

Review

Selenium and Selenoproteins in Health

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Abstract: Selenium is a trace mineral that is essential for health. After being obtained from food and taken up by the liver, selenium performs various physiological functions in the body in the form of selenoproteins, which are best known for their redox activity and anti-inflammatory properties. Selenium stimulates the activation of immune cells and is important for the activation of the immune system. Selenium is also essential for the maintenance of brain function. Selenium supplements can regulate lipid metabolism, cell apoptosis, and autophagy, and have displayed significant alleviating effects in most cardiovascular diseases. However, the effect of increased selenium intake on the risk of cancer remains unclear. Elevated serum selenium levels are associated with an increased risk of type 2 diabetes, and this relationship is complex and nonlinear. Selenium supplementation seems beneficial to some extent; however, existing studies have not fully explained the influence of selenium on various diseases. Further, more intervention trials are needed to verify the beneficial or harmful effects of selenium supplementation in various diseases.

Keywords: selenium; selenoprotein; oxidative stress; immune system; brain function; cardiovascular disease; cancer; type 2 diabetes; heavy metals



Citation: Zhang, F.; Li, X.; Wei, Y. Selenium and Selenoproteins in Health. *Biomolecules* **2023**, *13*, 799. <https://doi.org/10.3390/biom13050799>

Academic Editors: Piotr Ceranowicz and Gregory Henderson

Received: 23 February 2023

Revised: 19 April 2023

Accepted: 27 April 2023

Published: 8 May 2023



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1. Introduction

Trace elements play an important role in maintaining fundamental physiological functions [1]. Selenium (Se) is a trace element first discovered in 1817 by the Swedish chemist, Jöns Jacob Berzelius. Originally, selenium was considered a naturally occurring toxicant [2]; however, this view changed following the unexpected discovery that selenium prevented liver necrosis in rats by Schwarz and Foltz in 1957 [3]. Since then, the perception of selenium as a health threat has changed. In fact, selenium began to be viewed as an element beneficial to health. Selenium from food exerts its physiological role by co-translationally incorporating many proteins as components of the amino acid selenocysteine (Sec) [4]. Notably, selenium provides selenoprotein molecules with a range of redox properties that maintain redox homeostasis [5,6].

2. Selenium Intake

The total amount of selenium in humans is approximately 3–20 mg. As an essential mineral micronutrient, selenium is mainly obtained from foods, such as cereals, meat, fish, and eggs [7]. Generally, selenium concentrations vary from food to food, and animal-based foods > vegetables > cereals > fruits. Cereals are the main source of selenium; however, their selenium content is relatively low, ranging from 0.01 to 0.55 µg/g. The selenium content is between 0.08 and 0.7 µg/g in animal-based foods and less than 0.1 µg/g in vegetables and fruits. Brazil nuts are the most abundant source of dietary selenium, with

selenium levels up to 512 g/g [8]. Soil is the main source of selenium in plants. Soil total selenium content below 0.1 mg/kg is considered selenium deficient, 0.2–0.3 mg/kg is generally selenium deficient, and more than 0.4 mg/kg is selenium enriched [9]. The bioavailability of plants to different forms of selenium in soil varies, and selenate > organic selenium > selenite > selenium > selenide. In addition, the uptake of selenium by plants is also influenced by soil pH, redox conditions, microbial activity, and organic matter, but these aspects will not be covered in detail here. The World Health Organization (WHO) recommends a selenium intake level of 55 µg/day for adults, with the tolerable upper limit set at 400 µg/day. Moderate selenium intake and a balanced diet are critical to maintain.

The form of selenium in food affects its absorption by humans. Generally, dietary selenium exists as organic selenium compounds, selenate, and selenite, with a bioavailability of 70–95% [10,11]. Selenoamino acids often have higher bioavailability than inorganic selenium [12], and selenium in plant foods is more bioavailable than that in animal foods [11]. Selenomethionine (SeMet), the chief nutritional form of selenium, cannot be synthesised by higher organisms. The synthesis of SeMet relies on plants and fungi [13]. Approximately 90% of the selenium in plants is present as SeMet. The bioavailability can reach 95–98% [14,15]. Selenocysteine (Sec) is another organic selenium compound derived mainly from animal foods. Inorganic selenium mainly accumulates in plants via the sulphur assimilation pathway but is also present in water. Selenates and selenites ingested by humans are eventually converted to SeMet.

3. Selenoproteins

Selenium from food is taken up and present in humans in the natural organic forms of selenocysteine and selenoprotein. They are stored in different organs and tissues: 30% in liver, 30% in muscle, 15% in kidney, 10% in plasma, and 15% in other organs [16]. The selenium concentration in liver reflects intestinal absorption levels. The liver synthesises selenoprotein P (SELENOP), which enters the bloodstream and supplies selenium to other tissues and organs [17–19]. The biological effects of selenium are primarily mediated by selenoproteins [20]. Almost all selenoproteins contain single Sec residues at their enzyme active sites [21], which are essential for their activity. Sec, the 21st naturally occurring, genetically coded amino acid, is a sulphur-to-selenium substituted variant of cysteine (Cys) [22]. Selenium and sulphur belong to the same group. Therefore, Sec and Cys exhibit similar chemical properties and participate in similar chemical reactions [23]. However, compared with Cys, Sec has higher nucleophilicity [24], oxidation susceptibility, and acidity, which is mainly reflected in its relatively lower pKa (5.2) [25,26]. Therefore, most side-chain selenols can be deprotonated at biological pH, and Sec is reactively superior to Cys [27,28].

