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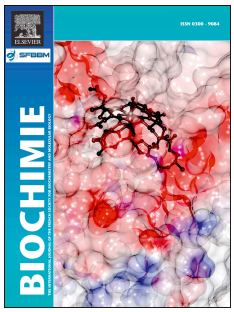

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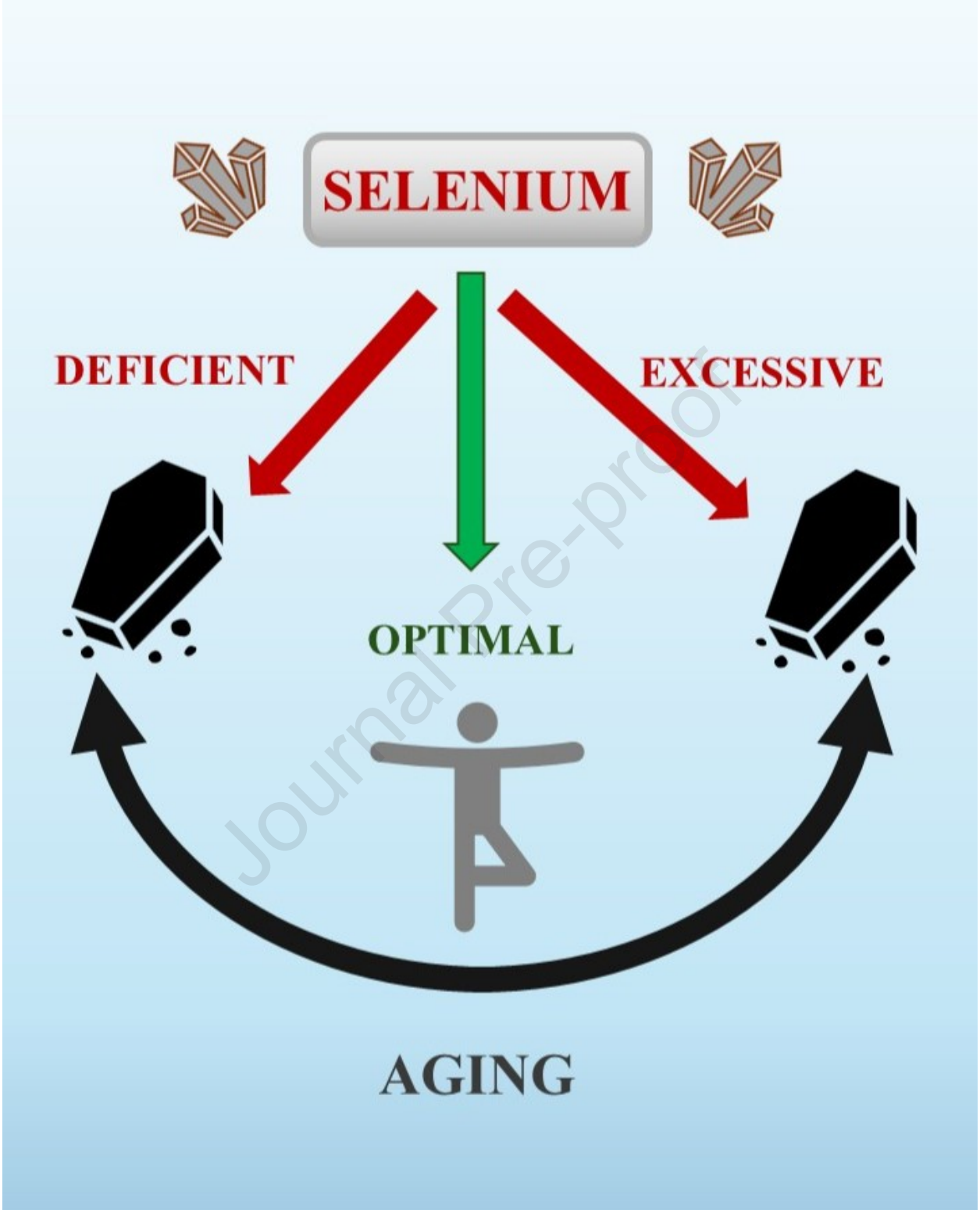

Selenium in Aging and Longevity

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Abbreviations: 27-OHC, 27-hydroxycholesterol; AD, Alzheimer's Disease; CHOP, C/EBP homologous protein; DIO, thyroxine deiodinase; ER, endoplasmic reticulum; FAD, flavin adenine dinucleotide; GPX, glutathione peroxidase; HR, hazard ratio; HSPA1L, 70 kDa heat-shock protein 1L; IGF-1, insulin-like growth factor-1; miR, microRNA; MSRB1, methionine sulfoxide reductase B1; NFATc2, nuclear factor of activated T-cells cytoplasmic-2; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; NMD, nonsense-mediated decay; PACAP. pituitary adenylate cyclase-activating polypeptide; PPARγ, peroxisome proliferator-activated receptor-γ; PTP, protein tyrosine phosphatase; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; RyR, ryanodine receptor/Ca^{2+}-release channel; SC, satellite cells; SECIS, selenocysteine insertion sequence; SELENBP, Se-binding protein; SELENOF selenoprotein F; SELENOH, selenoprotein H; SELENOI, selenoprotein I (CDP-ethanolamine phosphophatidyltransferase-1); SELENOK, selenoprotein K; SELENOM, selenoprotein M; SELENON, selenoprotein N; SELENOO, selenoprotein O; SELENOP, selenoprotein P; SELENOS, selenoprotein S; SELENOT, selenoprotein T; SELENOV, selenoprotein V; SELENOW, selenoprotein W; SeM, *L*-selenomethione; SERCA, SR/ER Ca^{2+}-ATPase pump; Sik-1, salt-induced kinase-1; U or Sec, selenocysteine; SLC7A11, cystine/glutamate transporter; SPHS2, selenophosphate synthetase 2; Txnrd, thioredoxin reductase.

Highlights

- Selenium is an essential micronutrient, exerting negative effects of longevity when it is deficient or in excess
- Selenium exerts biological effects through small-molecules, selenoproteins and selenium-binding proteins
- Effects of selenium-containing biomolecules on life-span and aging are presented in this review

Abstract

Selenium is an essential dietary micronutrient, exerting beneficial effects over a limited range of concentrations. Insufficient dietary intake of selenium increases the risk of type 2 diabetes, infertility, immune dysfunction, prostate cancer, cognitive decline, prostate cancer, colorectal cancer in females, skeletal muscle disorders, overall mortality and an endemic cardiomyopathy known as Keshan disease. Excessive intake of selenium is toxic, leading to a condition termed selenosis, that is associated with damage to the nails, dermatitis, alopecia, central nervous system dysfunction and death. Selenium exerts its biological effects through low-molecular weight molecules, through a small family of selenoproteins which contain the 21st amino acid selenocysteine, and via selenium-binding proteins, in which an atom of selenium is covalently bound to a cysteine residue. In addition to being regulated by body selenium status, the abundance and function of these biomolecules can be controlled by other dietary components (including copper, zinc, folic acid, resveratrol, vitamin A and α-linoleic acid) and other factors, such as exercise and caloric restriction. This review comprehensively surveys the effects of selenium-containing biomolecules on aging and aims to generate rationales underpinning the biphasic effects of this element on life-span, health-span and disease. This will provide a framework for understanding the effects of selenium on mechanisms of aging, as the starting point for development of interventions that will promote longevity and health-span.

