



Review

Role of Selenoproteins in Redox Regulation of Signaling and the Antioxidant System: A Review

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Abstract: Selenium is a vital trace element present as selenocysteine (Sec) in proteins that are, thus, known as selenoproteins. Humans have 25 selenoproteins, most of which are functionally characterized as oxidoreductases, where the Sec residue plays a catalytic role in redox regulation and antioxidant activity. Glutathione peroxidase plays a pivotal role in scavenging and inactivating hydrogen and lipid peroxides, whereas thioredoxin reductase reduces oxidized thioredoxins as well as non-disulfide substrates, such as lipid hydroperoxides and hydrogen peroxide. Selenoprotein R protects the cell against oxidative damage by reducing methionine-R-sulfoxide back to methionine. Selenoprotein O regulates redox homeostasis with catalytic activity of protein AMPylation. Moreover, endoplasmic reticulum (ER) membrane selenoproteins (SelI, K, N, S, and Sel15) are involved in ER membrane stress regulation. Selenoproteins containing the CXXU motif (SelH, M, T, V, and W) are putative oxidoreductases that participate in various cellular processes depending on redox regulation. Herein, we review the recent studies on the role of selenoproteins in redox regulation and their physiological functions in humans, as well as their role in various diseases.

Keywords: selenoprotein; oxidative stress; redox signaling; redox homeostasis; antioxidant

1. Introduction

Most reactive oxygen species (ROS) are generated as by-products of cellular redox processes, including mitochondrial respiration and are known to be harmful to human health when their cellular levels exceed the physiologically acceptable level. However, moderate ROS concentrations play a crucial role in regulating signal transduction and cellular functions, such as proliferation and differentiation, via protein oxidation [1]. Nevertheless, ROS are toxic and can damage various biological molecules, such as proteins, lipids, and nucleic acids. Thus, the imbalance between ROS production and antioxidant capability of the organism is often associated with the development of various chronic pathologies, including cancer, cardiovascular diseases (CVDs), diabetes, neurological disorders, ischemia/reperfusion injury, age-related alterations, dysfunctions related to immune defense and inflammatory responses, and other diseases [1–11].

Antioxidant enzymes such as superoxide dismutase, catalase, and other redox enzymes, including selenoproteins, and low weight antioxidant molecules such as carotenoids, ascorbate, vitamin E, α -lipoic acid, and glutathione (GSH) are essential for maintaining the “steady state” concentration of ROS, which helps to regulate the redox balance and maintain cellular homeostasis. Most functionally characterized selenoproteins have catalytic activities owing to their selenocysteine (Sec) residue and act to neutralize and remove ROS. Therefore, they protect against oxidative stress. Selenium was considered a toxic element for humans and other mammals but is now considered an important trace element, as the benefits of dietary selenium supplementation have been identified [12]. Selenium is widely distributed in various tissues and organs after absorption and performs important biological functions through regulating the synthesis of selenoproteins and being incorporated in selenoproteins [13]. Furthermore, some selenoproteins are also involved in regulating the activation of signaling pathways and cellular functions. In this review, we provide a brief overview of the various functions of selenoproteins and their roles in redox regulation and physiological functions.

2. Selenocysteine in Selenoproteins

Sulfur and selenium have similar physicochemical properties as both are members of the chalcogen group and undergo thiol-disulfide exchange reactions in the form of cysteine (Cys) or Sec, respectively [14]. However, Sec is more reactive than Cys under physiological conditions as it has a lower pKa (~5.2) than Cys (~8.0); thus, it can exist as a nucleophile without electrostatic interactions and, therefore, has enhanced catalytic efficiency. The Sec residue in most selenoproteins is located in the catalytic region, where it catalyzes the reduction of oxidized Cys residues, such as disulfide and sulfenic acid [15]. Studies have shown that removal of the Sec residues by oxidative selenium elimination, limited proteolysis [16], as well as specific alkylation of the Sec residues at pH 6.5 [16,17], leads to catalytic activity decrease. Moreover, the substitution of Sec with Cys also results in a marked reduction in catalytic efficiency [18–20].

Selenoproteins exist in three kingdoms of life, whereas yeast, fungi, and higher plants lack selenoproteins. Instead, they have alternative cysteine-containing homologs [21]. Sec is the 21st amino acid encoded by the in-frame UGA codon, which is usually recognized as a stop codon; therefore, it requires specialized machinery for its incorporation into proteins. This machinery comprises a selenocysteine tRNA (Sec-tRNA^{[Ser]Sec}), a secondary stem-loop structure named selenocysteine insertion sequence (SECIS), SECIS Binding Protein 2 (SBP2), and other protein factors [22,23]. However, its molecular mechanism remains unclear. For Sec-tRNA^{[Ser]Sec} synthesis, selenium can be intaken from dietary sources, including organic forms such as selenomethionine (Se-Met) and inorganic forms such as selenate and selenite [13]. To utilize selenium from Se-Mets, they are converted to Sec by the trans-selenation pathway similar to the trans-sulfuration pathway for Met. Then Sec is converted to H₂Se by Sec b-lyase [24]. In the case of selenite, it interacts with glutathione and is directly reduced to H₂Se. Both organic and inorganic selenium sources become H₂Se and is then converted to selenophosphate, which reacts with tRNA-bound serinyl residues to produce Sec-tRNA^{[Ser]Sec} [25]. In eukaryotes and archaea, SECIS is located in the 3'-untranslated region (UTR) and interacts with *trans*-acting factors [22,26]. This unique feature of SECIS elements and the in-frame UGA codon has been largely adopted for in silico selenoproteome identification in diverse organisms. This is a peculiar feature, considering that another sulfur-containing amino acid Met and Se-Met cannot be distinguished by a Met tRNA, and therefore, Se-Mets are incorporated in proteins randomly [27].

Selenoproteins are essential for survival in many organisms, including humans. For example, prostate epithelium-specific selenocysteine tRNA gene *Trsp* deletion leads to oxidative stress, early-onset intraepithelial neoplasia [28], and early embryonic death in mice [29]. Moreover, mammary gland-specific *Trsp* knockout (KO) mice showed that p53 and BRCA1 expression changed, resulting in enhancing susceptibility to cancer [30], which indicates that selenoproteins are essential for mammals. Based on Sec residue localization, selenoproteins can be divided into two groups. In the first group, which includes all thioredoxin reductases (TrxRs) and selenoprotein I (SelI), SelK, SelO,

SelR, and SelS, the Sec residue is located in the C-terminal region. The second group, which contains the rest of the selenoproteins (glutathione peroxidases, iodothyronine deiodinases, SelH, SelM, SelN, SelT, SelV, SelW, SPS2, and Sep15), is characterized by the presence of the Sec residue in the N-terminal region, as part of the redox-active thioredoxin (Trx)-like selenylsulfide/selenolthiol motif [31]. SelP has an N-terminal redox Sec and multiple C-terminal Sec residues [32]. Over half of the mammalian selenoproteins possess the Trx-like fold [33]; its common feature include a two-layer $\alpha/\beta/\alpha$ sandwich structure and a conserved CXXC motif (two Cys residues separated by two other amino acid residues). The CXXC motif is a “rheostat” in the active site [34], because changes in residues that separate the two cysteines influence redox potentials and pKa values of cysteines, configuring proteins for a particular redox function [35]. Altering the CXXC motif affects not only the reduction potential of the protein but also its ability to function as a disulfide isomerase and also affects its interaction with folding protein substrates and reoxidants [20]. The Trx-like fold is commonly observed in proteins, most of which function in disulfide bond formation and isomerization and regulate the redox state of the Cys residues for other functions. Sep15, SelH, SelM, SelO, SelT, SelP, SelW, and SelV contain a CXXU motif, indicating that they have an antioxidant activity, which corresponds to the CXXC motif of the Trx active site. A variety of approaches has been used to determine the biological function of these selenoproteins. However, most selenoproteins (thioredoxin glutathione reductase, SelH, SelI, SelM, SelO, SelT, SelV, SelW) have no known functions. Interestingly, the selenoproteins with identified functions (redox functions) are all oxidoreductases that contain Sec in the catalytic center and participate in various redox processes, such as antioxidant defense, redox signaling, redox regulation of biological functions, and many other processes that regulate intracellular redox homeostasis [31,36–38].

3. Glutathione Peroxidase

Glutathione peroxidase (GPx) is an intracellular antioxidant enzyme mainly protects the organism against oxidative stress by catalyzing the reduction of hydrogen peroxide, lipid hydroperoxides, and organic hydroperoxides to water or corresponding alcohols, using GSH as an essential cofactor [39]. It has also been reported that GPx dysfunction is associated with the incidence of various types of cancer [40,41], muscle disorders [42], CVDs [43,44], hepatopathies [45], renal failure [46,47], neurological disorders (such as Alzheimer’s disease (AD) and Parkinson’s disease (PD)) [48–50], immune defense dysfunction [51], and other diseases.

The selenol in the Sec residue of GPx is oxidized by H_2O_2 or other oxidants, which results in selenenic acid (GPx-SeOH) formation. Then, the GPx-SeOH is converted back to selenol via a two-step process. First, selenenyl sulfide (GPx-SeSG) is produced by the reaction between GPx-SeOH and GSH. Subsequently, the second GSH reduces GPx-SeSG back to selenol. Notably, owing to high levels of oxidative stress or low GSH concentrations, GPx-SeOH may be overoxidized to seleninic acid (GPx-SeO₂H) (Figure 1).

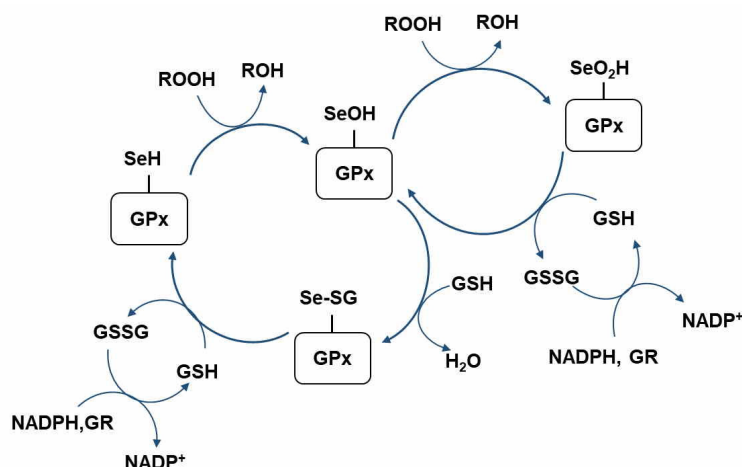


Figure 1. Catalytic redox cycle of glutathione peroxidase. GR, glutathione reductase; GSH, glutathione (reduced form); GSSG, glutathione disulfide; GPx-SeOH, selenenic acid; GPx-SeSG, selenenyl sulfide; GPx-SeO₂H, seleninic acid; ROOH, hydroperoxides (H₂O₂, peroxyinitrite or aliphatic hydroperoxide); ROH, H₂O or corresponding alcohol; NADPH, Nicotinamide adenine dinucleotide phosphate.

