Essential trace element selenium and redox regulation: its metabolism, physiological function, and related diseases

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Graphical abstract

Abstract

The essential trace element selenium plays a significant role in redox homeostasis in the human body. Selenium is very reactive and has a potent toxicity; however, the living body cleverly utilizes its reactivity for redox reactions. The biological function of selenium is mainly mediated by selenoproteins, which contain selenocysteine, a cysteine analogue that possesses selenium instead of sulphur. Twenty-five types of human selenoproteins have been identified, including glutathione peroxidase (GPX; for the reduction of hydrogen peroxide and lipid hydroperoxide) and thioredoxin reductase (for redox regulation). Selenoprotein P (SELENOP), which is a major selenoprotein in the plasma, is mainly synthesized in the liver and secreted into the plasma. As a multifunctional protein with selenium-transporting activity, GPX-like activity, and metal-binding properties, SELENOP plays a vital role in selenium metabolism and redox regulation. This review focuses on the relationship between selenium metabolism and redox regulation, particularly on the physiological role of selenoproteins and the pathophysiological implications of its disorder. Furthermore, the significant roles of selenium in infectious diseases and its utility for phylaxis are discussed.

Keywords
- selenoprotein
- selenocysteine
- oxidative stress
- type 2 diabetes
- infectious disease

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Introduction

More than 200 years have passed since the discovery of the essential trace element selenium. Selenium is a type of chalcogen in group 16 of the periodic table with a large electron orbital, which facilitates the emission and reception of electrons. The toxicity of selenium and its properties as an essential trace element have been clarified (Rayman 2012, Labunskyy et al. 2014, Saito 2021b). Selenium-containing proteins are called selenoproteins, which play a significant role in the removal of reactive oxygen species (ROS) and redox regulation. Selenoproteins are also a key factor in the antioxident system (Conrad et al. 2018, Dagnell et al. 2018). Although selenium is an essential element, it is highly toxic and has a particularly narrow appropriate range between deficiency and excess. This mini review focused on the role of selenoproteins in redox regulation, particularly on the regulation of selenium metabolism by selenoprotein P (SELENOP). Furthermore, the relationship between the physiological functions of selenoproteins and diseases, especially their involvement in the redox regulation, has been described. Finally, the importance of selenium in the protection against infection is described and the potential of selenium-containing compounds as pharmaceuticals is discussed.

Properties of the essential trace element selenium

Selenium was discovered in 1817 by the Swedish chemist Jöns Jacob Berzelius. It is an element that was named after the moon goddess ‘Selene’ because of its similarity to tellurium, which means the Earth. Selenium has a larger electron orbit and is more reactive than oxygen and sulphur, which belong to group 16 of the periodic table. Toxicity was first identified as the action of selenium on the living body (Barceloux 1999, Anan et al. 2015, Hadrup & Ravn-Haren 2020). Nausea, diarrhoea, headache, and neuropathy are symptoms of excessive selenium. A pathology associated with selenium deficiency was later identified as Keshan disease, which is associated with severe cardiomyopathy caused by selenium deficiency (Fairweather-Tait et al. 2011, Zhou et al. 2018). Keshan disease is an endemic disease in the Keshan region of China, where the selenium concentration in soil is low. In addition, the increased pathogenicity of coxsackievirus associated with selenium deficiency is deeply involved in the development of cardiomyopathy (Levander & Beck 1997, Cermelli et al. 2002). Associations with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported recently (see chapter 6), suggesting the importance of selenium in the protection against viral infection. In addition, the incidence of arteriosclerosis and cancer (e.g. prostate cancer) increases with the decrease in blood selenium concentration in areas where the concentration of selenium in soil is low (Burk 2002, Avery & Hoffmann 2018). These disorders caused by selenium deficiency have been improved by selenium supplementation, and the necessity of selenium has become widely recognized. Selenium is known as an element with a particularly narrow appropriate range between deficiency and excess compared with other elements and nutrients. In contrast, recent epidemiological studies have shown that the risk of lifestyle-related diseases, such as type 2 diabetes, increases with the elevation in the blood levels of selenium (Rayman & Stranges 2013, Rees et al. 2013, Vinceti et al. 2022). As a selenium-containing protein in the plasma, SELENOP is significantly involved in the onset and progression of type 2 diabetes (Misu et al. 2010, Saito 2020, Takamura 2020). The risk of disability and disease associated with selenium excess as well as deficiency clearly reflects the characteristics of this element.