Keywords: aging; selenoproteins; selenium-binding proteins; oxidative stress; Ca^{2+}; cell-death

1. Introduction

Selenium (Se) is an essential dietary trace element, with an adequate intake of 70 μg/day and a tolerable upper intake level of 400 μg/day for adults [1]. Chronic dietary deficiency of Se is endemic in some geographical regions and is linked to a life-threatening cardiomyopathy called Keshan disease, associated with coxsackievirus infection. Insufficient intake of Se is also associated with increased risk of prostate cancer, type 2 diabetes, infertility, cognitive decline, impaired immune function, colorectal cancer in females and increased overall mortality [2, 3]. Effects of excess Se intake have been documented in the contexts of supplementation trials, animal experimentation, accidental overdose, environmental exposure due to geographically high soil and water levels, or suicide attempts. Selenosis, or Se toxicity, is characterised by symptoms including alopecia, damage to the nails, dermatitis, central nervous system disorders and death [4]. In addition, ingestion of excess Se has also been linked to increased risk of type 2 diabetes, prostate cancer, amyotrophic lateral sclerosis and Parkinson's disease [3].

Se is present in soil and in water in multiple forms including elemental Se, selenides, selenates, selenites and organic species. The key bioavailable species of Se in the environment are *L*-selenomethionine (SeM) and selenate (SeO_4^{2-}) [5]. In animals, dietary sources of Se can be incorporated into low-molecular species (*Section 2*), can be competitively incorporated into proteins (with SeM replacing methionine residues), can be translationally incorporated into a small subset of selenoproteins in the form of selenocysteine (*Section 3*), or is covalently bound to Se-binding proteins (*Section 4*), *Fig. 1*.

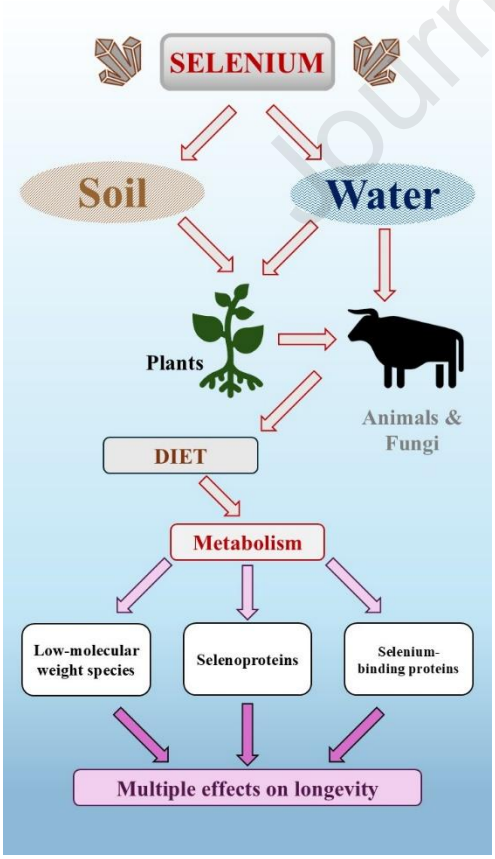

Figure 1. Overview of the supply of Se to the diet and the pathways by which this influences longevity. The Se content of local water and soil depends on the underlying geology: some areas are deficient in this micronutrient; in other regions it is in excess. Plants absorb Se directly from both soil and water; whereas in animals and fungi, Se intake depends on food and water. Se-containing compounds can be metabolised to low-molecular weight species, selenoproteins and Se-binding proteins, each having multiple effects on longevity.

2. Low molecular weight selenium species and aging

Major dietary sources of Se are selenomethionine, the 21st amino acid selenocysteine (Sec, U), and selenate. Via distinct pathways, these are all metabolized to selenide (SeH_2), a key intermediate in the formation of selenophosphate ($SePO_3^{3-}$), Sec and methylselenol. Excess SeM can be incorporated into proteins (competing with methionine). Selenide can be methylated to the volatile dimethylselenide (exiting via the breath), or water-soluble trimethylselenonium ions (excreted in the urine), and can also be converted to selenosugars [6] such as 1β-methylseleno-N-acetyl-D galactosamine, which leave the body in both urine and faeces, *for review see* [5]. An early study in rats indicated alterations in Se metabolism with age. Young rats (10-50 days old) excrete less injected radiolabelled selenium exclusively via the urine, whereas old rats (65-165 days old) excrete more, equally in both the breath and the urine. Old rats also display a 63-fold increase in the percentage of methylated selenium metabolites compared to young rats [7]. In another study tracing the fate of excess radiolabelled selenite administered in drinking water, found that young rats (5 weeks old) excreted the majority of Se as a selenosugar in the urine, with trimethylselenonium only appearing only above a threshold dose. By contrast, in old rats (36 weeks) urine trimethylselenonium did not increase with intake dose. These observations suggest that the sugar moiety precursor of urine selenosugar is more abundant in old than in young rats [8], potentially serving as a biomarker of biological aging. However, the chemical nature of this sugar source is currently unknown. In rats, disruption of conversion of S-adenosylmethionine to S-adenosylhomocysteine (using periodate-oxidized adenosine) decreases levels of both selenosugar and trimethylselenonium in the liver, kidneys and urine [9]. This might be important in the context of dietary Se supplementation in aging, where S-adenosylmethionine-dependent transmethylation is impaired.

Dietary Se can be supplemented in various ways, including intake of naturally high Se-content foods, multi-vitamins, SeM, selenate, selenite, Se nanoparticles and intentionally Se-biofortified foods, such as yeast [10]. In humans, Se status can be assayed directly by measuring elemental Se in plasma, urine or toenails [11], or by quantifying selenoprotein P (SELENOP, *Section 3.13*) and/or glutathione peroxidase 3 (GPX3, *Section 3.2*) in serum. Analysis of serum samples from the Berlin Aging Study-II revealed robust correlations between elemental Se concentrations and SELENOP levels in all groups, apart from in younger women (20-35 years old) [12].

Beneficial effects of Se supplementation on longevity have been reported in multiple experimental model organisms, including the yeast *Saccharomyces cerevisiae* [13], the nematode worm *Caenorhabditis elegans* [14, 15], the fruit-fly *Drosophila melanogaster* [16], mice [13] and in rats with drinking water supplemented with selenate, but not selenite [17]. However, an overall consensus on the impact of Se status on human longevity has been difficult to reach, with different supplementation trials yielding distinct outcomes, *for reviews see* [2, 18–20]. One factor contributing to this variability is the U-shaped relationship between Se status and deleterious outcomes. This phenomenon was first reported in aged dogs, in which DNA damage to prostate cells (modelling prostate cancer) was greatest in animals with either Se deficiency or excess, as assayed in toenail clippings [21]. Subsequently, U-shaped relationships between Se status in humans and risk of age-related diseases have been reported in the contexts of prostate cancer [22], type 2 diabetes [23], and all-cause and cardiovascular mortality in hypertensive patients [24]. A systematic review and meta-analysis of cohort studies revealed an inverse association between markers of Se status and all-cause, cancer and cardiovascular mortality [25]. As assessed by quantifying DNA methylation in the Berlin Aging Study-II, biological aging is associated with low levels of serum Se, SELENOP and GPX3 [26]. In a cross-sectional study, lower Se status is associated with frailty [27]. In American adults, low dietary Se intake correlate with age-related loss of muscle mass, termed sarcopenia .[28]. By contrast, a double-blind placebo controlled trial showed no correlation between Se supplementation and musculoskeletal health in older women [29].