Mammalian GPx has eight isoforms; of these, GPx1 (ubiquitous, cytosolic), GPx2 (gastrointestinal-specific), GPx3 (plasma), GPx4 (phospholipid hydroperoxide), and GPx6 (olfactory epithelium) contain a Sec residue in the active catalytic site and can, thus, catalyze H₂O₂ and lipid hydroperoxide reduction in conjunction with GSH with increased efficiency [52,53]. In contrast, GPx6 homologs in some mammals, GPx5 (epididymal androgen-related protein), GPx7, and GPx8 are not selenoproteins and utilize a conventional Cys residue instead of Sec [54]. GPx1, the first discovered selenoenzyme, is located in the cytosol. Moreover, it is the most abundant GPx and found in nearly all mammalian tissues. GPx1 can reduce H₂O₂ and organic hydroperoxides, including *tert*-butyl hydroperoxide and cumene hydroperoxide. Its peroxidase activity and expression are affected by Se status [55]. GPx1 loss is associated with the development of various types of cancer, including breast [41], lung [56], prostate [57], and bladder [58] cancers. GPx2 is an intestinal selenoenzyme highly and weakly expressed in the gastrointestinal mucosal epithelium and human liver, respectively. Moreover, it can catalyze H₂O₂, *tert*-butyl hydroperoxide, cumene hydroperoxide, and linoleic acid hydroperoxide reduction [59]. The main function of GPx2 is to protect the intestinal epithelium from oxidative stress and maintain mucosal homeostasis [60]. Florian et al. reported that GPx2 expression levels are much higher in crypt bases than in luminal sites. The crypts contain stem cells that participate in the proliferative zone, thereby suggesting that GPx2 might play a role in cell proliferation. GPx2 loss was also shown to increase apoptosis, mitosis, and GPx1 expression in mice intestines [61]. GPx3 is the only extracellular secreted member of the GPx family that catalyzes H₂O₂, organic hydroperoxides, and lipid hydroperoxides to reduce systemic oxidative stress [18]. GPx3 has been identified as a tumor suppressor in many cancers [62]. GPx3 promoter hypermethylation specifically downregulates its expression, which occurs commonly in human cancers, including prostate, gastric, breast, lung, and colon cancers [63–65]. GPx3 dysregulation is also associated with obesity and fat distribution and related to whole body insulin resistance [66]. GPx4 is the only known enzyme that can reduce lipid hydroperoxides, which arise in the membrane. Unlike other GPx, GPx4 not only uses GSH as an electron donor but also uses protein thiols as reducing substrates when GSH becomes limiting [67]. A study has shown that the pro-survival role of selenium in mammals is largely mediated by GPx4 [68]. GPx4 activity is essential to maintain lipid homeostasis, prevent toxic lipid ROS accumulation, and thereby block ferroptosis by its intrinsic resistance to irreversible inactivation [69,70]. GPx6, found in the olfactory epithelium and during embryonic development [54], is highly expressed in the olfactory bulb, striatum, and frontal cerebral cortex [71]. Synthetic lethal screening in the mammalian central nervous system has identified that the age-regulated *Gpx6* gene is a modulator of mutant huntingtin toxicity, and its overexpression can dramatically alleviate both behavioral and molecular phenotypes associated with a mouse model of Huntington's disease [71].

4. Thioredoxin Reductase

TrxR is an essential component of the Trx system, which comprises Trx, nicotinamide adenine dinucleotide phosphate (NADPH), and TrxR (Figure 2). The Trx/TrxR system functions as a protein disulfide oxidoreductase to maintain the redox status of intracellular substrate proteins, such as ribonuclease reductase, peroxiredoxin, glucocorticoid receptors, transcription factors, and protein tyrosine phosphatases such as PTEN [72,73]. The two subunits of TrxR are only active in their dimeric form and form a head-to-tail pattern in active homodimeric TrxRs. TrxR is indispensable for Trx function as it is the only enzyme that catalyzes the NADPH-dependent Trx reduction [74]. Three isoforms of TrxR are found in mammals: cytosolic TrxR (TrxR1), mitochondrial TrxR (TrxR2), and a testis-specific thioredoxin glutathione reductase (TrxR3) [75]. All three enzymes contain conserved Gly-Cys-Sec-Gly sites in the flexible C-terminal region, which is both reactive and solvent-accessible

[19,76–80]. In particular, the Sec residue is critical for TrxR reductase activity [81]. Mammalian TrxR1 and TrxR2 have another conserved site, namely the Cys-Val-Asn-Val-Gly-Cys motif, which is adjacent to the flavin adenine dinucleotide located in the N-terminal region [19,77]. Owing to these two conserved sites, mammalian TrxRs possess surprisingly multifaceted properties and functions beyond direct Trx reduction. In addition to Trx, mammalian TrxRs have a broad substrate specificity. As such, they can reduce glutaredoxin 2, protein disulfide isomerase, and many other disulfides in proteins. They also reduce some non-disulfide substrates, such as H_2O_2 [21], selenite [82], lipid hydroperoxides [83], ascorbic acid [84], α -lipoic acid [74,85–87], cytosolic peptide granulysin [88], antibacterial NK-lysine [89], dehydroascorbate [84], and cytochrome C [90]. Similar to other selenoproteins, such as SelR and GPx1, the expression of TrxRs depends on the concentration of selenium: selenium deficiency reduced TrxR synthesis; however, a high selenium concentration mediated Sec incorporation and increased TrxR enzyme activity without increasing protein synthesis [91,92].

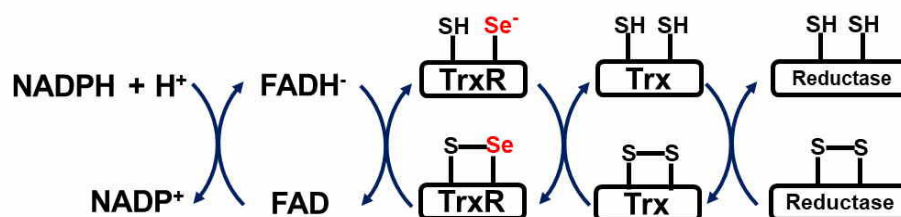


Figure 2. Catalytic redox cycle of the thioredoxin (Trx)/thioredoxin reductase (TrxR)/nicotinamide adenine dinucleotide phosphate (NADPH) system. FAD, flavin adenine dinucleotide.

TrxRs are ubiquitously expressed enzymes that regulate redox metabolism and play a critical role in protection against malignant transformation. There is increasing evidence that supports the idea that TrxRs inhibit multiple stages of tumor progression, from initiation to growth, invasion, and metastasis [93–95]. Interestingly, TrxR overactivation or dysfunction is associated with the onset of various diseases, such as CVDs, neurological disorders, type 2 diabetes, human immunodeficiency virus infection, and cancer [96–99]. Trx1 not only acts as an antioxidant but also plays an important role in cellular function by regulating signaling pathways via direct interaction with other small molecules, all of which are involved in ventricular remodeling inhibition after myocardial infarction [100]. Therefore, in CVD, TrxR functions via interactions with Trx1 [101].

The tumor suppressor PTEN negatively regulates the PI3K/AKT signaling pathway, which is pivotal for cell growth and survival. Numerous studies have demonstrated that PTEN catalytic activity is regulated via direct oxidation by ROS [102,103]. Therefore, its enzymatic activity recovery depends on cellular Trx/TrxR system availability [73]. Increased Trx1 expression in human tumors is associated with abnormal growth, which is caused by the binding of Trx1 to the C2 domain of PTEN, thereby resulting in the inhibition of its lipid phosphatase activity and membrane binding capacity [104]. It has been reported that Trx and TrxR are highly overexpressed in a variety of aggressive tumors and may increase tumor cell survival and proliferation [105–107], indicating that the Trx system has a dual function in cancer. The effect of TrxR inhibition on tumor cell survival and aggressiveness is robust, and tumor proliferation appears to be dependent on an active Trx system, making TrxR a potential target for cancer chemotherapy [108–112] (Figure 3). In this regard, the Sec residue in mammalian TrxR can be the primary target for the development of drugs that exert inhibitory effects on various type of cancers, including gold compounds and platinum-based drugs [113], alkylating anticancer agents such as nitrosoureas [114], nitrogen mustards, ifosfamide [115], and cyclophosphamide [116], arsenic trioxide [117], dinitrohalobenzenes such as 1-chloro-2,4-dinitrobenzene, 1-fluoro-2,4-dinitrobenzene, and 1-bromo-2,4-dinitrobenzene, and natural products such as curcumin [118], flavonoids [119], and quinones [120]. The irreversible TrxR inhibition by dinitrohalobenzenes and curcumin is accompanied by the alkylation of both the redox-active Sec⁴⁹⁷ and its neighboring cysteine residue Cys⁴⁹⁶. Moreover, this modified TrxR strongly induces NADPH oxidase activity, which leads to ROS production [118,121].

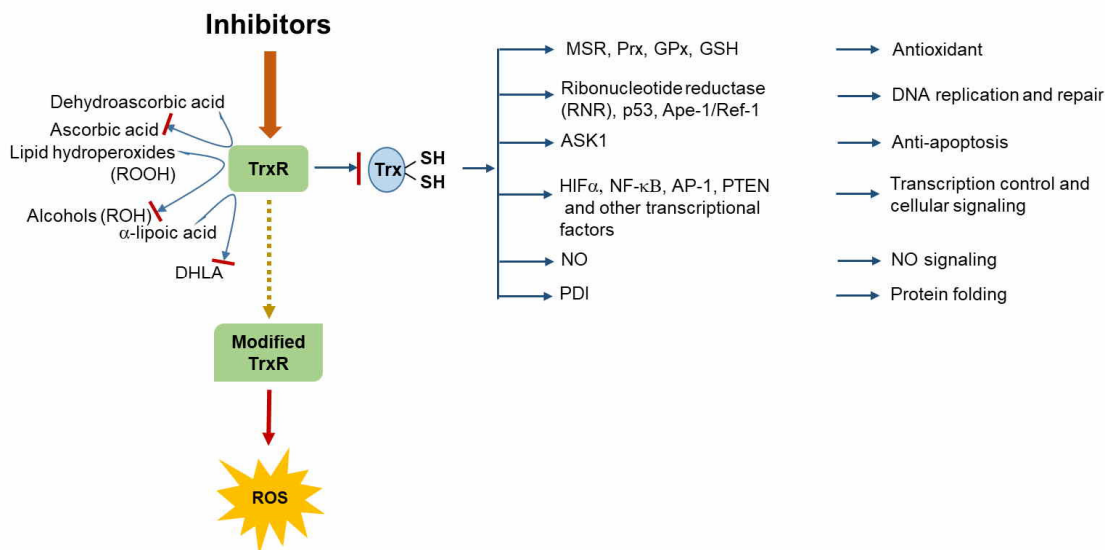


Figure 3. Thioredoxin reductase (TrxR) as a novel target for cancer therapy. Gold compounds, nitrosoureas, arsenic trioxide, dinitrohalobenzenes, curcumin, flavonoids, quinones, and other cancer chemotherapeutics have been shown to be TrxR inhibitors. TrxR inhibition blocks thioredoxin (Trx)-mediated activity in various processes, such as defense against oxidative stress, DNA replication and repair, apoptosis inhibition, transcription control, and protein folding via different signaling pathways. Some inhibitors, such as 1-chloro-2,4-dinitrobenzene (DNCB) and curcumin, modify TrxR via the alkylation of Cys⁴⁹⁶ and redox-active Sec⁴⁹⁷ residues and induce nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, finally leading to reactive oxygen species (ROS) production.