Role of selenoproteins in the antioxidative system and redox regulation

Selenoproteins contain selenium in the form of selenocysteine (Sec), which is an amino acid in which the sulphur in cysteine is replaced by selenium and plays an essential physiological role (Lee et al. 1989, Berry et al. 1991, Flohe 2009). Twenty-five types of selenoproteins have been identified in humans, which are related to several biological processes, including the antioxidant system and redox regulation (Table 1) (Kryukov et al. 2003, Hatfield et al. 2014). The functions of representative selenoproteins are given below.

Glutathione peroxidase (GPX), the first selenoprotein to be identified, is an enzyme that reduces and detoxifies hydroperoxides in the presence of glutathione (GSH) (Fig. 1A) (Flohe 2009, Brigelius-Flohe & Maiorino 2013). Sec forms the active site of GPX where the selenol (SeH) residue of Sec directly reacts with peroxides, such as hydrogen peroxide, and is then oxidized to SeOH while hydrogen peroxide is reduced to water. The SeOH is then reduced by GSH, returns to the SeH form, and reacts with the next peroxide in a ping-pong mechanism. Although six GPXs have been identified, GPX5 does not contain...
selenium and its antioxidative activity is unclear. GPX1 to GPX4 have been investigated extensively (Takahashi et al. 1990, Maiorino 2018, Saito 2021). GPX1, GPX2, and GPX3 mainly reduce hydrogen peroxide as a substrate, whereas GPX4 has a unique substrate specificity and directly reduces phospholipid hydroperoxide (PL-OOH) (Thomas et al. 1990, Takebe et al. 2002, Ursini et al. 2022). GPX4 was identified as a regulator of ferroptosis, a type of nonapoptotic cell death that depends on lipid peroxidation and iron metabolism (Dixon et al. 2012, Stockwell et al. 2017, Ursini & Maiorino 2020). Radical-scavenging lipophilic antioxidants, such as vitamin E and coenzyme Q10, and iron chelators, such as deferoxamine, inhibit ferroptosis (Conrad et al. 2018, Saito 2021). In turn, ferroptosis inducers, such as RSL3 and erastin, have inhibitory effects on GPX4 and the cystine transporter xCT, to maintain cellular GSH, underscoring the significance of the GSH-GPX4 axis in this form of cell death (Dixon et al. 2012, Stockwell et al. 2017, Ursini & Maiorino 2020).