It is unclear whether low molecular weight Se species can directly influence longevity, or if these effects are exerted indirectly through selenoproteins and Se-binding proteins. One pathway by which Se supplementation might contribute to extended lifespan is downregulation of insulin-like growth factor-1 (IGF-1) signalling. In mice, dietary supplementation of either sodium selenite or SeM increases health-span in a manner resembling methionine restriction, through inhibition of IGF-1 signalling [13]. In aged mice, Se-containing nanoparticles extend both life-span and health-span. Mechanistically, this is linked to increased selenoprotein expression, tightened endoplasmic reticulum (ER) Ca^{2+} regulation and decreased activation of the Ca^{2+}-dependent transcription factor, nuclear factor of activated T-cells cytoplasmic-2 (NFATc2). Consequently, Se drives decreased transcription of salt-induced kinase-1 (Sik1) and p16/p21, markers of cellular senescence [30]. At a cellular level, supplementation of culture medium with sodium selenite delays senescence

(decreased replicative ability with each cell division) in the human WI-38 fibroblast cell-line [31].

In humans, Se status influences the risk and progression of a variety of age-related diseases. In a population of 85-year olds in Northeast England, most had suboptimal Se status, as assayed by measuring serum Se, SELENOP and GPX3 [32]. In a group of 275 participants, low serum Se was identified as a risk factor in the development of age-related cataract [33]. In a longitudinal study of this group, serum Se concentration, but not the abundance of GPX3 or SELENOP, was positively associated with cognitive ability at baseline [34]. In a population of women over 45 years old, serum Se and SELENOP levels are associated with risk of type 2 diabetes, through a mechanism likely to involve inflammation [35].

3. Selenoproteins and longevity

Selenocysteine (Sec, U) is the 21st proteinogenic amino. It is inserted into a subset of 25 selenoproteins in humans, by recoding of specific UGA stop codons. In eukaryotes, this recoding requires a Sec insertion sequence (SECIS) downstream of the mRNA coding region, which recruits a specialised tRNA (Sec-tRNA^{sec}) and *trans*-acting factors to the ribosome [36]. Sec is an analogue of cysteine, but is more nucleophilic, making it more reactive with electrophiles [37]. Consequently, most selenoproteins of known function play roles in redox reactions. Based on mouse knockout or human mutant phenotypes, five selenoproteins (SELENOP, Txnrd1, Txnrd2, GPX4 and DIO3) were classified as essential and seven (GPX1-3, DIO1-2, MSRB1, and SELENOP) were deemed non-essential. During dietary Se deficiency, expression of essential selenoproteins is maintained, and that of non-essential selenoprotein is reduced, with the exception of DIO1 [38]. This suggests that there is a hierarchical utilisation of Se by selenoproteins [5]. A decade ago, selenoprotein nomenclature was consolidated [39]: in this review, these proteins will be referred to according to this convention, but their alternative names will also be provided. The subcellular localisations and roles of human selenoproteins are summarised in *Fig. 2*.

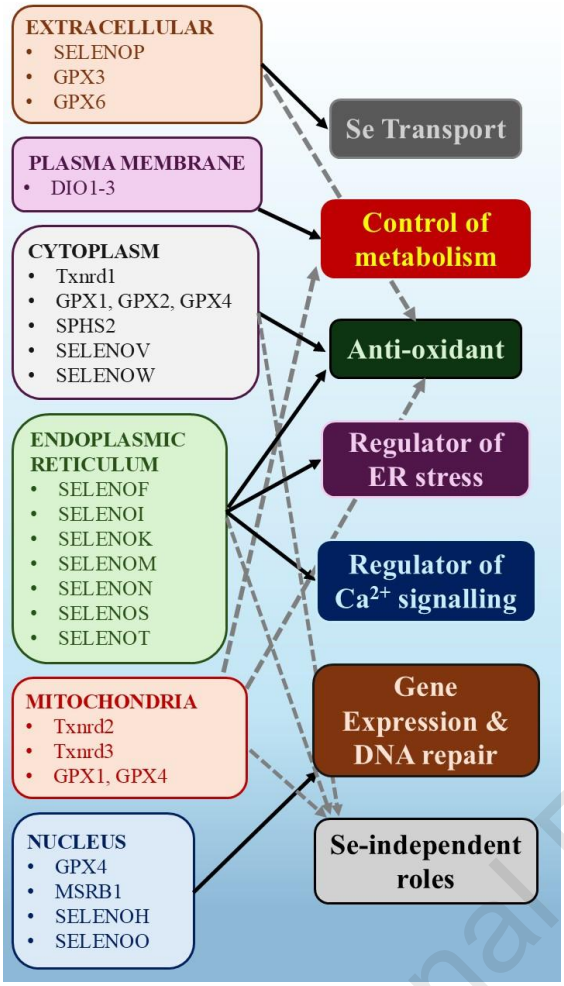

Figure 2. Categorisation of selenoproteins by subcellular locations and physiological roles. Note that several selenoproteins are located in multiple subcellular regions, often due to the generation of distinct proteins by alternate mRNA splicing. Most selenoproteins have several different functions.

3.1. Thioredoxin reductases (Txnrd1, Txnrd2, Txnrd3)

Mammalian thioredoxin reductases are a family of three selenoprotein enzymes (Txnrd1, Txnrd2, Txnrd3) which reduce thioredoxins, small protein regulators of cysteine reduction. Txnrd1 is cytosolic, whereas Txnrd2 and Txnrd 3 are mitochondrial. All Txnrds are homodimeric and contain a flavin adenine dinucleotide (FAD) prosthetic group. Genetic disruption of either thioredoxins or Txnrds shortens the lifespan of *Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster* and *Mus musculus, for review see* [40, 41]. Furthermore, the abundance of Txnrd2 protein is high in fibroblasts from long-lived compared with short-lived mammals [42].

In the cardiovascular system, ischemia-reperfusion injury can occur through cardiovascular disease, or during surgery, and results in the production of reactive oxygen species (ROS). In the hearts of aged rats (20-24 months), ischemia-reperfusion inactivates both Txnrd1 and Txnrd2 through nitration, to a greater extent than it does in young animals (6-8 months) [43]. Inducible heart-specific knockout of Txnrd2 in mice results in age-dependent contractile deficits, altered metabolism and autophagy [44]. Conversely, overexpression of Txnrd2 in transgenic mice promotes resistance to high-fat diet-induced metabolic disease, through enhanced tricarboxylic acid cycling and mitochondrial electron transport [45]. In human aortic endothelial cells, fish oil omega-3 polyunsaturated fatty acids reduce DNA damage due to oxidative stress, and enhance transcription of Txnrd1 [46].

Dietary caloric restriction and exercise are two lifestyle interventions that have robust benefits on life-span and health-span. Levels of Txnrd2 protein are reduced in the skeletal muscle and heart of aged relative to young rats, with this effect being corrected by caloric restriction [47]. The microRNA miR-23 inhibits myogenesis in the mouse C2C12 cell-line by repressing transcription of Txnrd1 [48]. In male rats, aerobic exercise prevents an age-dependent decrease in skeletal muscle Txnrd1 and Txnrd2, thereby decreasing apoptotic cell-death and preserving function [49].