5. Selenoprotein R

SelR (also designated as MsrB1) is an antioxidant enzyme that uses Met to defend cellular macromolecules against oxidative stress. Met is a sulfur-containing amino acid that is readily oxidized to Met sulfoxide by ROS; subsequently, Met sulfoxide reductases (Msr) such as SelR reduce Met sulfoxide back to Met [122]. Met sulfoxide contains two diastereomeric forms, Met-S-sulfoxide (Met-S-SO) and Met-R-sulfoxide (Met-R-SO) [123]. Met-R-SO is reduced by the MsrB family of proteins, including SelR, whereas Met-S-SO is reduced by the MsrA family of proteins [124]. Mammals have one MsrA and three MsrBs, namely, SelR, MsrB2, and MsrB3 [18]. Among these, SelR is the only selenoprotein that is localized in both the cytosol and nucleus. SelR is present specifically in vertebrates and appears to have evolved separately, having the lowest homology with other Msr enzymes [125].

SelR expression is regulated by dietary selenium; its mRNA expression level is low in a selenium-deficient diet, but this can be reversed by dietary selenium supplementation [126]. SelR activity was also found to reduce with age [127]. SelR has catalytic activity, especially for protein-bound and free Met-R-SO but has low catalytic efficiency. Like other Msr enzymes, SelR is an oxidoreductase that requires Trx/TrxR/NADPH to recycle its oxidized form to the reduced form (Figure 4A) [99]. Along with its catalytic activity toward protein-bound Met-R-SO, SelR plays a role in repairing oxidized proteins, thus protecting the structure and function of proteins against oxidative stress [128]. SelR also regulates biological processes via the reversible oxidation/reduction of Met residues in proteins. The oxidation of Met residues at certain sites by either ROS or enzymes often leads to changes in protein function, which can then be reversed by SelR-catalyzed reduction of the said Met residues [129]. For instance, it was found that F-actin disassembly caused by the stereospecific oxidation of the 44 and 47 Met residues in actin by MICAL proteins can be rescued by SelR [130]. Actin cytoskeleton dynamics regulation is important for many cellular responses, including neural development, muscle contraction, and filopodia formation [131–133]. Moreover, F-

actin assembly is known to be bidirectionally associated with the mitogen-activated protein kinase (MAPK) pathway, which controls many cellular processes, including cell proliferation [134]. Accordingly, SelR is a potentially redox-dependent regulator that participates in many cellular processes and signaling pathways related to actin cytoskeleton dynamics via F-actin assembly regulation.

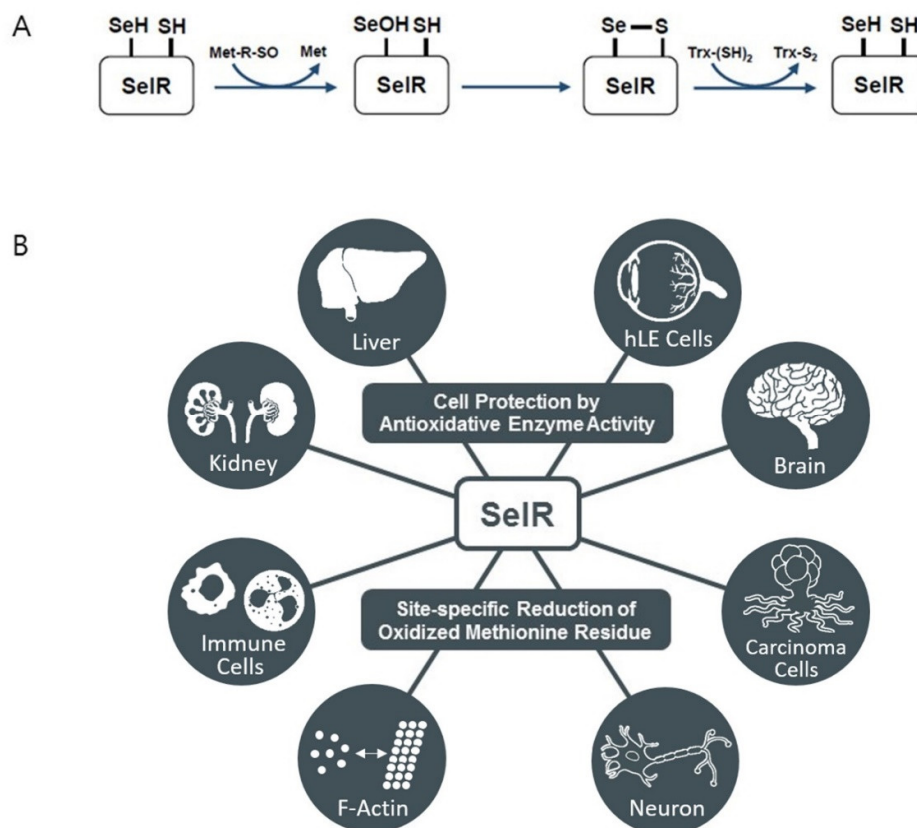


Figure 4. (A) Catalytic mechanism of SelR reducing methionine-R-sulfoxide (Met-R-SO). The catalytic selenocysteine (Sec) residue attacks Met-R-SO and forms the intermediate selenenic acid with Met release. The resolving cysteine (Cys) residue attacks the intermediate, resulting in the formation of intramolecular selenide-sulfide bond. The intramolecular selenide-sulfide bond of SelR is directly reduced by thioredoxin (Trx) system. (B) Role of SelR in various organs and cell types.

SelR KO mice exhibit increased oxidative stress in the liver and kidney with exacerbated hepatotoxicity [135,136]. SelR is also required for human lens epithelial (hLE) cell viability against oxidative stress-induced apoptosis and attenuates cataracts [137]. Since membrane-bound proteins in hLE cells from patients with cataract contain high levels of Met sulfoxide residues, SelR may directly retard cataract [138]. SelR appears to play an important role in innate immunity; however, its underlying mechanism is poorly understood. In macrophages, SelR expression is induced by lipopolysaccharides and is involved in controlling macrophage function by promoting the expression of anti-inflammatory cytokines, such as IL-10 and IL-1RA [139]. Neutrophils were also shown to have high levels of SelR expression in response to excessive ROS. Moreover, a recent study has suggested that decreased SelR activity in neutrophils might be associated with AD [140]. A study has also shown that SelR is highly expressed in carcinoma cells in response to increased oxidative stress, and may thus enhance carcinoma cell survival. Moreover, SelR expression upregulation aggravates oncogenesis by promoting proliferation via MAPK pathway activation and promotes invasion and metastasis by regulating actin cytoskeleton dynamics [141,142] (Figure 4B).

6. Selenoprotein O

SelO, the largest protein among the 25 mammalian selenoproteins, is expressed in a variety of organs, such as the brain, heart, liver, kidneys, lungs, and stomach [54,143]. Unlike SelR and GPx1 expression, SelO expression is not influenced by a selenium-deficient diet [143]. In higher eukaryotes, SelO contains a single Sec residue near the C-terminal region [54,143]. Notably, in lower eukaryotes and all prokaryotes, the Sec residue in SelO is replaced with an invariant Cys residue [144]. Mammalian SelO is located in the mitochondria [143,144], and the occurrence of the CXXU motif in the C-terminal region suggests that SelO might have a redox-active Sec residue, similar to other thiol-dependent oxidoreductases [143]. SelO activity in *Escherichia coli* is regulated by intramolecular disulfide bridge formation between a Cys residue in the activation loop (Cys272) and the Cys residue in the C-terminal region (Cys476), with the latter being replaced by a Sec residue in higher eukaryotes [144]. Using bioinformatic tools, Dudkiewicz et al. predicted that the three-dimensional structure of SelO may be similar to that of a protein kinase and that it might have phosphotransferase activity [145]. Recently, structural studies have shown that SelO is a highly conserved pseudokinase that transfers AMP from ATP to Ser, Thr, and Tyr residues in its substrate protein via a process known as AMPylation [144]. SelO plays a role in response to oxidative stress and regulates global S-glutathionylation levels via AMPylation in conjunction with glutaredoxin [144] (Figure 5). Furthermore, SelO has been shown to play an essential role in chondrocyte viability, proliferation, and chondrogenic differentiation [146]. However, the physiological functions of SelO remain unknown. As such, further research is needed to clarify its physiological functions, role in disease, and association with other redox enzymes.

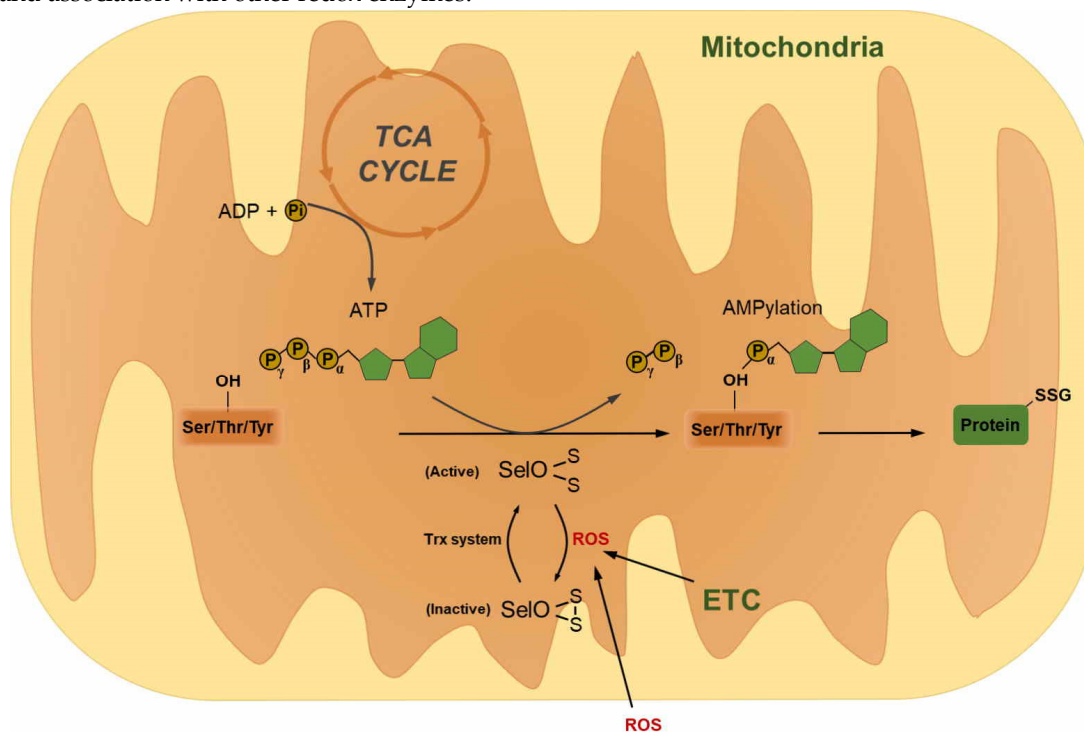


Figure 5. Selenoprotein O (SelO) mediates protein AMPylation and protects the cell from oxidative stress.