**Table 1** Function of selenoproteins.

| Selenoprotein | Abbreviation | Character and function |
|---------------|--------------|-----------------------|
| Glutathione peroxidase 1 | GPx1, GPX1 | KO mouse shows highly sensitive to oxidative stress |
| Glutathione peroxidase 2 | GPx2, GPX2 | Protein levels are maintained under selenium deficiency |
| Glutathione peroxidase 3 | GPx3, GPX3 | Synthesized in the kidney and secreted into plasma |
| Glutathione peroxidase 4 | GPx4, GPX4 | Cytoplasm/mitochondria/nucleolus-specific isoforms are present KO mouse is embryonic lethal |
| Glutathione peroxidase 6 | GPx6, GPX6 | Exists in olfactory |
| Iodothyronine deodinase 1 | D11, D1, D101 | Activates thyroid hormone |
| Iodothyronine deodinase 2 | D12, D2, D102 | Tissue-specific activation of thyroid hormone |
| Iodothyronine deodinase 3 | D13, D3, D103 | Tissue-specific inactivation of thyroid hormone |
| Thioredoxin reductase 1 | TrxR1, Trx1, TXNRD1 | KO mouse is embryonic lethal |
| Thioredoxin reductase 2 | TrxR2, Trx3, TXNRD2 | Mitochondria-specific Txnrd2 KO is embryonic lethal |
| Thioredoxin reductase 3 | TrxR3, Trx2, TXNRD3 | Testis-specific Glutaredoxin activity |
| Selenophosphate synthetase 2 | SPS2, SEPHS2 | Selenophosphate synthesis |
| Selenoprotein P | SeP, SELENOP, SeIP, SEPP1 | Selenium transport and GPx4-like activity |
| Methionine-R-sulphide reductase | MsrBl, Selr, SeIX, MSRB1 | KO mice have neuropathy and spermatogenesis failure |
| Selenoprotein F | Sep15, SEF15, SELENOF, SelF | Reduction of oxidized methionine |
| Selenoprotein H | SELENOH, SelH | Involved in protein folding in the endoplasmic reticulum |
| Selenoprotein I | SELENOI, SelI, SEPI, EPTI | Interaction with UGTR |
| Selenoprotein K | SELENOK, SelK | Antioxidative function |
| Selenoprotein M | SELENOM, SelM, SEPM | Synthesis of phospholipid (PE) |
| Selenoprotein N | SELENON, SelN, SEPNI | Involved in Ca2+ regulation via the endoplasmic reticulum |
| Selenoprotein 0 | SELENOO, SelO | Exists in the endoplasmic reticulum; necessary for muscle formation |
| Selenoprotein S | SELENOs, SelS, SEPSI, VIMP | Exists in the mitochondria |
| Selenoprotein T | SELENOT, SelT | Exists in the endoplasmic reticulum |
| Selenoprotein V | SELENOV, SelV | Exists in tests |
| Selenoprotein W | SELENOW, SelW, SEPW | Antioxidative function |

**Figure 1** Function of representative selenoproteins. (A) Glutathione peroxidase (GPX) reduces several hydroperoxides (hydrogen peroxide, H2O2; phospholipid hydroperoxide, PL-OOH) by using glutathione (GSH). (B) Thioredoxin (TRN) reductase (TRNRD) reduces oxidized TRN by using NADPH. (C) Domain structure and function of selenoprotein P.
et al. 2012, Friedmann Angeli et al. 2014). GPx4 KO mice exhibit embryonic lethality, and the reducing activity of PL-OOH has been shown to be essential for survival and cell proliferation (Imai et al. 2009, Ingold et al. 2018).

Thioredoxin reductase (TRNRD) is a selenoprotein that is responsible for redox control (Fig. 1B). TRNRD is an NADPH-dependent flavin enzyme that consumes NADPH and reduces TRN, and its active site is formed by Sec (Lu & Holmgren 2014, Dagnell et al. 2018). TRNRD1 is present in the cytoplasm and nucleus, whereas TRNRD2 is expressed in mitochondria. TRNRD3 is highly expressed in the testis. TRN has a CxxC motif (C: Cys; x: others), reduces protein disulphides and forms disulphide bonds with itself, to become oxidized TRN (Arner & Holmgren 2000, Lu & Holmgren 2014). TRN interacts with various molecules, such as peroxidase, ribonucleotide reductase, and the signalling molecule ASK1, and regulates their activity through redox reactions (Fujino et al. 2007). KO mice for either TRN or TRNRD exhibit embryonic lethality, thus demonstrating the importance of the TRN–TRNRD system.

Iodothyronine deiodinase (DI), which activates or inactivates the thyroid hormone, is also a selenoprotein that is represented by three types, that is, DI1, DI2, and DI3, which have different substrate characteristics and intracellular localizations (Kohrle 2000, 2013, Labunskyy et al. 2014). The physiological function of DI indicates that selenoproteins are involved not only in the antioxidant system but also in growth/development and energy metabolism.

As the major selenium-containing protein, SELENOP accounts for 50% of human plasma selenium, with the ‘P’ standing for ‘plasma’ (Fig. 1C). SELENOP is synthesized mainly in the liver and secreted into plasma (Saito & Takahashi 2002, Burk & Hill 2015). SELENOP has ten Sec residues in the polypeptide chain, which makes SELENOP multifunctional (Fig. 1C); SELENOP has GPx4-like reducing activity for PL-OOH and a Sec residue on the N-terminal side is the active site of this enzyme, while SELENOP has a selenium-transporting activity that efficiently delivers selenium to the cells, in which abundant nine Sec residues are inserted into the polypeptide chain (Fig. 2). The physiological function of DI indicates that selenoproteins are involved not only in the antioxidant system but also in growth/development and energy metabolism.