Although Txnrd activity is increased brain tissues from patients with Alzheimer's Disease (AD) relative to controls, this does not provide protection against cell-death, owing to reduced levels of thioredoxins [50]. A study of the ontology of Txnrd2 levels in rat and mouse hippocampi revealed distinct patterns: hippocampal Txnrd2 is highest in young mice and declines with age; whereas the converse is observed in rats [51]. Consequently, choice of experimental model is an important consideration in investigating the biological effects of Se and selenoproteins.

In vitro, glutathione reductase activity in human cataractous lens tissue can be restored using the Txnrd/thioredoxin system, indicating that decreased activity of this antioxidant pairing contributes to cataract formation with aging [52]. In other cases, Txnrds exert adverse effects in aging. Txnrd1 contributes to a senescence-associated secretory phenotype in IMR90 embryonic human lung fibroblasts, via a mechanism that is independent of its enzymatic activity, requiring direct protein-protein interaction with the cyclic GMP-AMP synthase [53].

3.2. Glutathione peroxidases (GPX1, GPX2, GPX3, GPX4, GPX6)

In humans, glutathione peroxidases (GPX) consist of a family of eight enzymes which convert hydrogen peroxide or organic peroxides to either water or the corresponding alcohol, usually using glutathione as a reducing agent. Of these enzymes, five are selenoproteins and the remaining three employ cysteine as their catalytic centre [54]. As major antioxidants, GPXs have key roles in aging and longevity. In the nematode, *C.elegans*, deletion of all four GPX homologues decreases life-span [55].

3.2.1. GPX1

GPX1 is found in the cytoplasm and mitochondria of most cell types. The levels and activity of GPX1 protein are decreased in endothelial progenitor cells from old patients (average age 72 years) compared with those from young humans (average age 24 years) [56]. Compared with young animals (2 or 6 months old), in old mice (12 month old) GPX1 knockout results in an increase in the S-glutathionylation and phosphorylation (both protein kinase C- and tyrosine kinase dependent) of endothelial nitric oxide (NO) synthase. This decreases production of the vasodilator NO, contributing to vascular dysfunction [57]. Hyperglycaemia and type 2 diabetes are age-related disorders. Culture of human umbilical vein endothelial cells in high glucose conditions increases carbonylation of GPX1 and decreases its abundance. However, this decrease in GPX1 protein is compensated for by an increase in its enzymatic activity [58]. Aged mice develop heart failure with preserved ejection fraction, which can be ameliorated by long-term dietary supplementation with the n3 fatty acid, α-linoleic acid. This dietary regime also increases transcription of GPX1 within the aortas of old mice [59]. Conversely, whole blood GPX1 transcription is positively correlated with both hypertension and frailty, potentially by increasing inflammatory and immune responses mediated by mononuclear phagocytes [60].

RNA sequencing of lymphoblastoid cells from middle-aged compared with centenarian women revealed age-related decreases in transcription of three selenoprotein genes, SELENOH, SELENOW and GPX1 [61]. In mice, GPX1 knockout accelerates age-dependent formation of optical aberrations and cataracts in the lens [62]. Overexpression of GPX1 in transgenic mice is protective against age-related proteome remodelling and pathology in the kidney, in a manner which is independent of the anti-aging hormone klotho and of the stress-response related transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) [63]. Within the auditory system, spiral ganglion neurons from GPX1 knockout mice are more adversely affected by the reactive nitrogen species, peroxynitrate, than wild-type controls. Protection by GPX1 is mediated by inhibition of the nuclear factor kappa B (NF-κB) pathway [64]. Extracts from the berries of the plant *Cleistocalyx nervosum* var. *paniala* protect the hippocampal HT22 cell-line from glutamate-induced cell-death. This protection involves increased GPX1 transcription, through the sirtuin-1/Nrf2 pathway [65].

3.2.2. GPX2

GPX2 is highly expressed in gastrointestinal tract [54]. In a rat model of premature cognitive aging, GPX2 expression is decreased relative to that in normal animals in both hippocampal neurons and cortical astrocytes [66].

3.2.3. GPX3

GPX3 is found in the extracellular fluid and can utilise a wide range of thiols as a source of reducing power [54]. In mouse skeletal muscle, estrogen increases the transcription of GPX3 in a fibre-type dependent manner, suggesting a role in the postmenopausal reduction of antioxidants in aging of this tissue [67]. The tendinopathy caused by aging or fluoroquinolone antibiotics can be reversed by the corticosteroid, dexamethasone. In a rat model, dexamethasone increases GPX3 expression and viral overexpression of GPX3 reverses tendinopathy, by decreasing oxidative stress [68]. In a prospective cohort study of atrial fibrillation patients, decreased GPX3 levels are a robust predictor of risk and GPX3 declines progressively with age [69]. Another study reported decreases in circulating GPX3 protein are associated with disorders of carbohydrate metabolism and with aging [70].

3.2.4. GPX4

GPX4 is found in most cell-types, within the cytoplasm, nucleus and mitochondria. It is particularly effective at reducing lipid peroxides and as a result, is protective against an iron-dependent form of cell death called ferroptosis, *for review see* [71]. Transgenic mice lacking GPX4 die *in utero*, during mid-gestation [72]. By contrast heterozygous GPX4 knockout mice display increased lifespan, with decreased susceptibility to age-related pathologies, related to increased sensitivity to apoptosis [73].

GPX4 has effects in multiple cell-types and organ systems. In chondrocytes (cartilage-producing cells), mechanical stress causes Ca^{2+} influx through Piezo 1 channels. In a mouse model of osteoarthritis, inhibition of Piezo 1 increases GPX4 transcription, and reduces ferroptosis and inflammation [74]. In osteoarthritic mice, P21 decreases ferroptosis by preventing ubiquitination and proteasomal degradation of GPX4 [75].

In aged mice, overexpression of GPX4 decreases sarcopenia (age-related loss of skeletal

muscle function) [76]. In rats, life-long aerobic training increases skeletal muscle GPX4 in a fibre-type dependent manner, through the Keap1/Nrf2 pathway. The protective effects of this training against sarcopenia are reversed on detraining [77]. Impairment of skeletal muscle excitation-contraction coupling in superoxide dismutase-1 knockout mice is restored by GPX4 overexpression [78]. In a mouse denervation model of sarcopenia, scavenging of lipid hydroperoxides using the pharmacological reagent CMD-35647 is protective against loss of contractile function [79]. In mouse quadriceps muscle, aging decreases GPX4 protein levels, whereas forced exercise increases its abundance, to a greater extent in aged female than in aged male animals [80].

Tendon stem cell senescence contributes to age-related deficits in tendon repair. In a rotator cuff tear rat model, platelet derived exosomes alleviate senescence, through activation of the AMPK/Nrf2/GPX4 pathway [81]. Curcumin decreases iron-overload induced inhibition of osteogenesis in bone marrow-derived stem cells, again by activating the Nrf2/GPX2 pathway [82].