In humans, Sec is the only naturally occurring amino acid that lacks a cognate aminoacyl-tRNA synthetase. Thus, Sec requires a specific biosynthetic pathway [29] (Figure 1). First, under the catalysis of seryl-tRNA synthetase (SerRS), selenocysteine-specific tRNA (tRNA^{Sec}) binds with Ser to form Seryl-tRNA^{Sec}, which is subsequently converted to Sec-tRNA^{Sec} by O-phosphoseryl-tRNA^{Sec} kinase (PSTK) and selenocysteine synthase [30,31]. Sec-tRNA^{Sec} can ligate to Sec insertion sequence-binding protein 2 (SBP2), which specifically recognises the stop codon UGA [32,33]. This process requires the participation of the Sec insertion sequence (SECIS) element in the 3' untranslated region of the mRNA to decode the UGA codon as Sec [34,35]. Finally, under the interaction of SECIS and SBP2, Sec is delivered to the ribosome and co-translationally inserted into nascent polypeptide chains [20].

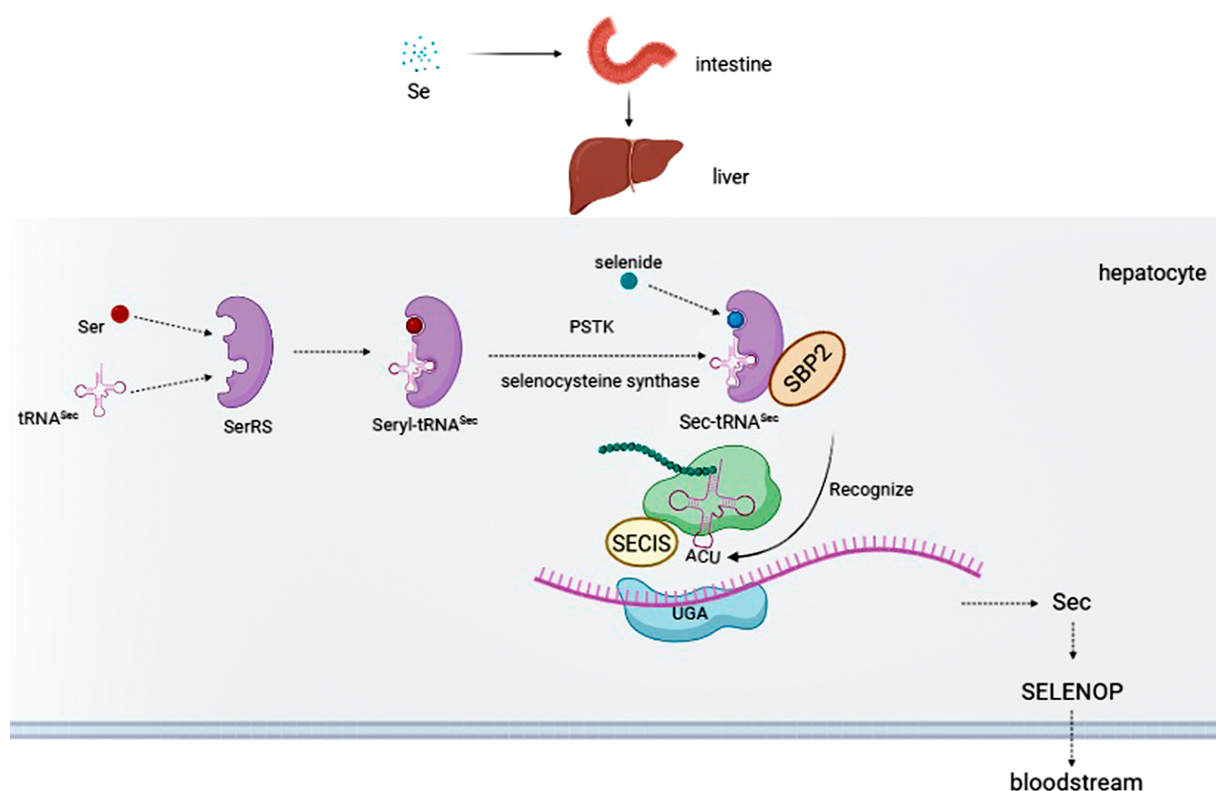


Figure 1. Selenium from food is transformed in the liver and inserted into polypeptide chains, and the liver synthesises SELENOP to supply selenium to the whole body. Selenide is first phosphorylated, then transferred to the ribosomal A site under the recognition of SBP2, and finally recognised by the UGA codon under the decoding action of SECIS.

