementation [219], and thus may have a role in the apparent increased risk of diabetes reported in recent selenium-supplementation studies [150,151]. Further research on the role of selenoproteins and diabetes is warranted.

CONCLUSIONS

Members of the selenoprotein family require a common set of cofactors for their synthesis, and are dependent upon dietary selenium intake. The cost to organisms in energy to produce these cofactors and synthesize selenoproteins suggests the collective importance of this protein family to cell function. However, the functions of these proteins are quite varied. Selenoproteins play important roles in numerous diseases and conditions, including neuromuscular and cardiovascular disorders, inflammation, cancer, neurodegeneration and endocrine disorders. Several of the known diseases involving selenoproteins are summarized in Table 1.

In view of the diverse roles of selenoproteins, strategies to target expression and/or function of specific selenoproteins could be considered for therapeutic treatment and prevention of disorders. Different dietary forms of selenium may selectively increase specific

selenoproteins. Pharmaceuticals could also target specific selenoproteins or factors involved in selenoprotein synthesis. The limited changes in selenoprotein levels with the observed mutations in *SBP2* highlight the possibility of targeting subsets of the selenoprotein family. The functions of many selenoproteins remain unknown. Thus understanding the function of each member of the selenoprotein family will be important in determining the health benefits of selenium.

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Abbreviations used

AD	Alzheimer's disease
COX	cyclo-oxygenase
CVB3	coxsackie virus B3
DIO	iodothyronine deiodinase
15d-PGJ_2	15-deoxy-$\Delta^{12,14}$-prostaglandin J_2
EFsec	selenocysteine tRNA-specific elongation factor
ER	endoplasmic reticulum
GPX	glutathione peroxidase
IκB	inhibitor of NF-κB
IKKβ	IκB kinase β
IL-1β	interleukin 1β
IL-2R	interleukin 2 receptor
LDL	low-density lipoprotein
NF-κB	nuclear factor κB
NPC	Nutritional Prevention of Cancer
PACAP	pituitary adenylate cyclase-activating polypeptide
PD	Parkinson's disease
PTZ	pentylentetrazol
ROS	reactive oxygen species
SBP2	selenocysteine insertion sequence-binding protein 2
Sec	selenocysteine
SECIS	selenocysteine insertion sequence
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SelH (etc.)	selenoprotein H (etc.)
Sep15	15 kDa selenoprotein
SIRS	systemic inflammatory response syndrome
SPS	selenophosphate synthetase
SR	sarcoplasmic reticulum

SRE	selenium-response element
Tat	transactivator of transcription
TCR	T-cell receptor
TNFα	tumour necrosis factor α
TPM	Topiramate
$tRNA^{Sec}$	selenocysteine tRNA
TRX	thioredoxin
TRXR	thioredoxin reductase
UTR	untranslated region
VCP	valosin-containing protein

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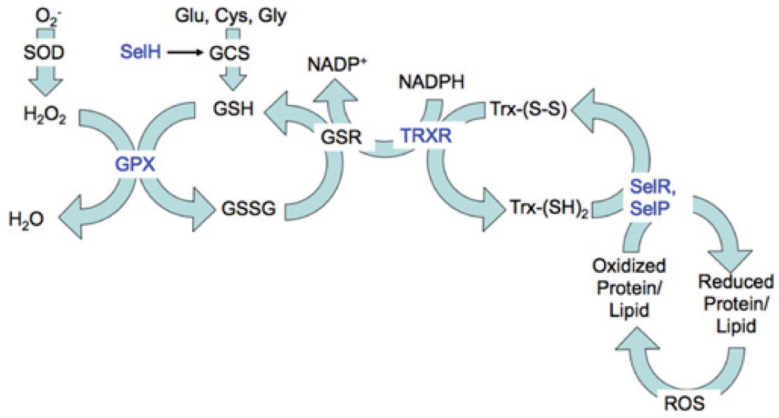

Figure 1. Selenoprotein involvement in cellular antioxidant systems

Selenoproteins (highlighted in blue) have critical roles in both the GSH-dependent and TRX-dependent antioxidant systems. GPXs catalyse the breakdown of peroxides into water. SelH increases expression of the GSH-synthesis enzyme GCS (γ-glutamylcysteine synthetase). TRXRs reduce oxidized TRXs. Certain selenoproteins, such as SelR and SelP, use TRX as an electron donor to form redox couples for detoxification of oxidized proteins and lipids. Protein/Lipid could be protein phosphatases, protein kinases, transcription factors or membrane protein/lipids. GSR, glutathione reductase; SOD, superoxide dismutase. An animated version of this Figure can be seen at http://www.BiochemJ.org/bj/422/0011/bj4220011add.htm.