Se-based interventions, mediated through GPX4, are protective against skin aging. Gelatin methacryloyl hydrogels incorporating SeM decrease epidermal skin stem cell senescence and aid skin healing by upregulating GPX4, preventing ferroptosis [83]. Hesperidin is a flavanone from the peel of citrous fruit, which ameliorates photoaging of cultured skin cells and organoids. These effects are mediated by stabilisation of the chaperone 70 kDa heat-shock protein 1L (HSPA1L), which enhances GPX4 protein abundance, thereby suppressing ferroptosis [84]. Sauchinone is a phenolic lignan from *Saururus chinensis* (Asian Lizard's Tail plant) which decreases UVB-induced photoaging by activating the Keap1/Nrf2/GPX4 pathway [85].

Folic acid suppresses aging-dependent neuronal ferroptosis in rats, by upregulating the expression of both the cystine/glutamate transporter SLC7A11 and of GPX4 [86]. As described elsewhere in this Special Issue, oxysterols are cholesterol oxidation products that can be consumed in the diet, or can be generated enzymatically or chemically, and are associated with cytotoxicity in age-related diseases [87]. In a microglial cell-line the oxysterol 27-hydroxycholesterol (27-OHC) downregulates GPX4, an effect which is ameliorated by the iron chelator, deferoxamine. In patients with AD (an age-related disorder), plasma 27-OHC levels are inversely associated with cognitive function [88]. Although it

promotes longevity and reduces markers of aging, caloric restriction negatively impacts the function of the germinative epithelium of testes in aged rats, in part by decreasing GPX4 levels [89].

3.2.5. GPX6

GPX6 displays a restricted tissue expression pattern, being detectable during embryogenesis in the olfactory epithelium and in the nervous system [54]. It is upregulated in the mouse cochlea during age-related hearing loss (presbycusis) [90]. In a mouse model of Huntington's disease, overexpression of GPX6 is neuroprotective [91]. Polymorphisms in the GPX6 gene are associated with risk of oesteoporotic bone fracture (Usategui-Martín et al., 2022). In a prospective epigenetic study, differences in methylation of the GPX6 gene are associated with the risk of developing type 2 diabetes [92].

3.3. Thyroxine deiodinases (Dio1, Dio2, Dio3)

Thyroxine deiodinases are selenoenzymes that convert the prohormone thyroxine (T4) into either active thyroid hormone (T3, by Dio1 and Dio2), or the inactive form, reverse T3 (by Doi3 and to a lesser extent, by Doi1). In a forced exercise model of osteoarthritis, Dio2(-/-) mice show decreased cartilage damage [93]. A common polymorphism in the *DIO2* gene (Thr92Ala in the Dio2 protein) is associated with increased risk of AD dementia [94]. Both the Dio2 Thr92Ala polymorphism and aging are associated with decreased sensitivity of the pituitary gland to thyroid hormone [95]. Transcription of DIO2 and DIO3 are increased in the skeletal muscle of aged compared with young mice [96]. *In vivo* replicative senescence of human adult adipose-derived stem cells is associated with deregulation of the DLK1-DIO3 locus (García-López et al., 2018). In mouse liver, aging decreases Dio1 and increased Dio3, decreasing thyroid hormone T3 levels. These aging effects on thyroid hormone signalling are synergistic with a Western-style diet in promoting liver steatosis [97].

3.4. Methionine sulfoxide reductase B1 (MSRB1)

MSR enzymes reduce methionine sulfoxide to methionine, in a Txnrd-dependent manner, *see Section 3.1*. In humans, MSRB1 is the only member of this four gene family (MSRA,

MRSB1-3) that is a selenoprotein. It is expressed at high levels in the gastrointestinal tract, the liver, kidneys and immune system [98]. In mouse liver, MSRB1 is positively regulated by dietary Se intake and declines with age [99]. Zinc-deficiency is associated with aging. In human lens epithelial cells, zinc increases the abundance of MSRB1 and is protective against oxidative stress [100].

3.5. Selenophosphate synthetase 2 (SPHS2)

SPHS2 is a selenoenzyme converts selenide and ATP into monoselenophosphate, the Se donor for formation of Sec and subsequently, of all selenoproteins. During dietary Se deficiency, there is a hierarchy of selenoprotein synthesis, with the mRNAs of non-essential selenoproteins being degraded by nonsense-mediated decay (NMD). One exception to this is SPHS2, which is less susceptible to NMD [101]. A key cause of intervertebral disc degeneration is nucleus pulposus cell senescence. In a rat model, age-related disc degeneration is reduced by overexpression of SPHS2 and by inhibition of the Hippo-Yap/Taz transcriptional pathway [102].

3.6. SELENOF

SELENOF (previously named 15 kDa selenoprotein, or Sep15) is resident in the lumen of the ER, playing roles in protein folding and quality control [103]. A polymorphism in *SELENOF* is associated with higher verbal memory scores in elderly adults [104]. In the ovaries of aging mice, levels of SELENOF and follicle viability are enhanced by increased dietary Se intake [105].

3.7. SELENOH

SELENOH is a Trxnd-like selenoprotein located in the cell nucleus [106]. In the human fibroblast MRC-5 cell-line, knockdown experiments demonstrated a role for SELENOH in preventing cellular senescence, by protecting against DNA damage and redox stress [107]. SELENOH is one of three selenoproteins which shows an age-dependent decline in transcription in lymphoblastoid cell-lines derived from middle-aged and centenarian women [61].

3.8. SELENOI

SELENOI is an ER-resident CDP-ethanolamine phosphophatidyltransferase, involved in the synthesis of phosphatidylethanolamine, a major membrane phospholipid. Transgenic mice lacking SELENOI die early during embryogenesis [108]. Age upregulates the transcription of SELENOI in the kidneys of female mice, but the physiological consequences of this have not been determined [31].

3.9. SELENOK

SELENOK is an ER-membrane selenoprotein which regulates protein folding, Ca^{2+} signalling and the ER-stress response [109]. Dietary Se supplementation increases transcription and protein abundance of SELENOK in ovaries of aged mice, and also enhances *in vitro* development of blastocysts from MII oocytes [110]. In mice, proteosomal degradation of both SELENOK and its interacting partner SELENOS are required for peroxisome proliferator-activated receptor-γ (PPARγ)-dependent stimulation of adipogenesis (*Section 3.14*.) [111]. An Se-containing nanoparticle food supplement extends the lifespan of aged mice, in part by increasing SELENOK levels and maintaining Ca^{2+} homeostasis [30].

3.10. SELENOM

SELENOM is located in the ER lumen and is likely to function as an oxidoreductase, given that it possesses a consensus CxxU motif [112]. As described for SELENOK (*Section 3.9*), dietary Se supplementation enhances ovary SELENOM levels and oocyte to blastocyst development in aged mice [110].

3.11. SELENON

SELENON (formerly called SEPN1) is a type II transmembrane glycoprotein residing in the ER membrane. It was the first selenoprotein shown to be directly involved in inherited human disease, specifically early-onset congenital neuromuscular disorders termed SELENON-related myopathies [113]. These are characterised by axial muscle weakness, spinal rigidity, severe scoliosis, respiratory insufficiency, and histological minicores: focal regions of sarcomeric disarray and mitochondrial depletion within muscle fibres [114]. SELENON is a

regulator of Ca^{2+} fluxes across the ER and sarcoplasmic reticulum (SR). It interacts directly with ryanodine receptor (RyR) Ca^{2+} release channels, controlling the redox-dependency of their gating (opening and closing) [115]. It also interacts with the type 2b SR/ER Ca^{2+} ATPase (SERCA2b) pump, reducing inhibitory disulphide bonds in luminal loop 4, thereby enhancing Ca^{2+} accumulation into the SR/ER [116].