Selenium metabolism and selenoprotein P synthesis

Selenium metabolism is strictly regulated in our body, and Sec contained in selenoprotein is uniquely synthesized on tRNA using inorganic selenium (Fig. 2). Sec is encoded by one of the stop codons UGA and is also called the 21st amino acid that is translated (Berry et al. 1991, Hatfield et al. 2014). Serine binds to tRNA^sec, which has the anticodon of UGA, and the hydroxyl group (-OH) of Ser undergoes phosphorylation (Fig. 2, lower scheme). Selenophosphate synthetase 2 (SPS2) produces selenophosphate (H₄SePO₄) from inorganic selenium and ATP. SPS2 is a selenoprotein and is thought to be involved in the self-regulation of the Sec synthesis system. By the action of Sec synthase, selenol group (-SeH) is generated from H₄SePO₄ and phosphorylated Ser-tRNA^sec, and the synthesis of Sec on tRNA is completed (Mihara et al. 2000). The translation mechanism by which Sec-tRNA^sec is inserted into the polypeptide chain is shown in Fig. 3. For the translation of Sec, Sec-insertion sequence (SECIS), a stable loop structure in the 3′-UTR (3′UTR) of mRNA, is indispensable (Fig. 3A). SECIS-binding protein 2 (SBP2), eucaryote elongation factor for Sec translation (eEFSec), and Sec-tRNA^sec form a complex in SECIS (Fig. 3B). When the translation reaches UGA, Sec-tRNA^sec is supplied from the SECIS complex (Copeland et al. 2000). Then, translation continues, and translation stops at a stop codon other than UGA. SECIS structure is found in 3′UTR of all selenoprotein mRNAs and is important for the stability of mRNA (Seydali & Berry et al. 2012).
Selenoprotein mRNA without SBP2 and Sec-tRNA<sub>Sec</sub> is degraded by nonsense-mediated mRNA decay (NMD) because of the presence of the stop codon UGA in the open reading frame (ORF). Under selenium-deficient condition with the decrease of Sec-tRNA<sub>Sec</sub>, UPF1, which is essential for NMD, binds to selenoprotein mRNA and promotes its degradation (Seyedali & Berry 2014). The affinity between SECIS and SBP2 is not uniform and is different between selenoproteins (Low et al. 2000). SECIS of TRNRD and GPX4 have a strong affinity for SBP2, while that of GPX1 has a low affinity. Under selenium-deficient condition with low Sec-tRNA<sub>Sec</sub>, the biosynthesis of GPX1 is suppressed and instead selenium is preferentially used for the biosynthesis of TRNRD and GPX4. It is interesting to note that SELENOP is the only selenoprotein that has two SECISs in 3'UTR of its mRNA. This machinery is understood as a system...

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**Figure 2**
Synthetic pathway of selenocysteine (Sec) from selenium-containing amino acids. SeMet is converted to Sec by Met metabolizing enzymes (#1–#5) indistinguishable from sulphur. CBS (#4) and CSE (#5) are also known as cysteine persulphide-producing enzymes. Inorganic selenium is generated from Sec by Sec lyase and is converted to selenophosphate by SPS2.

By the action of SecS, Sec is produced on tRNA from selenophosphate and phosphorylated Ser-tRNA<sub>Sec</sub>.

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**Figure 3**
Translation mechanism of selenoprotein. (A) Structure of selenoprotein mRNA. (B) Mechanism of selenocysteine insertion. eEFsec, eukaryotic elongation factor for Sec translation; elf4a3, eukaryotic initiation factor; SBP2, SECIS-binding protein 2; RPL30, ribosomal protein L30.
that efficiently utilizes limited selenium for important selenoprotein synthesis.