A total of 25 selenoprotein genes have been described in humans, and most of these genes encode redox enzymes [36,37]. Selenoproteins are distributed in different organs and tissues, and have different substrate specificities and functions (Table 1). The glutathione peroxidase (GPX) and thioredoxin reductase (TxnRd) families are involved in cellular antioxidative defense systems and the maintenance of intracellular redox states to maintain cell viability [38,39] (though see below). These families often function in parallel in humans. The three iodothyronine deiodinases (Dio1,2,3) are selenoproteins with developmental-, cell-, and pathology-related expression patterns. Dio1 and Dio2 participate in the production of the active thyroid hormone T3 [40], while Dio3 contributes to the generation of the inactive rT3 and T2. Human SELENOP is a monomeric glycoprotein containing 10 selenocysteine residues, an important feature that distinguishes it from other selenoproteins. Therefore, SELENOP, a selenium transport protein, accounts for approximately 40% of the total selenium concentration in human plasma and can bind to specific receptors on cell membranes to deliver selenium to other cells, such as low-density lipoprotein receptor-related protein 8 (LRP8) and megalin receptors on kidney proximal tubule epithelial cells [17,41]. SELENOP also has redox properties and is associated with the protection of endothelial function. SELENOP binds heparin and participates in insulin resistance. Selenoprotein S is associated with inflammatory responses and endoplasmic reticulum stress [42,43]. Selenoproteins W (SELENOW) and N participate in muscle development and maintenance [44,45]. However, the functions of many selenoproteins have not been fully elucidated and require further investigation. Selenium functions as a redox centre in these selenoproteins. Therefore, a deficiency in the trace element selenium can cause several disorders.

Table 1. The functions of 25 selenoproteins and their health effects.

	Function	Health Effects
GPX1	Antioxidant activity; reduce cellular H ₂ O ₂ .	Cancers [46]; chondrogenic differentiation [47]; T2DM [48]; depression [49]; Keshan disease [50]; cataracts [51]; macular degeneration [52].
GPX2	Antioxidant activity, protect the mucosa of the gastrointestinal tract and various endothelial cells from oxidative damage.	Cancers [53]; intestinal inflammation [54].
GPX3	Reduce lipid hydro peroxides and H ₂ O ₂ .	Cancers [55]; myocardial fibrosis [56]; ventricular remodeling [57].
GPX4	Antioxidant activity; decrease phosphatidylcholine hydroperoxide; suppress cellular ferroptosis.	Osteoarthritis [58]; cancers [59]; cardiomyopathy [60]; ischemia-reperfusion injury [61]; brain function [62].
GPX6	Not known.	Huntington's disease [63].
TXNRD1	Antioxidant activity; regenerate thioredoxin; suppress cell ferroptosis.	Idiopathic pulmonary arterial hypertension [64] hepatocellular carcinoma [65]; osteoarthritis [66]; genetic generalized epilepsy [67]; Keshan disease [50].
TXNRD2	Regenerate thioredoxin; regulate cell proliferation and apoptosis.	Primary open-angle glaucoma [68]; CVDs [69,70]; cancers [71]; glaucoma [72].
TXNRD3	Antioxidant activity; suppress pyroptosis.	Male reproduction [73]; colitis and carcinogenesis [74].
DIO1	Activate T3.	Thyroid hormone metabolism [75]; inhibit hepatosteatoses [76]; renal cancer [77].
DIO2	Activate T3.	Osteoarthritis [78]; obesity [79]; mental retardation [80].
DIO3	Inactivate T3.	Osteoarthritis [81]; brain development [82]; sepsis and septic shock [83].
MSRB1	Antioxidant activity; anti-inflammatory effect; regulate immune responses.	Hepatocellular carcinoma [84]; inflammatory response [85].
SEPHS2	Sec synthesis.	Cancers [86].
SELENOF	Immunomodulation; regulate glycogenolysis and lipogenesis; participate in vitamin A metabolism.	Cancers [87]; glucose metabolism disorder [88].
SELENOH	Regulate cell cycle progression and proliferation.	Colorectal cancer [89].
SELENOI	Critical enzyme in the central nervous system; T cell activation; neural development; plasmalogen maintenance.	Hereditary spastic paraplegia 81 [90].
SELENOK	Oxidation resistance; Ca ²⁺ flux regulation; immune regulation; apoptosis regulation; suppress cellular ferroptosis.	AD [91]; cervical cancer [92].

Table 1. *Cont.*

	Function	Health Effects
SELENOM	Glucose metabolism; Ca ²⁺ flux regulation; apoptosis regulation.	Glioblastoma [93]; non-alcoholic fatty liver disease [94]; synaptic deficits and cognitive dysfunction [95].
SELENON	Muscle development; calcium haemostasis.	Myopathies [96].
SELENOO	Not known.	Thyroid cancer [97].
SELENOP	Antioxidant activity; maintain neuronal activity; transport selenium to tissues; regulate pancreatic β cell function.	Cancers [98–100]; seizures and ataxia [101]; CVDs [102].
SELENOS	Regulate inflammation; induce ER stress apoptosis; immune regulation.	Hashimoto's thyroiditis [103]; CVDs [104].
SELENOT	Promote nerve regeneration; Ca ²⁺ flux regulation; apoptosis regulation; maintain endoplasmic reticulum homeostasis; regulate glucose and lipid metabolism.	Glioblastoma [105]; AD [106]; CVDs [107].
SELENOV	Regulate glucose and lipid metabolism; prevent endoplasmic reticulum stress and oxidative injury; maintain male reproduction.	Not known.
SELENOW	Oxidation resistance; regulate bone metabolism; support erythroblast development; muscle development.	Osteoporosis [108]; anemia [109].