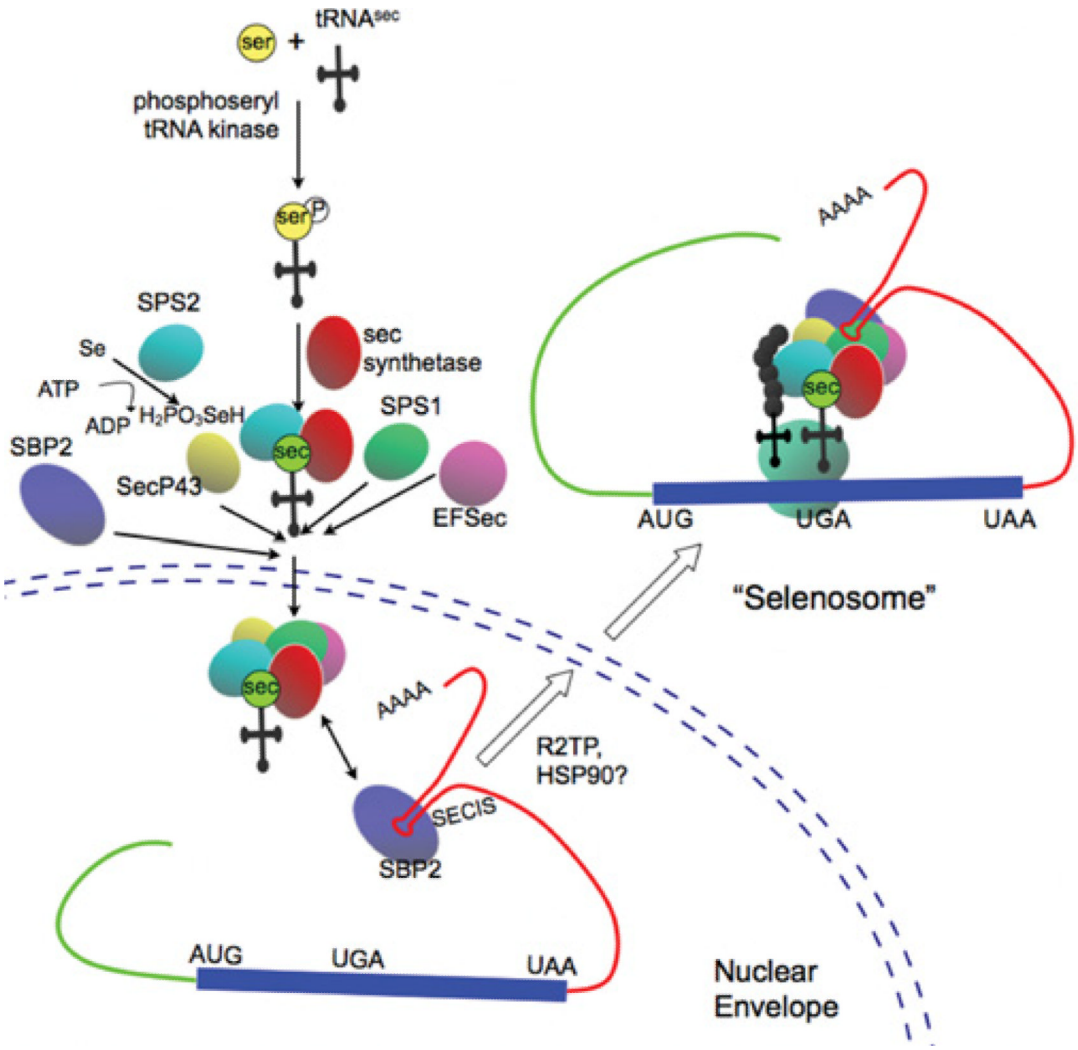

Figure 2. Machinery involved in synthesis of selenoproteins

Selenium phosphorylated by SPS1 is used to synthesize Sec from serine directly on the $tRNA^{Sec}$ by the enzyme Sec synthetase. $tRNA^{Sec}$ is transported to the nucleus with many cofactors bound. The protein SBP2 binds to the SECIS element in the 3′-UTR of selenoprotein mRNAs, and recruits the $tRNA^{Sec}$ complex along with bound cofactors. The assembled complex is transported from the nucleus for translation to protein. HSP90, heat-shock protein 90.