Selenium for the Sec synthesis is from foods. After being digested, selenium is absorbed from the digestive tract and enters the synthetic pathway of selenoprotein, but the metabolic pathway depends on the chemical form of selenium. In the case of Sec in the food, the inorganic selenium produced by Sec lyase enters the Sec synthesis system (Fig. 2, upper scheme) (Mihara et al. 2000). On the other hand, selenomethionine (SeMet), a methionine homolog containing selenium instead of sulphur, is one of the main selenium sources absorbed in the body (Schrauzer 2000). Absorbed SeMet is metabolized indistinguishable from methionine, and a part of it is directly incorporated into proteins. SeMet is occasionally converted to Sec by the methionine metabolic enzyme and then enters the Sec synthesis system through the action of Sec lyase (Fig. 2, upper scheme).

The liver plays a central role in selenium metabolism (Fig. 4). Of the selenium absorbed in the liver, the selenium used for the biosynthesis of SELENOP is secreted into the blood and used for the synthesis of selenoprotein in each organ (Hill et al. 2012, Saito 2021b). Absorbed SeMet is randomly distributed to blood and tissues. In addition, there are other routes that enter the systemic circulation as small molecules and routes that are excreted into urine as selenosugar and trimethylselenonium (Kobayashi et al. 2002).

SELENOP expression is regulated by several factors (Fig. 4) (Saito 2020a). Selenium deficiency reduces SELENOP expression through a decrease in Sec-tRNA^Sec. The expression of SELENOP is also regulated by transcription; the levels of SELENOP mRNA are lowered by cytokines such as interleukin 6, tumour necrosis factor alpha, interferon gamma, and transforming growth factor beta, as well as by insulin. On the other hand, SELENOP mRNA levels are increased under hyperglycaemia and high fat (Takamura 2020). The nuclear translocation of the transcription factor FoxO3a and the expression of SELENOP increase by the decrease of AMP-activated protein kinase (AMPK) activity that is associated with hyperglycaemia (Misu et al. 2010). Transcriptional regulation of SELENOP via FoxO1, PGC1α, and HNF4α has also been known, and selenoprotein expression is closely related to glucose and energy metabolism (Saito 2020a). Recently, long ncRNA (IncRNA) that inhibits selenoprotein P translation, L-IST, has been identified (Mita et al. 2021). This IncRNA interacted with the SELENOP mRNA and inhibited its binding to the SBP2, resulting in the decrease of ribosome binding.

Selenoproteins related diseases and redox regulation

Disorders due to selenium deficiency or excess have been recognized for a long time, but in recent years, a relationship between changes in selenoprotein expression and lifestyle-related diseases has been found (Rayman & Stranges 2013, Rees et al. 2013, Vincetti et al. 2022). In type 2 diabetes patients, levels of SELENOP mRNA in the liver and blood SELENOP protein were increased (Misu et al. 2010). A positive correlation was observed between the blood SELENOP levels and the blood glucose levels after glucose loading and the fasting blood glucose, indicating the relationship between the increase in SELNO and the deterioration of glucose metabolism. Since insulin resistance increases in mice administered with SELENOP corresponding to the increased amount in diabetic patients, excess SELENOP is considered to act as a ‘bad guy’ involved in the onset and progression of diabetes (Misu et al. 2010). It was also clarified that excess SELENOP impairs the function of pancreatic β-cells and reduces insulin secretory capacity (Mita et al. 2017). Further, excess SELENOP increases exercise resistance and impairs cold-induced thermogenesis in brown fat, indicating systematic deteriorating effects on glucose and energy metabolism (Misu et al. 2017, Oo et al. 2022). Insulin resistance and insulin secretion are improved by the administration of a neutralizing antibody that suppresses the intracellular uptake of SELENOP in diabetes model mice, suggesting that excess SELENOP is a good target of lifestyle-related diseases (Mita et al. 2017). Furthermore, the increased expression of SELENOP is involved in the formation of lesions in pulmonary hypertension, suggesting that the abnormal expression control of SELENOP is involved in various diseases (Kikuchi et al. 2018).