4. Health Effects of Selenium and Selenoproteins

The unique biological characteristics of the trace mineral selenium make it indispensable for health. Although selenium is present at very low levels in the human body, selenium deficiency can cause dysfunction in various systems. Selenium cannot be synthesised in the human body and is mainly obtained from food. The physiological function of selenium is mainly reflected in selenoproteins, which have excellent efficacy in resisting oxidative stress, inflammation, and other adverse factors. Appropriate supplementation of selenium can not only activate the immune system but also affect brain function, cardiovascular diseases (CVDs), cancer, and heavy metal-based illness. Although studies have suggested that high selenium levels have negative effects on some specific diseases such as type 2 diabetes mellitus (T2DM), further exploration of selenium is still beneficial and may provide new ideas for the treatment of various diseases.

4.1. Oxidative Stress

Redox homeostasis is the basis for maintaining life activities. Oxidative stress manifests as an imbalance between the cellular oxidative and antioxidant systems. This imbalance is mainly reflected in the production of large amounts of reactive oxygen species (ROS) that exceed the scavenging capacity of antioxidant defense systems, ultimately leading to structural and functional damage to DNA, lipids, and proteins. The mitochondria are considered a major source of ROS, and excessive ROS can cause structural damage to the mitochondria. Hydroperoxides, especially hydrogen peroxide (H₂O₂), serve as the major ROS in redox regulation, and are responsible for cell signaling, enzymatic reactions, energy metabolism, and cell cycle. However, superabundant hydroperoxides result in unspecific proteins oxidation and biomolecules damage. The removal of hydroperoxides relies on

efficient reducing systems. Selenium acts as a critical antioxidant in affecting various tissues and cells and contributes to the removal of ROS, especially the removal of hydroperoxides. This effect has been reported in the heart [110], liver [111], kidneys [112], thyroid [113], and brain [114] (the mechanism is described later). In addition, the antioxidant effect of selenium may be responsible for its resistance to inflammation, apoptosis, and autophagy.

The defense of selenium on ROS is primarily mediated by selenoproteins, which have redox activity and can catalyse the reduction of hydroperoxides by thiols; however, some differences exist in their substrate specificity. The best known are the GPXs and the thioredoxin (Trx) system, which are the main members of the antioxidant system. Five of the eight human GPXs are selenoproteins, and their active site contains a Sec, while the active site of other three is cysteine. However, the catalytic efficiency of GPXs is conspicuous irrespective of their substrate or active site. The active site of GPXs contains a conserved tetrad formed by peroxidatic Sec, glutamine, tryptophan, and asparagine [115]. The Sec residue can be oxidised by hydroperoxides and forms selenenic acid or a selenenylamide intermediate. These intermediates will be reduced back to selenate soon by thiol [116]. Due to the high reactivity of Sec residues, GPXs react on H_2O_2 with high second-order rate constants, which helps to reduce the cellular H_2O_2 concentration. GPX1 was the first mammalian selenoprotein to be identified and is the most abundantly expressed GPX. GPX1 is present in the mitochondria and cytoplasm. GPX1 utilizes glutathione (GSH) to reduce hydroperoxides and is highly sensitive to selenium levels. GPX2 has similar substrate specificities to GPX1 and is mainly found in the mucosa of the gastrointestinal tract and various endothelial cells [117]. GPX2 maintains mucosal homeostasis and regulates intestinal regeneration. The expression of GPX2 was only found to be downregulated in patients with severe selenium deficiency [118]. GPX3 is an extracellular glycoprotein that accepts the oxidation of GSH, Trx, and glutaredoxin and is present at high levels in white and brown adipose tissues [119]. GPX4 is found to be the only isoform which can decrease phosphatidylcholine hydroperoxide [120]. It is present in the mitochondria and cytoplasm; however, only the mitochondrial form of GPX4 protects cells from oxidative stress. GPX6 is a close homologue of plasma GPX3 and is expressed in the embryonic and olfactory systems. Not enough is known about GPX6 yet.