7. Other Selenoproteins

SelS (also designated as SEPS1, VIMP, and Tanis) is a single-pass transmembrane protein [54] that has an extensive tissue distribution, being present in the liver, kidneys, adipose tissue, skeletal muscle, pancreatic islets, and blood vessels [147]. SelS participates in the endoplasmic reticulum (ER)-associated protein degradation (ERAD) pathway, which is responsible for transporting unfolded or misfolded proteins from the ER to the cytoplasm, followed by degradation via the ubiquitin–

proteasome system [148]. SelS is a Trx-dependent reductase that catalyzes H₂O₂ and cumene hydroperoxide reduction [149]. An NF- κ B-binding site is located within the SelS gene promoter region in Bama mini-pigs [150]. Moreover, SelS can regulate the production of inflammatory cytokines, such as IL-1 β and IL-6, in stimulated astrocytes [151]. This suggests that SelS is involved in inflammation, oxidative stress, and endoplasmic stress [152,153].

Human SelT is a 22 kDa protein localized to the Golgi apparatus and ER and present in the plasma membrane [154]. SelT possesses a Trx-like fold and a conserved CXXU motif, which are common structural domains in oxidoreductases with a catalytic Sec residue. Moreover, SelT knockdown was found to increase the expression of Cbr3 and SelW, which are involved in redox regulation, thereby supporting the idea that this protein might function as an oxidoreductase [155]. SelT is a trophic neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP)-regulated gene involved in intracellular Ca²⁺ mobilization and neuroendocrine secretion. Sec-containing SelT overexpression in PC12 cells was found to increase intracellular Ca²⁺ concentrations, whereas the Sec-to-Ala SelT mutant overexpression had no effect on Ca²⁺ release, suggesting that SelT regulates intracellular Ca²⁺ mobilization via the redox-active Sec residue [156]. SelT has also been reported to protect dopaminergic neurons against oxidative stress and prevent early and severe movement impairment in Parkinson's disease (PD) animal models [157].

SelN is a 65 kDa transmembrane glycoprotein, which is localized to the ER that contains a transmembrane-addressing site in proximity to the EF-hand motif, which is a helix-loop-helix structural motif found in a large family of calcium-binding proteins. [158]. Human SelN mRNA is detected in most fetal tissues, but its level reduces in adult tissues [159]. Moreover, its expression increases in proliferating cells, such as fibroblasts and myoblasts, and gradually decreases during the differentiation of myoblasts to myotubes [158]. SelN is so far the only selenoprotein directly linked to human genetic disorders. Certain mutations in the SelN gene cause SEPN1-related myopathy (SEPN1-RM), which is an early-onset muscle disease that is characterized by muscle weakness, spinal rigidity, and respiratory insufficiency. SelN plays an important role in conferring resistance against oxidative stress and maintaining Ca²⁺ homeostasis in human skeletal muscle cells [160]. Moreover, SelN-deficient fibroblasts and muscle cells have been shown to have an increased susceptibility to H₂O₂-induced oxidative stress [160]. Notably, in SelN-deficient muscle cells, the generated ROS/NO have been found to regulate intracellular Ca²⁺ concentrations via the modulation of Ca²⁺ channels, followed by Ca²⁺ release or leaking [160].

8. Conclusions

Organisms contain an array of defense systems, such as the thiol-dependent antioxidant system, which coordinate to remove ROS and reactive nitrogen species. This review focused on several mammalian selenoproteins, discussing their splicing forms, structures, and relationships with oxidative stress and disease. Although the functions of some selenoproteins still remain unclear, up-to-date research is advancing in the characterization of some of the less known selenoproteins, as well as their role in the development of various diseases as they may act as potential drug targets. Further studies should focus on revealing the detailed molecular mechanisms underlying the functions of selenoproteins, which can further help develop new guidelines for novel therapies in various diseases.

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References

1. Valko, M.; Rhodes, C.J.; Moncol, J.; Izakovic, M.; Mazur, M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.* **2006**, *160*, 1–40, doi:10.1016/j.cbi.2005.12.009.
2. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* **2007**, *39*, 44–84, doi:10.1016/j.biocel.2006.07.001.
3. Dalle-Donne, I.; Rossi, R.; Colombo, R.; Giustarini, D.; Milzani, A. Biomarkers of oxidative damage in human disease. *Clin. Chem.* **2006**, *52*, 601–623, doi:10.1373/clinchem.2005.061408.
4. Dhalla, N.S.; Temsah, R.M.; Netticadan, T. Role of oxidative stress in cardiovascular diseases. *J. hypertens.* **2000**, *18*, 655–673.
5. Jenner, P. Oxidative stress in Parkinson's disease. *Ann. Neurol.* **2003**, *53 Suppl 3*, S26–36; discussion S36–28, doi:10.1002/ana.10483.
6. Sayre, L.M.; Smith, M.A.; Perry, G. Chemistry and biochemistry of oxidative stress in neurodegenerative disease. *Curr. Med. Chem.* **2001**, *8*, 721–738.
7. Brownlee, M.; Cerami, A. The biochemistry of the complications of diabetes mellitus. *Annu. Rev. Biochem.* **1981**, *50*, 385–432, doi:10.1146/annurev.bi.50.070181.002125.
8. Kasparova, S.; Brezova, V.; Valko, M.; Horecky, J.; Mlynarik, V.; Liptaj, T.; Vancova, O.; Ulicna, O.; Dobrota, D. Study of the oxidative stress in a rat model of chronic brain hypoperfusion. *Neurochem. Int.* **2005**, *46*, 601–611, doi:10.1016/j.neuint.2005.02.006.
9. Harman, D. Aging: A theory based on free radical and radiation chemistry. *J. gerontol.* **1956**, *11*, 298–300.
10. Choi, S.M.; Kim, D.-H.; Chun, K.-S.; Choi, J.-S. Carnosol induces apoptotic cell death through ROS-dependent inactivation of STAT3 in human melanoma G361 cells. *Appl. Biol. Chem.* **2019**, *62*, doi:10.1186/s13765-019-0463-z.
11. Utaipan, T.; Boonyanuphong, P.; Chuprajob, T.; Suksamrarn, A.; Chunglok, W. A trienone analog of curcumin, 1,7-bis(3-hydroxyphenyl)-1,4,6-heptatrien-3-one, possesses ROS- and caspase-mediated apoptosis in human oral squamous cell carcinoma cells in vitro. *Appl. Biol. Chem.* **2020**, *63*, doi:10.1186/s13765-020-0491-8.
12. Avery, J.C.; Hoffmann, P.R. Selenium, Selenoproteins, and Immunity. *Nutrients* **2018**, *10*, doi:10.3390/nu10091203.
13. Wang, N.; Tan, H.Y.; Li, S.; Xu, Y.; Guo, W.; Feng, Y. Supplementation of Micronutrient Selenium in Metabolic Diseases: Its Role as an Antioxidant. *Oxid. Med. Cell Longev.* **2017**, *2017*, 7478523, doi:10.1155/2017/7478523.
14. Wessjohann, L.A.; Schneider, A.; Abbas, M.; Brandt, W. Selenium in chemistry and biochemistry in comparison to sulfur. *Biol. Chem.* **2007**, *388*, 997–1006, doi:10.1515/bc.2007.138.
15. Lobanov, A.V.; Hatfield, D.L.; Gladyshev, V.N. Eukaryotic selenoproteins and selenoproteomes. *Biochim. et biophys. acta* **2009**, *1790*, 1424–1428, doi:10.1016/j.bbagen.2009.05.014.
16. Gromer, S.; Wissing, J.; Behne, D.; Ashman, K.; Schirmer, R.H.; Flohe, L.; Becker, K. A hypothesis on the catalytic mechanism of the selenoenzyme thioredoxin reductase. *Biochem. J.* **1998**, *332*, 591–592.
17. Gorlatov, S.N.; Stadtman, T.C. Human selenium-dependent thioredoxin reductase from HeLa cells: Properties of forms with differing heparin affinities. *Arch. Biochem. Biophys.* **1999**, *369*, 133–142, doi:10.1006/abbi.1999.1356.
18. Chung, S.S.; Kim, M.; Youn, B.S.; Lee, N.S.; Park, J.W.; Lee, I.K.; Lee, Y.S.; Kim, J.B.; Cho, Y.M.; Lee, H.K., et al. Glutathione peroxidase 3 mediates the antioxidant effect of peroxisome proliferator-activated receptor gamma in human skeletal muscle cells. *Mol. Cell. Biol.* **2009**, *29*, 20–30, doi:10.1128/mcb.00544-08.
19. Lee, S.R.; Bar-Noy, S.; Kwon, J.; Levine, R.L.; Stadtman, T.C.; Rhee, S.G. Mammalian thioredoxin reductase: Oxidation of the C-terminal cysteine/selenocysteine active site forms a thioselenide, and replacement of selenium with sulfur markedly reduces catalytic activity. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2521–2526, doi:10.1073/pnas.050579797.
20. Quan, S.; Schneider, I.; Pan, J.; Von Hacht, A.; Bardwell, J.C. The CXXC motif is more than a redox rheostat. *J. Biol. Chem.* **2007**, *282*, 28823–28833, doi:10.1074/jbc.M705291200.
21. Johansson, L.; Gafvelin, G.; Arner, E.S. Selenocysteine in proteins-properties and biotechnological use. *Biochim. biophys. Acta* **2005**, *1726*, 1–13, doi:10.1016/j.bbagen.2005.05.010.
22. Berry, M.J.; Banu, L.; Chen, Y.Y.; Mandel, S.J.; Kieffer, J.D.; Harney, J.W.; Larsen, P.R. Recognition of UGA as a selenocysteine codon in type I deiodinase requires sequences in the 3' untranslated region. *Nature* **1991**, *353*, 273–276, doi:10.1038/353273a0.