Various relationships have been shown between cancer and selenoproteins (Rayman 2012, Hatfield et al. 2014). In ‘initiation,’ irreversible changes of genomic information during the carcinogenesis, antioxidant systems, and selenoproteins act to protect against ROS-induced DNA damage. On the other hand, in ‘promotion,’ in which cells with DNA damage start to proliferate, and in ‘progression,’ in which new properties as cancer cells are acquired and malignancy increases, the enhancement of selenoprotein expression promotes the growth of cancer cells. GPX4 and TRNRD1 have been identified as a target for anticancer agents (Dagnell et al. 2018, Stockwell et al. 2017). GPX4 inhibitors try to use for the induction of ferroptosis for cancer cells. TRNRD1 is involved in DNA repair, has
the effect of activating the tumor suppressor p53, and is thought to act on the suppression of carcinogenesis. On the other hand, TRNRD1 is highly expressed in cancer cells, and inactivation of TRNRD1 is effective in suppressing the growth of cancer cells. TRNRD1 is considered to be involved in the onset and progression of cancer in terms of both merits and demerits.

**Selenium and infectious disease**

The significance of selenium levels in the defence against infection is strongly recognized, and the fact that Keshan disease, which was first reported as selenium deficiency, is associated with the virulence of the Coxsackie virus reflects its consequence (Levander et al. 1997, Cermelli et al. 2002). In human immunodeficiency virus patients, the decreases in survival rate with the decline in selenium level have been known, and the significance of the selenium levels against several infectious diseases, such as influenza virus, hepatitis virus, and West Nile virus, has been shown (Verma et al. 2008, Himoto et al. 2011, Yu et al. 2011, Rayman 2012). Furthermore, the relevance of the coronavirus disease 2019 (COVID-19) has been actively investigated, and the correlation between selenium levels and the risk of aggravation or the cure rate in the infection of SARS-CoV-2 has been reported (Zhang et al. 2020). Particularly, CL\textsuperscript{pro} is an attractive drug discovery target because it is involved in the maturation of multiple viral proteins, including spike protein. Approximately 10,000 compounds have been screened to identify the inhibitors of CL\textsuperscript{pro}, and ‘ebselen’ has been identified as a compound that inhibits CL\textsuperscript{pro} and suppresses virus growth (Jin et al. 2020).

Ebselen is a selenium-containing compound developed as a GPX mimic that removes ROS by using a GSH as a reductant (Sies & Parnham 2020). It was investigated up to Phase III as a brain metabolism improving drug, but its development was abandoned due to hepatotoxicity of long-term administration and insufficient efficacy compared to existing drugs. Since the inhibitory effect of ebselen on cysteine proteases, such as papain, has been known, it is not strange that ebselen inhibits CL\textsuperscript{pro} activity (Sies & Parnham 2020). The inhibitory effect of ebselen on the *Mycobacterium tuberculosis*-derived transpeptidase with reactive cysteine and the formation of selenosulphide (Se–S) bonds with active cysteine have also been reported (de Munnik et al. 2019). In addition, the inhibitory effect of...
ebselen derivatives on CD20 and the formation of a covalent bond with reactive cysteine were reported (Menendez et al. 2020). Furthermore, ebselen is expected to have an inhibitory effect on cytokine storms by reducing ROS and might be an effective therapeutic drug for the COVID-19 (Sies & Parham 2020). In the future, it is necessary to verify the effects of SARS-CoV-2 in vivo, but we can expect the development of selenium-containing compounds as therapeutic agents for a wide range of infectious diseases.

**Conclusion**

Selenium is a unique element for living organisms and has properties that are acting as a poison, nutrient, and medicine. Alteration of selenoproteins, which are responsible for redox regulation, has been discussed mainly on selenium intake and its hierarchy, but the involvement of expression changes in various diseases has been clarified, and now selenoproteins have become therapeutic targets. In drug discovery targeting selenoproteins, how to control selenoproteins, which play an essential role, will be the key, and understanding of lesions at the molecular level will be indispensable. In addition, it is expected to develop highly safe selenium-containing compounds with low toxicity in the development of pharmaceuticals that utilize the characteristics of selenium, especially in the provision against infectious diseases.

**Declaration of interest**

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