The thioredoxin system is composed of nicotinamide adenine dinucleotide phosphate (NADPH), Trx, and thioredoxin reductase (TXNRD). Trx and TXNRD provide a coupled redox system required for redox reactions. The thioredoxin system prevents oxidative damage to cells and maintains redox homeostasis. Trx exerts its antioxidant activity by transferring electrons to thioredoxin peroxidases and reducing oxidised Cys disulphide or Cys-SOH in proteins to thiols. Trx can also participate in shaping intracellular H_2O_2 gradients. TXNRD belongs to the pyridine nucleotide disulphide oxidoreductase family of enzymes and can reduce the oxidised form of Trx using NADPH as a co-substrate. Three TXNRD isoforms have been identified in mammals: cytosolic (TXNRD1), mitochondrial (TXNRD2), and thioredoxin glutathione reductase (TXNRD3). The Trx system performs its antioxidant functions by reducing methionine sulfoxide reductases and ribonucleotide reductases. This system also regulates the activity of redox-sensitive transcription factors (especially AP-1 and NF- κ B). The antioxidant properties of the Trx system indicate its vital contribution to the antioxidant defense system and the maintenance of cell homeostasis.

4.2. Immune System

Numerous studies have suggested that selenium supplementation enhances the immune response to various harmful conditions. Selenium supplementation is involved in both innate and adaptive immunity [121–124]. Based on existing research, the selenium supplement is mainly considered as an immunomodulator as it has regulatory effects on various immune cells [125–127] (Figure 2). Prior results provide important insights into the mechanisms by which selenium affects immunity.

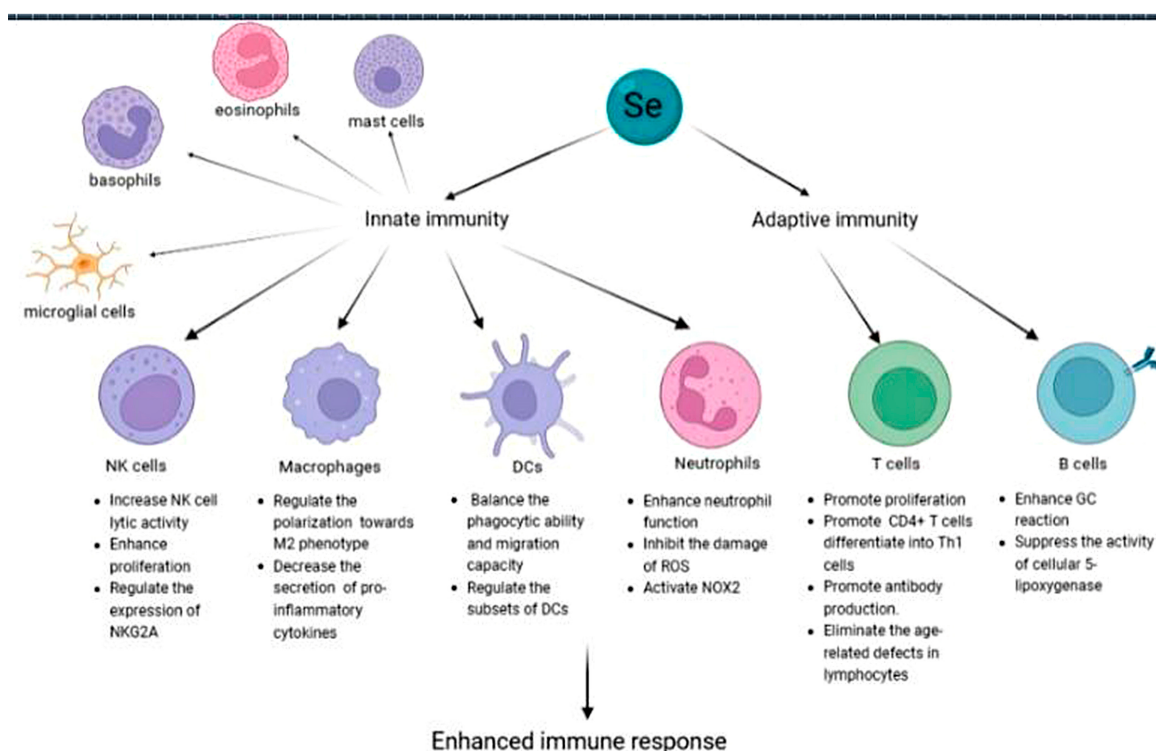


Figure 2. The role of selenium in the immune system. Selenium regulates the viability of NK cells, macrophages, DCs, granulocytes, mast cells, and microglia in innate immunity. Selenium affects the proliferation and differentiation of T cells, and regulates B cell differentiation and viability by affecting Tfh cells and 5-lipoxygenase activity.