23. Bellinger, F.P.; Raman, A.V.; Reeves, M.A.; Berry, M.J. Regulation and function of selenoproteins in human disease. *Biochem. J.* **2009**, *422*, 11–22, doi:10.1042/bj20090219.
24. Mattmiller, S.A.; Carlson, B.A.; Sordillo, L.M. Regulation of inflammation by selenium and selenoproteins: Impact on eicosanoid biosynthesis. *J. Nutr. Sci.* **2013**, *2*, e28, doi:10.1017/jns.2013.17.
25. Fairweather-Tait, S.J.; Collings, R.; Hurst, R. Selenium bioavailability: Current knowledge and future research requirements. *Am. J. Clin. Nutr.* **2010**, *91*, 1484S–1491S, doi:10.3945/ajcn.2010.28674J.
26. Hatfield, D.L.; Gladyshev, V.N. How selenium has altered our understanding of the genetic code. *Molecular and cellular biology* **2002**, *22*, 3565–3576.
27. Spallholz, J.E. Selenomethionine and Methioninase: Selenium Free Radical Anticancer Activity. *Methods Mol. Biol.* **2019**, *1866*, 199–210, doi:10.1007/978-1-4939-8796-2_15.
28. Luchman, H.A.; Villemare, M.L.; Bismar, T.A.; Carlson, B.A.; Jirik, F.R. Prostate epithelium-specific deletion of the selenocysteine tRNA gene Trsp leads to early onset intraepithelial neoplasia. *Am. J. Pathol.* **2014**, *184*, 871–877, doi:10.1016/j.ajpath.2013.11.025.
29. Bosl, M.R.; Takaku, K.; Oshima, M.; Nishimura, S.; Taketo, M.M. Early embryonic lethality caused by targeted disruption of the mouse selenocysteine tRNA gene (Trsp). *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 5531–5534.
30. Kumaraswamy, E.; Carlson, B.A.; Morgan, F.; Miyoshi, K.; Robinson, G.W.; Su, D.; Wang, S.; Southon, E.; Tessarollo, L.; Lee, B.J., et al. Selective removal of the selenocysteine tRNA [Ser]Sec gene (Trsp) in mouse mammary epithelium. *Mol. Cell. Biol.* **2003**, *23*, 1477–1488.
31. Papp, L.V.; Lu, J.; Holmgren, A.; Khanna, K.K. From selenium to selenoproteins: Synthesis, identity, and their role in human health. *Antioxid. Redox Signal.* **2007**, *9*, 775–806, doi:10.1089/ars.2007.1528.
32. Burk, R.F.; Hill, K.E. Selenoprotein P: An extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu. Rev. Nutr.* **2005**, *25*, 215–235, doi:10.1146/annurev.nutr.24.012003.132120.
33. Qi, Y.; Grishin, N.V. Structural classification of thioredoxin-like fold proteins. *Proteins* **2005**, *58*, 376–388, doi:10.1002/prot.20329.
34. Chivers, P.T.; Prehoda, K.E.; Raines, R.T. The CXXC motif: A rheostat in the active site. *Biochemistry* **1997**, *36*, 4061–4066, doi:10.1021/bi9628580.
35. Chivers, P.T.; Laboissiere, M.C.; Raines, R.T. The CXXC motif: Imperatives for the formation of native disulfide bonds in the cell. *EMBO J.* **1996**, *15*, 2659–2667.
36. Reeves, M.A.; Hoffmann, P.R. The human selenoproteome: Recent insights into functions and regulation. *Cell. Mol. Life Sci.* **2009**, *66*, 2457–2478, doi:10.1007/s00018-009-0032-4.
37. Lee, B.C.; Peterfi, Z.; Hoffmann, F.W.; Moore, R.E.; Kaya, A.; Avanesov, A.; Tarrago, L.; Zhou, Y.; Weerapana, E.; Fomenko, D.E., et al. MsrB1 and MICALs regulate actin assembly and macrophage function via reversible stereoselective methionine oxidation. *Mol. Cell.* **2013**, *51*, 397–404, doi:10.1016/j.molcel.2013.06.019.
38. Hawkes, W.C.; Alkan, Z. Regulation of redox signaling by selenoproteins. *Biol. Trace Elem. Res.* **2010**, *134*, 235–251, doi:10.1007/s12011-010-8656-7.
39. Kieliszek, M.; Blazejak, S. Selenium: Significance, and outlook for supplementation. *Nutrition* **2013**, *29*, 713–718, doi:10.1016/j.nut.2012.11.012.
40. Hu, Y.; Benya, R.V.; Carroll, R.E.; Diamond, A.M. Allelic loss of the gene for the GPX1 selenium-containing protein is a common event in cancer. *J. Nutr.* **2005**, *135*, 3021s–3024s.
41. Hu, Y.J.; Diamond, A.M. Role of glutathione peroxidase 1 in breast cancer: Loss of heterozygosity and allelic differences in the response to selenium. *Cancer Res.* **2003**, *63*, 3347–3351.
42. El Haddad, M.; Jean, E.; Turki, A.; Hugon, G.; Vernus, B.; Bonnieu, A.; Passerieux, E.; Hamade, A.; Mercier, J.; Laoudj-Chenivisse, D., et al. Glutathione peroxidase 3, a new retinoid target gene, is crucial for human skeletal muscle precursor cell survival. *J. cell Sci.* **2012**, *125*, 6147–6156, doi:10.1242/jcs.115220.
43. Hoffmann, F.W.; Hashimoto, A.S.; Lee, B.C.; Rose, A.H.; Shohet, R.V.; Hoffmann, P.R. Specific antioxidant selenoproteins are induced in the heart during hypertrophy. *Arch. Biochem. Biophys.* **2011**, *512*, 38–44, doi:10.1016/j.abb.2011.05.007.
44. Tanguy, S.; Rakotova, A.; Jouan, M.G.; Ghezzi, C.; de Leiris, J.; Boucher, F. Dietary selenium intake influences Cx43 dephosphorylation, TNF-alpha expression and cardiac remodeling after reperfused infarction. *Mol. Nut. Food Res.* **2011**, *55*, 522–529, doi:10.1002/mnfr.201000393.

45. Carlson, B.A.; Tobe, R.; Yefremova, E.; Tsuji, P.A.; Hoffmann, V.J.; Schweizer, U.; Gladyshev, V.N.; Hatfield, D.L.; Conrad, M. Glutathione peroxidase 4 and vitamin E cooperatively prevent hepatocellular degeneration. *Redox Boil.* **2016**, *9*, 22–31, doi:10.1016/j.redox.2016.05.003.
46. Zachara, B.A.; Gromadzinska, J.; Zbrog, Z.; Swiech, R.; Wasowicz, W.; Twardowska, E.; Jablonska, E.; Sobala, W. Selenium supplementation to chronic kidney disease patients on hemodialysis does not induce the synthesis of plasma glutathione peroxidase. *Acta Biochim. Pol.* **2009**, *56*, 183–187.
47. Taccone-Gallucci, M.; Noce, A.; Bertucci, P.; Fabbri, C.; Manca-di-Villahermosa, S.; Della-Rovere, F.R.; De Francesco, M.; Lonzi, M.; Federici, G.; Scaccia, F., et al. Chronic treatment with statins increases the availability of selenium in the antioxidant defence systems of hemodialysis patients. *J. Trace Elem. Med. Biol.* **2010**, *24*, 27–30, doi:10.1016/j.jtemb.2009.06.005.
48. Cardoso, B.R.; Hare, D.J.; Bush, A.I.; Roberts, B.R. Glutathione peroxidase 4: A new player in neurodegeneration? *Mol. Psychiatry* **2017**, *22*, 328–335, doi:10.1038/mp.2016.196.
49. Hambright, W.S.; Fonseca, R.S.; Chen, L.; Na, R.; Ran, Q. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. *Redox Boil.* **2017**, *12*, 8–17, doi:10.1016/j.redox.2017.01.021.
50. Chen, L.; Hambright, W.S.; Na, R.; Ran, Q. Ablation of the Ferroptosis Inhibitor Glutathione Peroxidase 4 in Neurons Results in Rapid Motor Neuron Degeneration and Paralysis. *J. Biol. Chem.* **2015**, *290*, 28097–28106, doi:10.1074/jbc.M115.680090.
51. Matsushita, M.; Freigang, S.; Schneider, C.; Conrad, M.; Bornkamm, G.W.; Kopf, M. T cell lipid peroxidation induces ferroptosis and prevents immunity to infection. *J. Exp. Med.* **2015**, *212*, 555–568, doi:10.1084/jem.20140857.
52. Gromer, S.; Eubel, J.K.; Lee, B.L.; Jacob, J. Human selenoproteins at a glance. *Cell. Mol. Life Sci.* **2005**, *62*, 2414–2437, doi:10.1007/s00018-005-5143-y.
53. Neiers, F.; Sonkaria, S.; Olry, A.; Boschi-Muller, S.; Branlant, G. Characterization of the amino acids from *Neisseria meningitidis* methionine sulfoxide reductase B involved in the chemical catalysis and substrate specificity of the reductase step. *J. Biol. Chem.* **2007**, *282*, 32397–32405, doi:10.1074/jbc.M704730200.
54. Kryukov, G.V.; Castellano, S.; Novoselov, S.V.; Lobanov, A.V.; Zehab, O.; Guigo, R.; Gladyshev, V.N. Characterization of mammalian selenoproteomes. *Science* **2003**, *300*, 1439–1443, doi:10.1126/science.1083516.
55. Sunde, R.A.; Raines, A.M.; Barnes, K.M.; Evenson, J.K. Selenium status highly regulates selenoprotein mRNA levels for only a subset of the selenoproteins in the selenoproteome. *Biosci. Rep.* **2009**, *29*, 329–338, doi:10.1042/bsr20080146.
56. Moscow, J.A.; Schmidt, L.; Ingram, D.T.; Gnarr, J.; Johnson, B.; Cowan, K.H. Loss of heterozygosity of the human cytosolic glutathione peroxidase I gene in lung cancer. *Carcinogenesis* **1994**, *15*, 2769–2773.
57. Hardell, L.; Degerman, A.; Tomic, R.; Marklund, S.L.; Bergfors, M. Levels of selenium in plasma and glutathione peroxidase in erythrocytes in patients with prostate cancer or benign hyperplasia. *Asian Pac. J. Cancer Prev.* **1995**, *4*, 91–95.
58. Ichimura, Y.; Habuchi, T.; Tsuchiya, N.; Wang, L.; Oyama, C.; Sato, K.; Nishiyama, H.; Ogawa, O.; Kato, T. Increased risk of bladder cancer associated with a glutathione peroxidase 1 codon 198 variant. *J. Urology* **2004**, *172*, 728–732, doi:10.1097/01.ju.0000130942.40597.9d.
59. Wingler, K.; Muller, C.; Schmehl, K.; Florian, S.; Brigelius-Flohe, R. Gastrointestinal glutathione peroxidase prevents transport of lipid hydroperoxides in CaCo-2 cells. *Gastroenterology* **2000**, *119*, 420–430.
60. Roman, M.; Jitaru, P.; Barbante, C. Selenium biochemistry and its role for human health. *Metallomics* **2014**, *6*, 25–54, doi:10.1039/c3mt00185g.
61. Florian, S.; Krehl, S.; Loewinger, M.; Kipp, A.; Banning, A.; Esworthy, S.; Chu, F.F.; Brigelius-Flohe, R. Loss of GPx2 increases apoptosis, mitosis, and GPx1 expression in the intestine of mice. *Free Radic. Biol. Med.* **2010**, *49*, 1694–1702, doi:10.1016/j.freeradbiomed.2010.08.029.
62. Barrett, C.W.; Ning, W.; Chen, X.; Smith, J.J.; Washington, M.K.; Hill, K.E.; Coburn, L.A.; Peek, R.M.; Chaturvedi, R.; Wilson, K.T., et al. Tumor suppressor function of the plasma glutathione peroxidase gpx3 in colitis-associated carcinoma. *Cancer Res.* **2013**, *73*, 1245–1255, doi:10.1158/0008-5472.can-12-3150.
63. An, B.C.; Jung, N.-K.; Park, C.Y.; Oh, I.-J.; Choi, Y.-D.; Park, J.-I.; Lee, S.-W. Epigenetic and Glucocorticoid Receptor-Mediated Regulation of Glutathione Peroxidase 3 in Lung Cancer Cells. *Mol. Cells* **2016**, *39*, 631–638, doi:10.14348/molcells.2016.0164.