Loss of SELENON disrupts this Ca^{2+}-redox axis, with direct aging-related consequences in skeletal muscle. In SELENON-deficient myotubes, resting cytosolic Ca^{2+} levels are elevated and SR Ca^{2+} stores are depleted, leading to chronic ER stress and activation of the maladaptive C/EBP homologous protein (CHOP) branch of the unfolded protein response (UPR) [117]. SELENON knockout (-/-) mice do not display an overt phenotype, unless challenged by prolonged forced swimming or other stressors [118]. SELENON (-/-) mice fed a high-fat diet developed pronounced ER stress in skeletal muscle, with impaired insulin-mediated glucose uptake and compromised force production [119]. Deficits in SELENON function also contribute to depletion of skeletal muscle satellite cells (SC), stem cells which play key roles in regeneration following injury or aging [120]. Sarcopenia is closely linked to declining SC number and regenerative capacity [121]. In skeletal muscle of SELENON (-/-) mice, cardiotoxin-induced injury causes dramatic depletion of SCs that completely prevents subsequent regeneration. Exhaustion of SC populations is also observed in muscle biopsies from patients with SELENON-related myopathy [122]. Average daily voluntary running activity, peak muscle twitch and tetanic force, and SR Ca^{2+} release all decreased in old (22 month) relative to young (4 month) wildtype mice. These sarcopenic alterations were associated with decreased abundance of skeletal muscle SELENON and RyR1, and increased proteolysis of RyR1. Both life-long exercise training and dietary Se supplementation could prevent these reductions in force production, SR Ca^{2+} release and SELENON protein levels [123], highlighting approaches to reduce sarcopenia during aging. Lipidomic profiling of diaphragm tissue from young, old and SELENON (-/-) revealed differences in abundance of approximately 10% of phospholipids between wildtype mice and those lacking SELENON, with these changes also being distinct between male and female animals [124].

3.12. SELENOO

SELENOO is located in mitochondria and displays a broad tissue distribution. Since it contains a CxxU motif, it probably an oxidoreductase, and its levels are maintained under Se-

deficient conditions [125]. It also possesses a pseudokinase domain, which catalyses the AMPylation (addition of AMP derived from ATP to S, T or Y residues) of target proteins involved in responses to oxidative stress [126]. Knockdown of SELENOO suppresses differentiation of a chondrocyte cell-line, suggesting a role for this selenoprotein in osteoarthropathy, an age-related disorder [127].

3.13. SELENOP

Human SELENOP (previously known as SEPP1 or SelP) is unique among the 25 selenoproteins, in that in contains up to 10 U residues, whereas all other members containing just one [5]. SELENOP is predominantly synthesised in the liver and secreted into plasma, where it serves as the principal Se transport protein, delivering this essential trace element to peripheral tissues including the brain, testes, and kidneys. A single U residue in the N-terminus of the protein participates in lipid hydroperoxidase activity, with the remaining U residues being involved in Se transport [128].

SELENOP expression and function can be influenced by dietary factors, in addition to Se. Copper ions increase both intracellular Se and SELENOP accumulation in hepatocytes, thereby decreasing systemic Se transport. Wilson's disease is due to mutations in the transporter ATP7B, which leads to intracellular accumulation of copper and decreased plasma SELENOP abundance [129]. Despite their anti-aging potential, components of multi-vitamin supplements can have deleterious effects. In particular, vitamin A suppresses hepatic SELENOP synthesis and secretion [130]. Resveratrol is a plant stilbenoid, suggested to increase lifespan. However, a screen of a compound library of FDA-approved drugs in HepG2 hepatocytes revealed resveratrol as a potent inhibitor of extracellular SELENOP protein abundance [131].

In the ESTHER cohort, a German population-based study of 7,186 adults aged 50–74 years followed for 17.3 years, demonstrated that serum SELENOP concentration was inversely associated with all-cause mortality with an L-shaped relationship (plateau above 4.1 mg/L), and significantly elevated mortality risk at concentrations below approximately 4.1 mg/L. Participants in the lowest SELENOP tertile had a 35% increased risk of all-cause mortality compared with those in the highest tertile, with increased risks extending to cardiovascular (Hazard Ratio (HR) 1.24), cancer (HR 1.31), respiratory (HR 2.06), and gastrointestinal mortality (HR 2.04) [132]

These associations were stronger in men than women, consistent with known sex differences in Se metabolism. The Berlin Aging Study II (BASE-II) demonstrated that low serum SELENOP levels are associated with accelerated biological aging, as measured by DNA methylation-based clocks [26]. These findings were robust after adjustment for age, sex, body mass index, smoking, and genetic ancestry, supporting the notion that adequate SELENOP status is protective against biological aging. The British 1946 Birth Cohort (Medical Research Council National Survey of Health and Development) tracked 1,803 individuals from birth to late life. A pre-print (non-peer reviewed) publication based on this study identified SELENOP as a plasma protein strongly predictive of longevity. Low circulating SELENOP levels tracked with increased mortality risk during follow-up [133].

SELENOP delivers Se to the brain via interaction with apolipoprotein E receptor-2 (ApoER2) at the blood–brain barrier. Knockout of either SELENOP or ApoER2 in mice reduces brain Se content from approximately 120 ng/g to 50 ng/g, and under conditions of mild dietary Se deficiency, results in severe neurodegeneration and death [134]. SELENOP immunohistochemically co-localises with amyloid-β plaques and neurofibrillary tangles in AD brain tissue [135] and increased levels of this protein have been detected in the choroid plexus and cerebrospinal fluid of AD patients, possibly reflecting a compensatory responses to oxidative stress [136]. The histidine-rich domain of SELENOP suppresses metal-induced aggregation and neurotoxicity of both amyloid-β and tau protein *in vitro*, and when delivered to the hippocampal CA3 region of triple-transgenic AD mice using a viral vector, it ameliorated neuropathology and cognitive deficits through modulation of TrkB signalling and zinc homeostasis [137]. Epidemiological evidence further supports this neuroprotective role: low Se status in older adults is associated with faster cognitive decline, with three epidemiological studies indicating beneficial effects of adequate Se and SELENOP levels on cognitive function [138].

Paradoxically, SELENOP functions as a hepatokine with adverse metabolic effects when present in excess. Hepatic overexpression of SELENOP causes insulin resistance in the liver and skeletal muscle, and circulating SELENOP levels are elevated in patients with type 2 diabetes [139]. Excess SELENOP impairs pancreatic β-cell insulin secretion [140]; inhibits angiogenesis in vascular endothelial cells by causing resistance to vascular endothelial growth factor [141]; promotes exercise resistance in skeletal muscle by decreasing beneficial levels of ROS [142]; and exacerbates myocardial ischaemia–reperfusion injury [143]. In a

prospective study of healthy Japanese subjects, baseline SELENOP concentrations predicted the onset of hyperglycaemia at four-year follow-up, implicating excess SELENOP in the age-related deterioration of glucose homeostasis. This relationship is independent of other factors, including serum Se concentration [144].