4.2.1. Innate Immunity

The immunostimulatory effect of selenium is applicable even in individuals with sufficient selenium. A daily supplement of 200 µg selenium to selenium-replete US patients for 8 weeks increased the lytic activity of NK cells, as selenium could regulate the expression of NK cell inhibitory receptor CD94/Natural Killer G2A (NKG2A) [128]. Compared with baseline, individuals replenished with selenium showed an 82.3% increase in NK cell activity [127,129]. Selenium exhibits special regulation on macrophages. Mice fed with both selenium-enriched and selenium-deficient diets were found to have a faster resolution of inflammation in the Se-enriched group. Macrophages can be activated and eventually differentiate into the classical M1 and the alternative M2. Selenium regulates the polarization of macrophages towards the anti-inflammatory M2 phenotype, and reduce the pro-inflammatory M1 phenotype. Selenium can also decrease the secretion levels of pro-inflammatory cytokines such as iNOS, IL-1 β , IL-10, PTGe, and NF-Kb [130]. The effects of selenium on dendritic cells (DCs) are multifaceted. A mediate selenium supplement contributes to keeping balance between phagocytic ability and migration capacity of immature DCs. It also contributes to the chemotactic migration of mature DCs. Selenium regulates the subsets of DCs. It is reported that a selenium supplement is able to reduce the proportion of activated DCs while increasing tolerogenic DCs [126,131]. As a constituent of selenoproteins, selenium is integral for the proper functioning of neutrophils. Their effects depend to a great extent on their ability to activate membrane-associated nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2), which is essential for the microbicidal activity of neutrophils [132]. Selenoproteins, especially GPX1, are probably involved in the regulation of ROS-dependent neutrophil extracellular traps (NETs) through affecting cytoplasmic and mitochondrial ROS accumulation [122]. Selenium deficiency was reported to impair the bacterial killing ability of mouse neutrophils during in vitro tests [133]. These things considered, selenium could protect mast cells, eosinophils, and basophils from

ROS [125], thus regulating their proliferation, differentiation, and recruitment [134]. It was found to reduce mast cell infiltration in ischemia-reperfusion injury [135,136]. Mast cells pre-treated with selenium selenite are related to less mediator release [137]. Regression of eosinophilic enteritis and eosinophilia was reported in selenium-deficient rats when fed a selenium-supplemented diet for 4–5 weeks [138]. Basophils in selenium-deficient rats have 35% of control of phospholipid hydroperoxide GPXs activity and <1% of control of GPXs activity. A selenium supplement helps to reverse these changes [139]. Selenium eliminates the ROS-induced microglial cells migration [140]. It increases the GPXs and TXNRD levels to prevent the transcription of pro-inflammatory cytokines such as IL-1 β and iNOS [141].

4.2.2. Adaptive Immunity

T cell selenoprotein-deficient mice displayed moderate to severe atrophy of the lymph nodes, thymus, and spleen, with a 50–80% reduction in cellularity [142]. Generally, TCRs are coupled to multiple intracellular signaling molecules, and T cells are stimulated by TCR/CD3 complexes [143,144]. This process is accompanied by the rapid production of ROS and increased expression of IL-2, which exert a feedforward and autocrine effect on the proliferation of T cells [145,146]. The function of selenium is related to the capacity of the selenium to enhance the expression of the alpha (p55) and/or beta (p70/75) subunits of the growth regulatory lymphokine interleukin-2 receptor (IL-2R), thereby promoting their interaction with interleukin-2 and ultimately increasing the rate at which cells proliferate and differentiate into cytotoxic cells [147,148]. Selenium can enhance the stimulation of Ca²⁺ mobilization in T cells and inhibit the ROS-mediated inhibition of T cell activation [149,150]. Selenium may also eliminate age-related defects in lymphocytes from elderly hosts in response to stimulation via proliferation and differentiation into cytotoxic effector cells [151]. A previous study found that a daily dose of 100 μ g of yeast selenium to elderly patients in institutions increased their lymphocyte response to pokeweed mitogen [152,153]. In a case-control study of 32 patients with Crohn's disease and low concentrations (<80 μ g/L) of serum selenium, excessive Th1-cell-mediated immune responses in the colon were significantly inhibited when sodium selenite was administered orally at a dose of 360 μ g/d for 8–10 weeks [126]. Such findings suggest that a selenium supplementation enhances T cell viability by promoting the differentiation of CD4⁺ T cells into T-helper-1 (Th1) cells, leading to higher interferon-gamma and CD40 ligand levels [154,155]. Th1 cells drive the type-1 pathway, effectively defending against intracellular pathogens and stimulating delayed-type hypersensitivity (DTH) skin reactions [156,157]. In a 48 week randomised controlled trial of healthy North American men, volunteers who took 300 μ g of high-selenium yeast daily increased their blood selenium concentration by 50% and had a normal DTH skin response, while those who took low-selenium yeast exhibited anergy in DTH skin responses [157]. The same results were found when patients with intrinsic asthma were supplemented with selenium [158].

T follicular helper (Tfh) cells are a specialized subset of CD4⁺ T cells. They play an essential role in the formation of germinal centres (GCs), which are the site where B cells can differentiate into memory B cells and antibody-secreting plasma cells. GPX4 was confirmed to protect Tfh cells from ferroptosis [159], thus enhancing GC reaction. This explains part of the effect of selenium on B cells. Selenoenzymes are also reported to suppress the activity of cellular 5-lipoxygenase in B cells to protect them from oxidative stress [160]. Insufficient or excessive selenium reduces the number of peripheral B cells and B cells in the spleens of mice [161,162].

4.3. Brain Function

Brain metabolism is highly dependent on selenium levels. The selenium content of the human brain is approximately 90–110 ng/mg wet weight, which is lower than that of the liver. However, when selenium is depleted, brain selenium levels are maintained. These findings demonstrate the significance of selenium in brain function. SELENOP, glutathione peroxidase 4 (GPX4), and SELENOW are the three most highly expressed selenoproteins in

the brain, implying that they probably play important roles in brain function (Figure 3). Selenium deficiency can cause irreversible brain injury.