64. Chen, B.; Rao, X.; House, M.G.; Nephew, K.P.; Cullen, K.J.; Guo, Z. GPx3 promoter hypermethylation is a frequent event in human cancer and is associated with tumorigenesis and chemotherapy response. *Cancer Lett.* **2011**, *309*, 37–45, doi:10.1016/j.canlet.2011.05.013.
65. Mohamed, M.M.; Sabet, S.; Peng, D.F.; Nouh, M.A.; El-Shinawi, M.; El-Rifai, W. Promoter hypermethylation and suppression of glutathione peroxidase 3 are associated with inflammatory breast carcinogenesis. *Oxid Med Cell Longev.* **2014**, *2014*, 787195, doi:10.1155/2014/787195.
66. Langhardt, J.; Flehmig, G.; Kloting, N.; Lehmann, S.; Ebert, T.; Kern, M.; Schon, M.R.; Gartner, D.; Lohmann, T.; Dressler, M., et al. Effects of Weight Loss on Glutathione Peroxidase 3 Serum Concentrations and Adipose Tissue Expression in Human Obesity. *Obes. facts* **2018**, *11*, 475–490, doi:10.1159/000494295.
67. Mauri, P.; Benazzi, L.; Flohe, L.; Maiorino, M.; Pietta, P.G.; Pilawa, S.; Roveri, A.; Ursini, F. Versatility of selenium catalysis in PHGPx unraveled by LC/ESI-MS/MS. *Biol. Chem.* **2003**, *384*, 575–588, doi:10.1515/bc.2003.065.
68. Friedmann Angeli, J.P.; Conrad, M. Selenium and GPX4, a vital symbiosis. *Free Radic. Biol. Med.* **2018**, *127*, 153–159, doi:10.1016/j.freeradbiomed.2018.03.001.
69. Ingold, I.; Berndt, C.; Schmitt, S.; Doll, S.; Poschmann, G.; Buday, K.; Roveri, A.; Peng, X.; Porto Freitas, F.; Seibt, T., et al. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. *Cell* **2018**, *172*, 409–422.e421, doi:10.1016/j.cell.2017.11.048.
70. Stockwell, B.R.; Friedmann Angeli, J.P.; Bayir, H.; Bush, A.I.; Conrad, M.; Dixon, S.J.; Fulda, S.; Gascon, S.; Hatzios, S.K.; Kagan, V.E., et al. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. *Cell* **2017**, *171*, 273–285, doi:10.1016/j.cell.2017.09.021.
71. Shema, R.; Kulicke, R.; Cowley, G.S.; Stein, R.; Root, D.E.; Heiman, M. Synthetic lethal screening in the mammalian central nervous system identifies Gpx6 as a modulator of Huntington's disease. *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, 268–272, doi:10.1073/pnas.1417231112.
72. Powis, G.; Mustacich, D.; Coon, A. The role of the redox protein thioredoxin in cell growth and cancer. *Free radical biology & medicine* **2000**, *29*, 312–322, doi:10.1016/s0891-5849(00)00313-0.
73. Han, S.J.; Zhang, Y.; Kim, I.; Chay, K.O.; Yoon, H.J.; Jang, D.I.; Yang, S.Y.; Park, J.; Woo, H.A.; Park, I., et al. Redox regulation of the tumor suppressor PTEN by the thioredoxin system and cumene hydroperoxide. *Free Radic. Biol. Med.* **2017**, *112*, 277–286, doi:10.1016/j.freeradbiomed.2017.07.029.
74. Mustacich, D.; Powis, G. Thioredoxin reductase. *The Biochemical journal* **2000**, *346 Pt 1*, 1–8.
75. Lu, J.; Holmgren, A. Selenoproteins. *J. Biol. Chem.* **2009**, *284*, 723–727, doi:10.1074/jbc.R800045200.
76. Urig, S.; Becker, K. On the potential of thioredoxin reductase inhibitors for cancer therapy. *Semin. Cancer Biol.* **2006**, *16*, 452–465, doi:10.1016/j.semcancer.2006.09.004.
77. Cheng, Q.; Sandalova, T.; Lindqvist, Y.; Arner, E.S. Crystal structure and catalysis of the selenoprotein thioredoxin reductase 1. *J. Biol. Chem.* **2009**, *284*, 3998–4008, doi:10.1074/jbc.M807068200.
78. Sandalova, T.; Zhong, L.; Lindqvist, Y.; Holmgren, A.; Schneider, G. Three-dimensional structure of a mammalian thioredoxin reductase: Implications for mechanism and evolution of a selenocysteine-dependent enzyme. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 9533–9538, doi:10.1073/pnas.171178698.
79. Biterova, E.I.; Turanov, A.A.; Gladyshev, V.N.; Barycki, J.J. Crystal structures of oxidized and reduced mitochondrial thioredoxin reductase provide molecular details of the reaction mechanism. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 15018–15023, doi:10.1073/pnas.0504218102.
80. Fritz-Wolf, K.; Kehr, S.; Stumpf, M.; Rahlfs, S.; Becker, K. Crystal structure of the human thioredoxin reductase-thioredoxin complex. *Nature Commun.* **2011**, *2*, 383, doi:10.1038/ncomms1382.
81. Zhong, L.; Holmgren, A. Essential role of selenium in the catalytic activities of mammalian thioredoxin reductase revealed by characterization of recombinant enzymes with selenocysteine mutations. *J. Biol. Chem.* **2000**, *275*, 18121–18128, doi:10.1074/jbc.M000690200.
82. Kumar, S.; Bjornstedt, M.; Holmgren, A. Selenite is a substrate for calf thymus thioredoxin reductase and thioredoxin and elicits a large non-stoichiometric oxidation of NADPH in the presence of oxygen. *Eur. J. Biochem.* **1992**, *207*, 435–439, doi:10.1111/j.1432-1033.1992.tb17068.x.
83. Lu, J.; Berndt, C.; Holmgren, A. Metabolism of selenium compounds catalyzed by the mammalian selenoprotein thioredoxin reductase. *Biochim. Biophys. Acta* **2009**, *1790*, 1513–1519, doi:10.1016/j.bbagen.2009.04.013.
84. May, J.M.; Mendiratta, S.; Hill, K.E.; Burk, R.F. Reduction of dehydroascorbate to ascorbate by the selenoenzyme thioredoxin reductase. *J. Biol. Chem.* **1997**, *272*, 22607–22610, doi:10.1074/jbc.272.36.22607.