This apparently paradoxical relationship between SELENOP levels and effects on health likely reflects a U-shaped dependency that mirrors the broader effects of Se on longevity. At physiologically optimal concentrations, SELENOP ensures adequate Se delivery to critical organs and provides antioxidant protection. However, supraphysiological SELENOP levels may create a state of reductive stress by eliminating the physiological ROS bursts required for intracellular signal transduction. For example, insulin signalling depends on transient inactivation of protein tyrosine phosphatases (PTPs) by hydrogen peroxide at the cell membrane; excessive selenoprotein-mediated ROS scavenging preserves PTP activity and thereby attenuates the insulin signal [145]. This hormetic dose-response is consistent with observations that Se-deficient mice engage nutrient-sensing pathways associated with pro-longevity mechanisms, and that SELENOP-deficient mice exhibit enhanced endurance after exercise training through increased AMP-dependent protein kinase activity [146].

3.14. SELENOS

SELENOS is a membrane protein that regulates the ER-associated degradation pathway in cell protein quality control. This is facilitated through formation of multi-protein complexes, including interactions with SELENOK (*Section 3.9.*) [147]. A substantial body of literature supports roles for SELENOS in metabolism and energy storage, and age-related disorders of these processes. In mice, either the corticosteroid analogue dexamethasone or stimulation of PPARγ, promote adipogenesis via a mechanism that requires SELENOS degradation by the ubiquitin-proteasome system [111, 148]. In a mouse preadipocyte cell-line, sodium selenate suppresses differentiation by inducing SELENOS, decreasing expression of the adipogenic transcription factors X-box binding protein-1 and CCAAT-enhancer binding protein-α [149]. It is likely that such effects on adipogenesis will impact the risk of development of other metabolic disorders. A genotyping study of a Chinese population demonstrated an association between polymorphisms of the SELENOS gene and type 2 diabetes [150]. Analyses of the blood proteomes of 9775 Europeans found that risk of myocardial infarction correlates with circulating levels of SELENOS protein [151].

Alterations in SELENOS function underlie cardiovascular diseases. Polymorphisms in the SELENOS gene are associated with coronary heart disease and stroke in Finnish [152], European American [153] and Chinese [154] populations. The SELENOS protein is highly expressed in blood vessels and has an anti-apoptotic role in smooth muscle cells [155]. It inhibits inflammation induced calcification of vascular smooth muscle, a key step in the etiology of atherosclerosis [156]. SELENOS also prevents high-glucose induced apoptosis in vascular endothelial cells, through activation of the protein kinase C/Janus kinase/Bcl-2 pathway [157]. It also protects the vascular endothelium from damage due to high glucose or oxidised low-density lipoprotein by stimulating Akt/mTOR and reducing autophagy [158].

Impaired SELENOS function might play a role in sarcopenia. Knockout of SELENOS in mice reduces force production in fast-twitch, but not slow-twitch, muscles [159]. Reduced exercise performance in SELENOS (-/-) or (-/+) mice is not due to increased inflammation or stress, but is postulated to involve effects on skeletal muscle microvasculature [160].

SELENOS has multiple roles in the skeleton. It has an epistatic relationship with interleukin-1, in determining susceptibility to rheumatoid arthritis [161]. It stimulates osteogenic differentiation of bone marrow mesenchymal stem cells [162]. The proliferative zone of chondrocytes in the epiphyses of bones is reduced in depth in SELENOS (-/-), indicating a role in cartilage growth [163]. Kashin-Beck disease is an osteochondropathy linked to chondrocyte damage on oxidative stress, due to dietary Se deficiency and decreased levels of protective selenoproteins. In SELENOS (-/-) mice, cartilage thickness and chondrocyte differentiation are reduced, through activation of Wnt/β-catenin signalling. SELENOS expression increases during osteogenesis. Decreased levels of SELENOS promote expression of the transcription factor Sp7, upregulating genes involved in chondrocyte differentiation [162]. These observations imply tight regulation of the effects of SELENOS on osteogenesis.

In a neuroblastoma cell-line model of AD, knockdown of SELENOS increases ER stress-induced phosphorylation of tau [164]. In a rat model of Parkinson's disease, intraperitoneal injection of sodium selenite enhances expression of SELENOS in the substantia nigra, reducing accumulation of α-synuclein and decreasing motor deficits [165].

3.15. SELENOT

SELENOT (SelT) is an ER-localised thioredoxin-like protein [166] whose transcription is stimulated by the trophic neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP). SELENOT is expressed at high levels in most embryonic tissues and its abundance decreases during development in most cell types. In children and adults, SELENOT is induced during growth and regeneration of metabolic, nervous and endocrine tissues [167]. SELENOT overexpression increases cytoplasmic Ca^{2+} concentration and enhances PACAP-stimulation of growth hormone secretion by the PC-12 phaeochromocytoma cell-line [168]. It is present at high levels in pancreatic β- and δ-cells, with knockout mice displaying impaired glucose tolerance [169].

In a rat model of ischaemia-reperfusion injury, a SELENOT-derived, U-containing peptide PSELT (FQICVSUGYR) protects the myocardium against ER-stress, apoptosis, oxidative stress [170, 171]. PSELT also protects the rat H9c2 cardiomyocytes against palmitate-induced lipotoxicity, preserving mitochondrial function and cellular metabolic state [172]. Both the scavenger receptor CD36 and SELENOT are upregulated in senescent cardiomyocytes. PSELT inhibits senescence-associated upregulation of CD36, and immunoprecipitation assays demonstrate physical interaction between this receptor and SELENOT [173]. Conversely, in chronic obstructive pulmonary disease, decreased levels of the microRNA miR-126 with consequent increased levels of its target SELENOT, are associated with the severity of impairment of airflow [174].

In mouse models of Parkinson's Disease, the oxidoreductase activity of SELENOT is protective against loss of dopaminergic neurons [175]. Furthermore. mice with a nerve-specific knockout of SELENOT display neurodevelopmental abnormalities and hyperactivity [176].

3.16. SELENOV

SELENOV (SelV) is a small, cytosolic selenoprotein that possesses a thioredoxin fold and is highly expressed in the testes [166]. In mice, SELENOV knockout decreases protection from ER and oxidative stress [177]. SELENOV knockout also increases adiposity by upregulating genes involved in lipogenesis and downregulating those involved in lipolysis. Loss of SELENOV decreases oxygen consumption and metabolic rate. SELENOV protein interacts

with O-GlcNAc transferase, with knockout animals showing decreased O-GlcNAcylation in adipose tissues [178].

3.17. SELENOW

SELENOW (SelW, SepW1) is a cytosolic selenoprotein which contains a thioredoxin domain and is present at greatest abundance in striated muscles [166]. In the mouse C2C12 myogenic cell-line, SELENOW transcription increases during differentiation, through a mechanism involving the transcription factor MyoD [179]. In chicken muscle and myoblasts, either Se deficiency or SELENOW downregulation alters the expression of various Ca^{2+} channels and transporters, and increases Ca^{2+} leak from the SR [180]. SELENOW knockout does not alter oxidative stress or insulin sensitivity in skeletal muscle from high-fat fed obese mice, suggesting that its key role is not in anti-oxidant defence [181]. SELENOW levels are increased with aging and during dexamethasone-induced skeletal muscle atrophy. SELENOW knockout exacerbated skeletal muscle loss in both mouse models, through decreased protein synthesis and increased ubiquitin-proteasomal degradation [182].