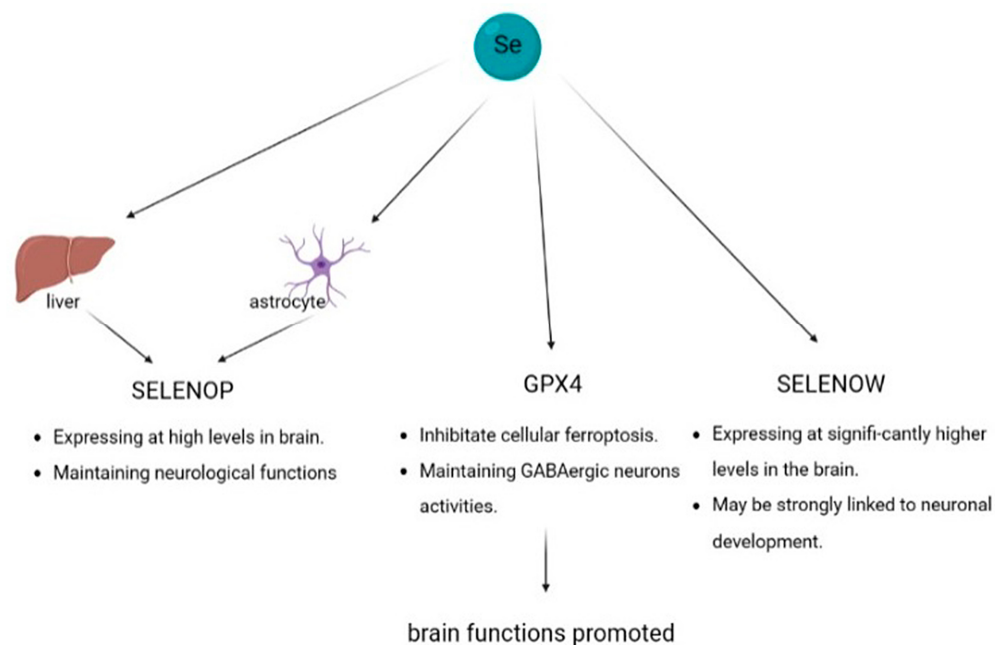


Figure 3. Mechanisms of selenium effects on brain functions. Selenium supplements promote neuronal activities and brain functions by increasing SELENOP, GPX4, and SELENOW levels in brain.

Selenium deficiency can lead to neurological and motor disorders. Plasma selenium levels and erythrocyte GPXs activity are significantly reduced in patients with Alzheimer’s disease (AD) [163,164]. Accordingly, exogenous selenium supplementation has been found to mitigate neurodegeneration and reverse memory deficits in an AD model [165,166]. Parkinson’s disease (PD), a neurodegenerative disease characterised by the dysregulation of motor control, has been found to correlate with selenium levels [167,168]. Selenium reduces bradykinesia in a rat model of PD [169]. Patients with epilepsy usually have lower serum selenium levels than healthy individuals [170–172].

4.3.1. Selenoprotein P

The brain can ingest SELENOP from the plasma to acquire selenium. Selenoproteins do not enter the blood–brain barrier and individual cells directly, but are transmembrane via endocytosis of the LRP family receptors, especially LRP8 [173,174]. However, the administration of a selenium-supernutritional diet to Sepp1 knockout mice was found to prevent brain dysfunction, suggesting that plasma SELENOP is not the only route for the brain to obtain selenium, and selenite can be a direct or indirect source of selenium in the brain. Plasma SELENOP levels were almost undetectable in hepatic SELENOP conditional knockout mice, indicating that almost all plasma SELENOP was secreted by the liver. Interestingly, selenium was still incorporated into the brain, and no significant impairment of brain function was observed in SELENOP conditional knockout mice [175]. In contrast, the brain failed to maintain normal function when SELENOP was completely knocked out in mice [176], and the protein levels of two other selenoproteins, GPX4 and SELENOW, were decreased in SELENOP knockout mice. These results confirm that local SELENOP, but not plasma SELENOP, is essential for maintaining brain function, and SELENOP can be stored and recycled in the brain, forming the SELENOP cycle. In addition to being obtained from the blood plasma, astrocytes in the brain may also produce and secrete SELENOP [177].

SELENOP deficiency is associated with neurological deficits and impaired motor functions. It is expressed in over 90% of the brain region at high levels. SELENOP

was the first selenoprotein associated with synaptic signaling. Numerous studies have demonstrated that SELENOP promotes neuronal activity and the thalamus, brainstem, and hippocampal neurogenesis are adversely affected when it is under-expressed [17,178,179]. Notably, ataxic manifestations were observed in SELENOP knockout mice [101].