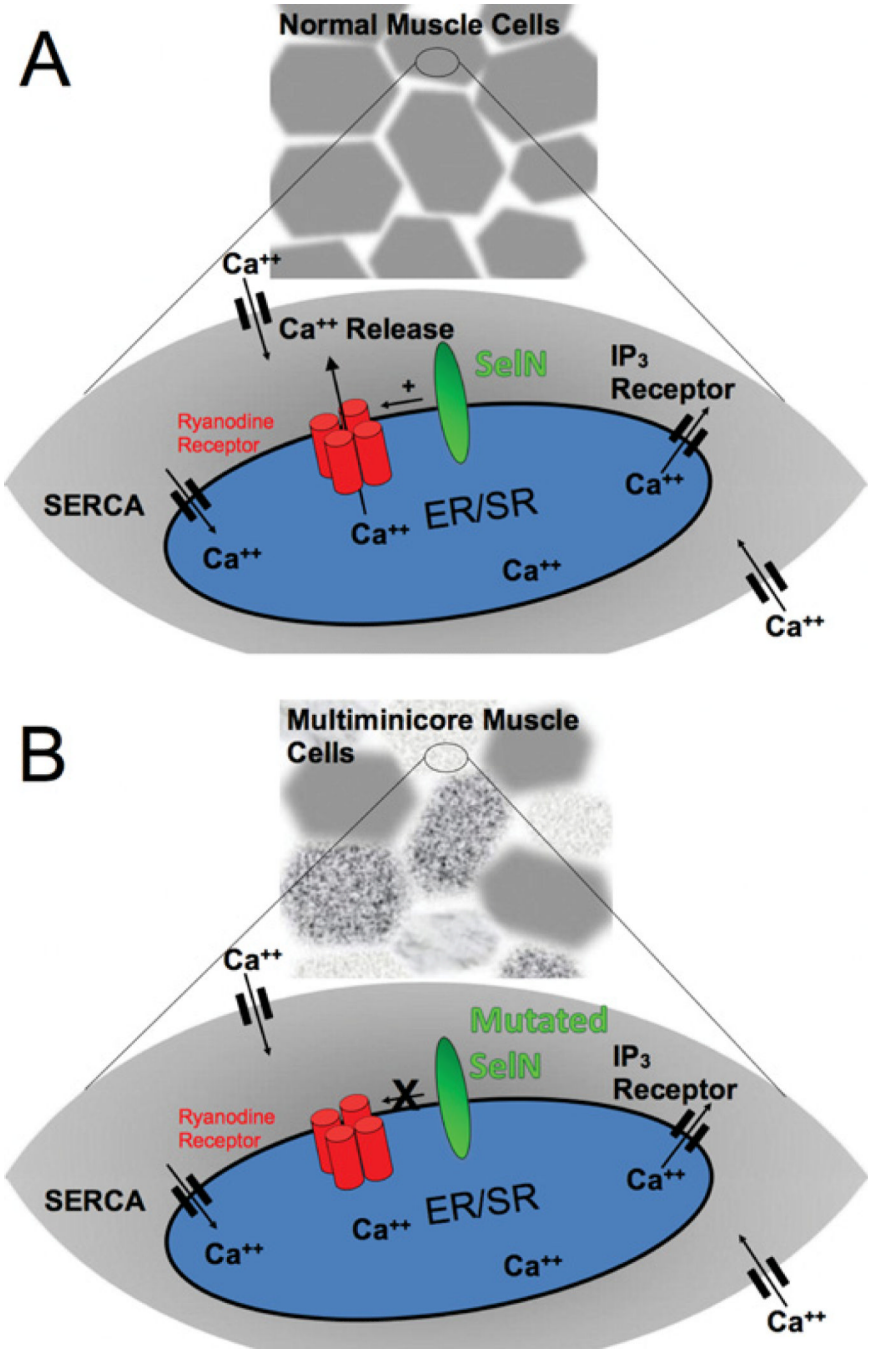

Figure 3. SelN and ryanodine receptors

(**A**) SelN interacts with ryanodine receptors to control release of calcium from intracellular stores. (**B**) Mutations in both SelN and ryanodine receptors can cause multiminicore disease, a form of muscular dystrophy. IP_3, inositol trisphosphate; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum.

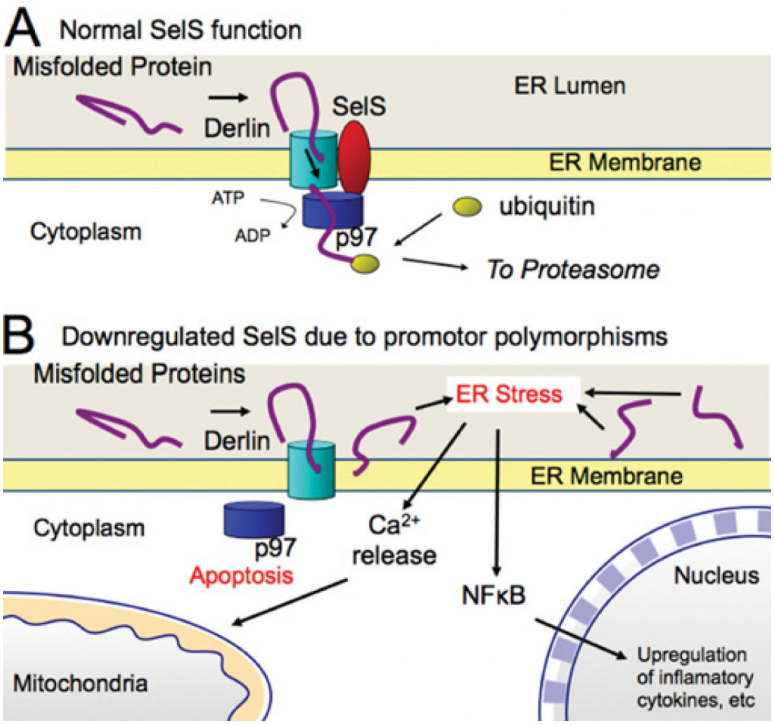

Figure 4. Role of SelS in removal of misfolded proteins from ER

(**A**) SelS is an ER membrane protein that interacts with the ER membrane protein derlin and the cytosolic ATPase p97 to transport misfolded proteins out of the ER. Once in the cytosol, the protein is tagged with ubiquitin via the E3 ubiquitin ligase and shuttled to the cell proteasome. (**B**) Promoter SelS polymorphisms can down-regulate expression of SelS, causing a build up of misfolded proteins in the ER. Stress to the ER can induce NF-κB, which can up-regulate inflammatory cytokines, and can also lead to apoptosis.

Table 1

Examples of selenoproteins in human diseases

Disorder	Cause	Selenoprotein or cofactor	Function	Reference(s)
Keshan disease	Selenium deficiency/ coxsackie B virus	Various, GPX?	??	[10]
Kashin–Beck disease	Selenium/iodine deficiency	DIO	Thyroid hormone production	[34]
Epilepsy	Selenium deficiency?	GPX?	Oxidative stress	[197]
Multiminicore disease	Mutations	SelN	Calcium signalling	[39]
Thyroid dysfunction	Mutations	SBP2	Selenoprotein synthesis	[205]
Inflammation responses	Polymorphisms	SelS	Removal of misfolded proteins	[136]
Neurodegeneration	??	SelP, SelM, ??	Oxidative stress	[175]
Cancer	Polymorphisms/Expression	GPX1, GPX2 and GPX4, SelS, SelP, Sep15, TRXR	Various	[10,145,147,148]
HIV	Virus	TRXR1, GPX?	Viral gene expression, oxidative stress	[220]