85. Nordberg, J.; Arner, E.S. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. *Free Radic. Biol. Med.* **2001**, *31*, 1287–1312, doi:10.1016/s0891-5849(01)00724-9.
86. Karlenius, T.C.; Tonissen, K.F. Thioredoxin and Cancer: A Role for Thioredoxin in all States of Tumor Oxygenation. *Cancers* **2010**, *2*, 209–232, doi:10.3390/cancers2020209.
87. Arner, E.S.; Holmgren, A. Physiological functions of thioredoxin and thioredoxin reductase. *Eur. J. Biochem.* **2000**, *267*, 6102–6109, doi:10.1046/j.1432-1327.2000.01701.x.
88. Bjorkhem-Bergman, L.; Jonsson-Videsater, K.; Paul, C.; Bjornstedt, M.; Andersson, M. Mammalian thioredoxin reductase alters cytolytic activity of an antibacterial peptide. *Peptides* **2004**, *25*, 1849–1855, doi:10.1016/j.peptides.2004.06.012.
89. Andersson, M.; Holmgren, A.; Spyrou, G. NK-lysin, a disulfide-containing effector peptide of T-lymphocytes, is reduced and inactivated by human thioredoxin reductase. Implication for a protective mechanism against NK-lysin cytotoxicity. *J. Biol. Chem.* **1996**, *271*, 10116–10120.
90. Nalvarte, I.; Damdimopoulos, A.E.; Spyrou, G. Human mitochondrial thioredoxin reductase reduces cytochrome c and confers resistance to complex III inhibition. *Free Radic. Biol. Med.* **2004**, *36*, 1270–1278, doi:10.1016/j.freeradbiomed.2004.02.072.
91. Berggren, M.M.; Mangin, J.F.; Gasdaka, J.R.; Powis, G. Effect of selenium on rat thioredoxin reductase activity: Increase by supranutritional selenium and decrease by selenium deficiency. *Biochem. Pharmacol.* **1999**, *57*, 187–193, doi:10.1016/s0006-2952(98)00283-4.
92. Miller, S.; Walker, S.W.; Arthur, J.R.; Nicol, F.; Pickard, K.; Lewin, M.H.; Howie, A.F.; Beckett, G.J. Selenium protects human endothelial cells from oxidative damage and induces thioredoxin reductase. *Clin. Sci.* **2001**, *100*, 543–550.
93. Khan, I.A.; Luduena, R.F. Possible regulation of the in vitro assembly of bovine brain tubulin by the bovine thioredoxin system. *Biochim. Biophys. Acta* **1991**, *1076*, 289–297, doi:10.1016/0167-4838(91)90280-d.
94. Shinozaki, Y.; Koizumi, S.; Ohno, Y.; Nagao, T.; Inoue, K. Extracellular ATP counteracts the ERK1/2-mediated death-promoting signaling cascades in astrocytes. *Glia* **2006**, *54*, 606–618, doi:10.1002/glia.20408.
95. Hellfritsch, J.; Kirsch, J.; Schneider, M.; Fluege, T.; Wortmann, M.; Frijhoff, J.; Dagnell, M.; Fey, T.; Esposito, I.; Kolbe, P.; et al. Knockout of mitochondrial thioredoxin reductase stabilizes prolyl hydroxylase 2 and inhibits tumor growth and tumor-derived angiogenesis. *Antioxid. Redox Signal.* **2015**, *22*, 938–950, doi:10.1089/ars.2014.5889.
96. Kondo, N.; Nakamura, H.; Masutani, H.; Yodoi, J. Redox regulation of human thioredoxin network. *Antioxid. Redox Signal.* **2006**, *8*, 1881–1890, doi:10.1089/ars.2006.8.1881.
97. Arner, E.S. Focus on mammalian thioredoxin reductases—important selenoproteins with versatile functions. *Biochim. Biophys. Acta* **2009**, *1790*, 495–526, doi:10.1016/j.bbagen.2009.01.014.
98. Holmgren, A.; Lu, J. Thioredoxin and thioredoxin reductase: Current research with special reference to human disease. *Biochem. Biophys. Res. Commun.* **2010**, *396*, 120–124, doi:10.1016/j.bbrc.2010.03.083.
99. Gladyshev, V.N.; Stadtman, T.C.; Hatfield, D.L.; Jeang, K.T. Levels of major selenoproteins in T cells decrease during HIV infection and low molecular mass selenium compounds increase. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 835–839, doi:10.1073/pnas.96.3.835.
100. Wande, Y.; Jie, L.; Aikai, Z.; Yaguo, Z.; Linlin, Z.; Yue, G.; Hang, Z. Berberine alleviates pulmonary hypertension through Trx1 and beta-catenin signaling pathways in pulmonary artery smooth muscle cells. *Exp. Cell. Res.* **2020**, *390*, 111910, doi:10.1016/j.yexcr.2020.111910.
101. Ago, T.; Sadoshima, J. Thioredoxin and ventricular remodeling. *J. Mol. Cell. Cardiol.* **2006**, *41*, 762–773, doi:10.1016/j.yjmcc.2006.08.006.
102. Kwon, J.; Lee, S.R.; Yang, K.S.; Ahn, Y.; Kim, Y.J.; Stadtman, E.R.; Rhee, S.G. Reversible oxidation and inactivation of the tumor suppressor PTEN in cells stimulated with peptide growth factors. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 16419–16424, doi:10.1073/pnas.0407396101.
103. Lee, S.R.; Yang, K.S.; Kwon, J.; Lee, C.; Jeong, W.; Rhee, S.G. Reversible inactivation of the tumor suppressor PTEN by H₂O₂. *J. Biol. Chem.* **2002**, *277*, 20336–20342, doi:10.1074/jbc.M111899200.
104. Meuillet, E.J.; Mahadevan, D.; Berggren, M.; Coon, A.; Powis, G. Thioredoxin-1 binds to the C2 domain of PTEN inhibiting PTEN's lipid phosphatase activity and membrane binding: A mechanism for the functional loss of PTEN's tumor suppressor activity. *Arch. Biochem. Biophys.* **2004**, *429*, 123–133, doi:10.1016/j.abb.2004.04.020.

105. Berggren, M.; Gallegos, A.; Gasdaska, J.R.; Gasdaska, P.Y.; Warneke, J.; Powis, G. Thioredoxin and thioredoxin reductase gene expression in human tumors and cell lines, and the effects of serum stimulation and hypoxia. *Anticancer Res.* **1996**, *16*, 3459–3466.
106. Lincoln, D.T.; Ali Emadi, E.M.; Tonissen, K.F.; Clarke, F.M. The thioredoxin-thioredoxin reductase system: Over-expression in human cancer. *Anticancer Res.* **2003**, *23*, 2425–2433.
107. Shao, L.; Diccianni, M.B.; Tanaka, T.; Gribi, R.; Yu, A.L.; Pullen, J.D.; Camitta, B.M.; Yu, J. Thioredoxin expression in primary T-cell acute lymphoblastic leukemia and its therapeutic implication. *Cancer Res.* **2001**, *61*, 7333–7338.
108. Biaglow, J.E.; Miller, R.A. The thioredoxin reductase/thioredoxin system: Novel redox targets for cancer therapy. *Cancer Biol. Ther.* **2005**, *4*, 6–13.
109. Hashemy, S.I.; Ungerstedt, J.S.; Zahedi Avval, F.; Holmgren, A. Motexafin gadolinium, a tumor-selective drug targeting thioredoxin reductase and ribonucleotide reductase. *J. Biol. Chem.* **2006**, *281*, 10691–10697, doi:10.1074/jbc.M511373200.
110. Smart, D.K.; Ortiz, K.L.; Mattson, D.; Bradbury, C.M.; Bisht, K.S.; Sieck, L.K.; Brechbiel, M.W.; Gius, D. Thioredoxin reductase as a potential molecular target for anticancer agents that induce oxidative stress. *Cancer Res.* **2004**, *64*, 6716–6724, doi:10.1158/0008-5472.can-03-3990.
111. Duan, D.; Zhang, J.; Yao, J.; Liu, Y.; Fang, J. Targeting Thioredoxin Reductase by Parthenolide Contributes to Inducing Apoptosis of HeLa Cells. *J. Biol. Chem.* **2016**, 10.1074/jbc.M115.700591, doi:10.1074/jbc.M115.700591.
112. Zou, P.; Xia, Y.; Chen, W.; Chen, X.; Ying, S.; Feng, Z.; Chen, T.; Ye, Q.; Wang, Z.; Qiu, C., et al. EF24 induces ROS-mediated apoptosis via targeting thioredoxin reductase 1 in gastric cancer cells. *Oncotarget* **2016**, 10.18632/oncotarget.7633, doi:10.18632/oncotarget.7633.
113. Witte, A.B.; Anestel, K.; Jerremalm, E.; Ehrsson, H.; Arner, E.S. Inhibition of thioredoxin reductase but not of glutathione reductase by the major classes of alkylating and platinum-containing anticancer compounds. *Free Radic. Biol. Med.* **2005**, *39*, 696–703, doi:10.1016/j.freeradbiomed.2005.04.025.
114. Gromer, S.; Schirmer, R.H.; Becker, K. The 58 kDa mouse selenoprotein is a BCNU-sensitive thioredoxin reductase. *FEBS Lett.* **1997**, *412*, 318–320.
115. Wang, X.; Zhang, J.; Xu, T. Thioredoxin reductase inactivation as a pivotal mechanism of ifosfamide in cancer therapy. *Eur. J. Pharmacol.* **2008**, *579*, 66–73, doi:10.1016/j.ejphar.2007.10.012.
116. Wang, X.; Zhang, J.; Xu, T. Cyclophosphamide as a potent inhibitor of tumor thioredoxin reductase in vivo. *Toxicol. Appl. Pharmacol.* **2007**, *218*, 88–95, doi:10.1016/j.taap.2006.10.029.
117. Lu, J.; Chew, E.H.; Holmgren, A. Targeting thioredoxin reductase is a basis for cancer therapy by arsenic trioxide. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 12288–12293, doi:10.1073/pnas.0701549104.
118. Fang, J.; Lu, J.; Holmgren, A. Thioredoxin reductase is irreversibly modified by curcumin: A novel molecular mechanism for its anticancer activity. *J. Biol. Chem.* **2005**, *280*, 25284–25290, doi:10.1074/jbc.M414645200.
119. Lu, J.; Papp, L.V.; Fang, J.; Rodriguez-Nieto, S.; Zhivotovsky, B.; Holmgren, A. Inhibition of Mammalian thioredoxin reductase by some flavonoids: Implications for myricetin and quercetin anticancer activity. *Cancer Res.* **2006**, *66*, 4410–4418, doi:10.1158/0008-5472.can-05-3310.
120. Xia, L.; Nordman, T.; Olsson, J.M.; Damdimopoulos, A.; Bjorkhem-Bergman, L.; Nalvarte, I.; Eriksson, L.C.; Arner, E.S.; Spyrou, G.; Bjornstedt, M. The mammalian cytosolic selenoenzyme thioredoxin reductase reduces ubiquinone. A novel mechanism for defense against oxidative stress. *J. Biol. Chem.* **2003**, *278*, 2141–2146, doi:10.1074/jbc.M210456200.
121. Nordberg, J.; Zhong, L.; Holmgren, A.; Arner, E.S. Mammalian thioredoxin reductase is irreversibly inhibited by dinitrohalobenzenes by alkylation of both the redox active selenocysteine and its neighboring cysteine residue. *J. Biol. Chem.* **1998**, *273*, 10835–10842.
122. Martinez, Y.; Li, X.; Liu, G.; Bin, P.; Yan, W.; Mas, D.; Valdivie, M.; Hu, C.A.; Ren, W.; Yin, Y. The role of methionine on metabolism, oxidative stress, and diseases. *Amino. Acids.* **2017**, *49*, 2091–2098, doi:10.1007/s00726-017-2494-2.
123. Bin, P.; Huang, R.; Zhou, X. Oxidation Resistance of the Sulfur Amino Acids: Methionine and Cysteine. *Biomed. Res. Int.* **2017**, *2017*, 9584932, doi:10.1155/2017/9584932.
124. Jiang, B.; Moskovitz, J. The Functions of the Mammalian Methionine Sulfoxide Reductase System and Related Diseases. *Antioxidants* **2018**, *7*, doi:10.3390/antiox7090122.