SELENOW also plays roles in aging in other systems. In a mouse model of AD, SELENOW promotes tau degradation through the ubiquitin-proteasome system [183]. Osteoclasts are cells which degrade bone and whose differentiation and activation are inhibited by receptor activator of nuclear factor-κB ligand (RANKL). SELENOW expression in osteoclasts is downregulated by RANKL. In transgenic mice, overexpression of RANKL promotes osteoporosis, whereas SELENOW knockout leads to high bone density [184]. In RWPE-1 prostate epithelial cells, silencing of SELENOW delays the cell cycle, through a mechanism involving p53 and p21, but not anti-oxidant effects. This observation potentially explains the link between adequate dietary Se intake and decreased risk of developing prostate cancer [185].

4. Selenium-binding proteins and longevity

Se-binding proteins-1 and -2 (SELENBP1 and SELENBP2) are two closely related proteins [186], which contain Se, not in the form of U, but directly and covalently bound to Cys57 [187]. SELENBP1 interacts with GPX1 [188] and displays copper-dependent thiol oxidase activity [189]. In the nematode worm *Caenorhabditis elegans*, an orthologue of SELENBP1

called SEMI-1 (or Y37A1B.5) decreases lifespan and protection against oxidative stress [190]; but increases survival during exposure to toxic selenite concentrations and promotes thermotaxis from colder towards more favourable temperatures [191].

Decreased expression of SELENBP1 has been reported in oesophageal adenocarcinoma [192], gastric carcinoma [193], hepatocarcinoma [194], lung squamous cell cancer [195] and cholangiocarcinoma [196]. In prostate cancer, there is an inverse association between glutathione peroxidase activity and SELENBP1 expression levels [197]. By its enzymatic production of hydrogen peroxide and hydrogen sulphide, overexpression of SELENBP1 in prostate cancer cells decreases oxidative phosphorylation and anchorage-independent growth, through inhibition of AMP-dependent kinase [198]. Cross-species proteomic analyses reveals SELENBP1 as a key marker of the invasiveness of malignant mesothelioma [199].

In renal tubule epithelial cells, SELENBP1 is protective against ischaemia-reperfusion injury, by increasing the expression of GPX4 and inhibition of ferroptosis [200]. SELENBP1 is also protective in a fructose-induced model of metabolic dysfunction associated steatotic liver disease [201].

5. Perspectives

This review reiterates the consensus that there is a U-shaped relationship between body Se status and adverse health effects: too much or too little is damaging. One mechanistic explanation for this is that insufficient Se results in depletion of essential selenoproteins, whereas excess is non-specifically incorporated into proteins and other biomolecules, negatively impacting their function [2, 5]. However, it is likely that additional factors contribute to the biphasic relationship between Se and health. Like Se, ROS have biphasic effects on aging: low amounts are essential for physiological processes to operate, whereas high concentrations are toxic. Inverted U-shaped relationships between longevity and exposure to different concentrations of three chemically distinct anti-oxidants (N-acetylcysteine, vitamin C and resveratrol) have been demonstrated in *C.elegans* [202]. Given that many selenoproteins are anti-oxidants, it is likely that they can exert effects on aging by modifying ROS levels, *Fig. 3*. Similar reasoning applies to interactions between selenoproteins and intracellular Ca^{2+} concentrations. Since both high and low levels of

cytoplasmic Ca^{2+} are cytotoxic [203], and several selenoproteins regulate Ca^{2+} transport mechanisms in a redox-dependent manner [204], links between Se, Ca^{2+} and cell-death are likely.

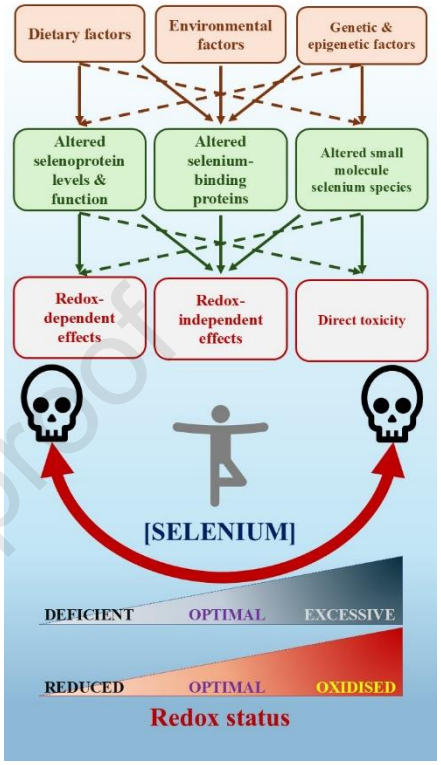

Figure 3. Multiple factors influence Se status and aging. Dietary factors include not only Se intake, but also the consumption of other dietary components that can influence the effects of Se: these include folic acid, resveratrol, vitamin A, a-linoleic acid, copper and zinc. Environmental, social and geopolitical factors can influence Se intake and action. This includes effects of globalisation of food supply (from regions differing in geological Se content) and of fertilisers that contain components that alter quantity and the uptake of Se (both phosphorus and sulphur inhibit uptake). Several examples of the direct effects of polymorphisms in selenoprotein genes on longevity are presented in the current review.

As exemplified by the inhibitory effect of mutations in the ATP7B copper ion transporter on SELENOP secretion, complex relationships can alter selenoprotein function. These factors all contribute to altered function and levels of small molecule Se-containing species, SELENBPs and selenoproteins. This in turn impacts aging through redox-dependent and independent mechanisms, and by direct toxicity. These complex interactions underlie the U-shaped effect of Se on aging, which is partially mirrored by the biphasic effect of redox status on aging.

Effects of Se status on longevity are also be context-dependent, varying between tissue-types, environmental and nutritional conditions, and the presence of different selenoproteins, *Fig. 3*. For example, heterozygous GPX4 knockout mice show extended lifespan due to increased sensitivity of cancer cells to apoptosis [73], whereas GPX4 over-expression is protective against sarcopenia [76] . Distinct selenoproteins can have opposing effects on the same outcome: for example elevated SELENOP levels promote insulin resistance [145], whereas SELENOT knockout impairs insulin secretion by pancreatic β-cells [169]. Effects of Se status can depend on environmental conditions: for example, a SELENBP1 homologue in *C.elegans* reduces lifespan, but is protective against selenite toxicity [205] . Another layer of

complexity is that selenoproteins and SELENBPs often have Se-independent functions. For example, Txnrd1 drives a senescence-associated secretory phenotype in a lung fibroblast cell-line, via direct interaction with cyclic GMP-AMP synthase, rather than through its redox activity [53].

As suggested by other authors, any life-span and health-span promoting effects of dietary Se supplementation must be carefully balanced against adverse effects caused by excessive intake. For each individual, this will require careful monitoring and titration of Se status. In most, though not all cases, serum SELENOP provides a suitable biomarker for this purpose [12]. In addition, engineered Se-supplements might provide a means of ensuring optimal Se delivery and action: these include Se-containing nanoparticles [123], small molecule Se-derivatives, such as diphenyl diselenide [206], and selenopeptides [173].

Declaration of generative use of AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, WGP used ChatGTP to develop outline versions of Sections 3.11 and 3.13. The authors reviewed and edited the output as needed and take full responsibility for the content of the published article.

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Declaration of interest

None