125. Hansel, A.; Heinemann, S.H.; Hoshi, T. Heterogeneity and function of mammalian MSRs: Enzymes for repair, protection and regulation. *J. Nutr. Biochem.* **2005**, *1703*, 239–247, doi:10.1016/j.bbapap.2004.09.010.
126. Cao, L.; Zhang, L.; Zeng, H.; Wu, R.T.; Wu, T.L.; Cheng, W.H. Analyses of Selenotranscriptomes and Selenium Concentrations in Response to Dietary Selenium Deficiency and Age Reveal Common and Distinct Patterns by Tissue and Sex in Telomere-Dysfunctional Mice. *J. Nutr.* **2017**, *147*, 1858–1866, doi:10.3945/jn.117.247775.
127. Novoselov, S.V.; Kim, H.-Y.; Hua, D.; Lee, B.C.; Astle, C.M.; Harrison, D.E.; Friguet, B.; Moustafa, M.E.; Carlson, B.A.; Hatfield, D.L. Regulation of selenoproteins and methionine sulfoxide reductases A and B1 by age, calorie restriction, and dietary selenium in mice. *Antioxid. Redox Signal.* **2010**, *12*, 829–838.
128. Lourenço dos Santos, S.; Petropoulos, I.; Friguet, B. The Oxidized Protein Repair Enzymes Methionine Sulfoxide Reductases and Their Roles in Protecting against Oxidative Stress, in Ageing and in Regulating Protein Function. *Antioxidants* **2018**, *7*, doi:10.3390/antiox7120191.
129. Kaya, A.; Lee, B.C.; Gladyshev, V.N. Regulation of protein function by reversible methionine oxidation and the role of selenoprotein MsrB1. *Antioxid. Redox Signal.* **2015**, *23*, 814–822, doi:10.1089/ars.2015.6385.
130. Hung, R.J.; Spaeth, C.S.; Yesilyurt, H.G.; Terman, J.R. SelR reverses Mical-mediated oxidation of actin to regulate F-actin dynamics. *Nat. Cell. Biol.* **2013**, *15*, 1445–1454, doi:10.1038/ncb2871.
131. Kawabata Galbraith, K.; Kengaku, M. Multiple roles of the actin and microtubule-regulating formins in the developing brain. *Neurosci. Res.* **2019**, *138*, 59–69, doi:10.1016/j.neures.2018.09.008.
132. Tang, D.D. The Dynamic Actin Cytoskeleton in Smooth Muscle. *Adv. Pharmacol.* **2018**, *81*, 1–38, doi:10.1016/bs.apha.2017.06.001.
133. Gallop, J.L. Filopodia and their links with membrane traffic and cell adhesion. *Semin. Cell. Dev. Biol.* **2019**, *10.1016/j.semcd.2019.11.017*, doi:10.1016/j.semcd.2019.11.017.
134. LEINWEBER, B.D.; LEAVIS, P.C.; GRABAREK, Z.; WANG, C.-L.A.; MORGAN, K.G. Extracellular regulated kinase (ERK) interaction with actin and the calponin homology (CH) domain of actin-binding proteins. *Biochem. J.* **1999**, *344*, 117–123, doi:10.1042/bj3440117.
135. Fomenko, D.E.; Novoselov, S.V.; Natarajan, S.K.; Lee, B.C.; Koc, A.; Carlson, B.A.; Lee, T.H.; Kim, H.Y.; Hatfield, D.L.; Gladyshev, V.N. MsrB1 (methionine-R-sulfoxide reductase 1) knock-out mice: Roles of MsrB1 in redox regulation and identification of a novel selenoprotein form. *J. Biol. Chem.* **2009**, *284*, 5986–5993, doi:10.1074/jbc.M805770200.
136. Kim, K.Y.; Kwak, G.H.; Singh, M.P.; Gladyshev, V.N.; Kim, H.Y. Selenoprotein MsrB1 deficiency exacerbates acetaminophen-induced hepatotoxicity via increased oxidative damage. *Arch. Biochem. Biophys.* **2017**, *634*, 69–75, doi:10.1016/j.abb.2017.09.020.
137. Jia, Y.; Zhou, J.; Liu, H.; Huang, K. Effect of methionine sulfoxide reductase B1 (SelR) gene silencing on peroxynitrite-induced F-actin disruption in human lens epithelial cells. *Biochem. Biophys. Res. Commun.* **2014**, *443*, 876–881, doi:10.1016/j.bbrc.2013.12.055.
138. Dai, J.; Liu, H.; Zhou, J.; Huang, K. Selenoprotein R Protects Human Lens Epithelial Cells against D-Galactose-Induced Apoptosis by Regulating Oxidative Stress and Endoplasmic Reticulum Stress. *Int. J. Mol. Sci.* **2016**, *17*, 231, doi:10.3390/ijms17020231.
139. Lee, B.C.; Lee, S.G.; Choo, M.K.; Kim, J.H.; Lee, H.M.; Kim, S.; Fomenko, D.E.; Kim, H.Y.; Park, J.M.; Gladyshev, V.N. Selenoprotein MsrB1 promotes anti-inflammatory cytokine gene expression in macrophages and controls immune response in vivo. *Sci. Rep.* **2017**, *7*, 5119, doi:10.1038/s41598-017-05230-2.
140. Achilli, C.; Ciana, A.; Minetti, G. Brain, immune system and selenium: A starting point for a new diagnostic marker for Alzheimer's disease? *Oxid. Med. Cell. Longev.* **2018**, *138*, 223–226, doi:10.1177/1757913918778707.
141. He, Q.; Li, H.; Meng, F.; Sun, X.; Feng, X.; Chen, J.; Li, L.; Liu, J. Methionine Sulfoxide Reductase B1 Regulates Hepatocellular Carcinoma Cell Proliferation and Invasion via the Mitogen-Activated Protein Kinase Pathway and Epithelial-Mesenchymal Transition. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 5287971, doi:10.1155/2018/5287971.
142. Li, H.; He, Q.; Meng, F.; Feng, X.; Chen, J.; Li, L.; Liu, J. Methionine sulfoxide reductase B1 regulates proliferation and invasion by affecting mitogen-activated protein kinase pathway and epithelial-mesenchymal transition in u2os cells. *Biochem. Biophys. Res. Commun.* **2018**, *496*, 806–813, doi:10.1016/j.bbrc.2018.01.151.
143. Han, S.J.; Lee, B.C.; Yim, S.H.; Gladyshev, V.N.; Lee, S.R. Characterization of mammalian selenoprotein o: A redox-active mitochondrial protein. *PLoS One* **2014**, *9*, e95518, doi:10.1371/journal.pone.0095518.

144. Sreelatha, A.; Yee, S.S.; Lopez, V.A.; Park, B.C.; Kinch, L.N.; Pilch, S.; Servage, K.A.; Zhang, J.; Jiou, J.; Karasiewicz-Urbanska, M., et al. Protein AMPylation by an Evolutionarily Conserved Pseudokinase. *Cell* **2018**, *175*, 809–821.e819, doi:10.1016/j.cell.2018.08.046.
145. Dudkiewicz, M.; Szczepinska, T.; Grynberg, M.; Pawlowski, K. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. *PLoS One* **2012**, *7*, e32138, doi:10.1371/journal.pone.0032138.
146. Yan, J.; Fei, Y.; Han, Y.; Lu, S. Selenoprotein O deficiencies suppress chondrogenic differentiation of ATDC5 cells. *Cell Biol. Int.* **2016**, 10.1002/cbin.10644, doi:10.1002/cbin.10644.
147. Ye, Y.; Fu, F.; Li, X.; Yang, J.; Liu, H. Selenoprotein S Is Highly Expressed in the Blood Vessels and Prevents Vascular Smooth Muscle Cells From Apoptosis. *J. Cell. Biochem.* **2016**, *117*, 106–117, doi:10.1002/jcb.25254.
148. Smith, M.H.; Ploegh, H.L.; Weissman, J.S. Road to ruin: Targeting proteins for degradation in the endoplasmic reticulum. *Science* **2011**, *334*, 1086–1090, doi:10.1126/science.1209235.
149. Liu, J.; Li, F.; Rozovsky, S. The intrinsically disordered membrane protein selenoprotein S is a reductase in vitro. *Biochemistry* **2013**, *52*, 3051–3061, doi:10.1021/bi4001358.
150. Zhang, N.; Jing, W.; Cheng, J.; Cui, W.; Mu, Y.; Li, K.; Lei, X. Molecular characterization and NF-kappaB-regulated transcription of selenoprotein S from the Bama mini-pig. *Mol. Biol. Rep.* **2011**, *38*, 4281–4286, doi:10.1007/s11033-010-0551-y.
151. Fradejas, N.; Serrano-Perez Mdel, C.; Tranque, P.; Calvo, S. Selenoprotein S expression in reactive astrocytes following brain injury. *Glia* **2011**, *59*, 959–972, doi:10.1002/glia.21168.
152. Curran, J.E.; Jowett, J.B.; Elliott, K.S.; Gao, Y.; Gluschenko, K.; Wang, J.; Abel Azim, D.M.; Cai, G.; Mahaney, M.C.; Comuzzie, A.G., et al. Genetic variation in selenoprotein S influences inflammatory response. *Nature Genet.* **2005**, *37*, 1234–1241, doi:10.1038/ng1655.
153. Du, S.; Liu, H.; Huang, K. Influence of SelS gene silence on beta-Mercaptoethanol-mediated endoplasmic reticulum stress and cell apoptosis in HepG2 cells. *Biochim. Biophys. Acta* **2010**, *1800*, 511–517, doi:10.1016/j.bbagen.2010.01.005.
154. Moustafa, M.E.; Antar, H.A. A bioinformatics approach to characterize mammalian selenoprotein T. *Biochem. Genet.* **2012**, *50*, 736–747, doi:10.1007/s10528-012-9516-2.
155. Sengupta, A.; Carlson, B.A.; Labunskyy, V.M.; Gladyshev, V.N.; Hatfield, D.L. Selenoprotein T deficiency alters cell adhesion and elevates selenoprotein W expression in murine fibroblast cells. *Biochem. Cell Biol.* **2009**, *87*, 953–961, doi:10.1139/o09-064.
156. Grumolato, L.; Ghzili, H.; Montero-Hadjadje, M.; Gasman, S.; Lesage, J.; Tanguy, Y.; Galas, L.; Ait-Ali, D.; Leprince, J.; Guerineau, N.C., et al. Selenoprotein T is a PACAP-regulated gene involved in intracellular Ca²⁺ mobilization and neuroendocrine secretion. *FASEB J.* **2008**, *22*, 1756–1768, doi:10.1096/fj.06-075820.
157. Boukhzar, L.; Hamieh, A.; Cartier, D.; Tanguy, Y.; Alsharif, I.; Castex, M.; Arabo, A.; Hajji, S.E.; Bonnet, J.J.; Errami, M., et al. Selenoprotein T Exerts an Essential Oxidoreductase Activity That Protects Dopaminergic Neurons in Mouse Models of Parkinson's Disease. *Antioxid. Redox Signal.* **2016**, *24*, 557–574, doi:10.1089/ars.2015.6478.
158. Petit, N.; Lescure, A.; Rederstorff, M.; Krol, A.; Moghadaszadeh, B.; Wewer, U.M.; Guicheney, P. Selenoprotein N: An endoplasmic reticulum glycoprotein with an early developmental expression pattern. *Hum. Mol. Genet.* **2003**, *12*, 1045–1053.
159. Lescure, A.; Gautheret, D.; Carbon, P.; Krol, A. Novel selenoproteins identified in silico and in vivo by using a conserved RNA structural motif. *J. Biol. Chem.* **1999**, *274*, 38147–38154.
160. Arbogast, S.; Beuvin, M.; Frayssé, B.; Zhou, H.; Muntoni, F.; Ferreira, A. Oxidative stress in SEPNI-related myopathy: From pathophysiology to treatment. *Ann. Neurol.* **2009**, *65*, 677–686, doi:10.1002/ana.21644.