4.3.2. Glutathione Peroxidase 4

GPX4 is a selenoprotein essential for neuronal activity and is found in the nucleus, mitochondria, and cytoplasm. GPX4 is a key molecule in the inhibition of cellular ferroptosis [180,181], and its redox properties contribute to the maintenance of mitochondrial function and inhibition of apoptosis. GPX4 has shown great importance in the brain and in life. Neuronal GPX4-specific knockout was found to be lethal in newborn mice, and was associated with a very high protein abundance during perinatal brain development, which decreased after birth [182]. Neuron-specific inactivation of GPX4 in adult mice leads to massive neurodegeneration, as inhibitory interneurons expressing parvalbumin (PV) are extremely GPX4-sensitive, and PV+ neurons account for 60% of all GABAergic neurons in the somatosensory cortex [183,184]. GPX4 deficiency will make neural activity maintenance difficult and can lead to cerebellar atrophy [185,186]. PD and AD have been found to correlate with GPX4 levels [187–189].

4.3.3. Selenoprotein W

Among all selenoproteins, SELENOW was found to be expressed at the highest level in the brain and exhibit representative redox activity. SELENOW is expressed at significantly higher levels in the brain of postnatal mice [190,191], suggesting that it may be strongly linked to neuronal development. Although the exact biological function of SELENOW has not been explored, its high protein levels imply that it may play an important role in the brain.

4.4. Cardiovascular System

Selenium is associated with the incidence of CVDs. The earliest evidence of this association is due to Keshan disease, an endemic adolescent disease characterised by cardiomyopathy, which is prevalent in some parts of China with low-selenium soils [192]. Subnormal whole-blood and serum selenium concentrations have been reported in patients with Keshan disease, and selenium supplementation is beneficial for improving this condition [193]. Since then, more cardiovascular effects of selenium have been reported (Figure 4).

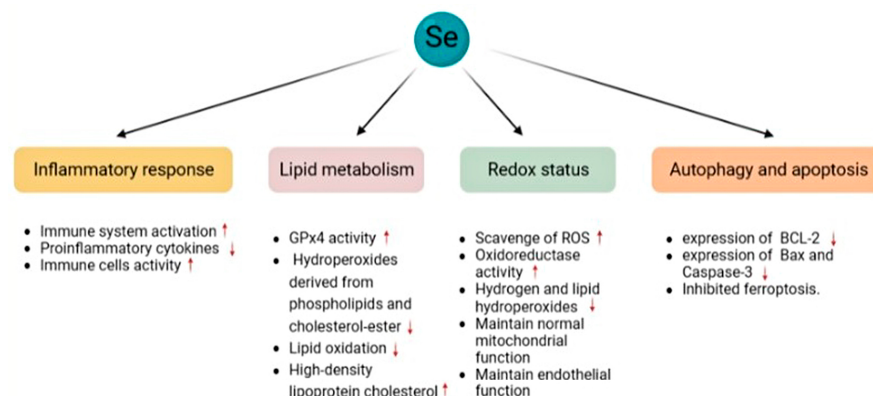


Figure 4. Mechanisms of selenium effects on cardiovascular diseases. Selenium exerts protective effects against CVDs by affecting inflammatory responses, lipid metabolism, oxidative stress, autophagy, and apoptosis in the cardiovascular system.

In a prior report, plasma selenium concentrations were measured using fluorimetry in 91 hospitalised patients. Based on the results, a significant negative association was found between plasma selenium levels and the severity of coronary atherosclerosis [194]. Animal

experiments have also revealed that oral selenium supplementation can reduce the area and degree of atherosclerotic plaques and alleviate vascular inflammation and vascular endothelial dysfunction [195–197]; this may be because selenium levels are associated with plasma cholesterol levels. In a double-blind evaluation, selenium supplementation increased serum selenium levels and GPXs activity [198]. GPX4 reduces phospholipids and cholesterol-ester-derived hydroperoxides through GSH, an activator of lipoxygenases and cyclooxygenases, and is necessary for the synthesis of hydroperoxides [199,200]. Therefore, increasing the serum selenium content can reduce lipid oxidation. Similar results were obtained in clinical trials. Plasma lipid peroxidation was reduced by 50% in patients receiving dietary supplementation of 200 g/day selenium compared with the placebo [201]. Increased lipid peroxide concentration due to selenium deficiency may alter prostaglandin synthesis from prostacyclin to thromboxane, resulting in platelet aggregation [202]. Serum selenium levels were found to be positively correlated with the concentration of the high-density lipoprotein cholesterol, which has anti-atherosclerotic effects [198,203].

As a component of selenoproteins, selenium is involved in the regulation of the redox status of cells and participates in the scavenging of ROS and the reduction of hydrogen and lipid hydroperoxides [204]. Therefore, selenium can delay the progression of CVDs and maintain normal cell growth and proliferation, protein folding, and mitochondrial function [181,197]. Selenium can increase the expression and phosphorylation of endothelial nitric oxide synthase to maintain the balance of superoxide anion/nitric oxide and regulate cell adhesion by controlling the expression of cell adhesion molecules, thereby protecting the structural and functional integrity of endothelial cells [205,206]. Selenium can also relieve CVDs by affecting apoptosis and autophagy; increasing the expression of the anti-apoptotic protein BCL-2; reversing the increased expression of the pro-apoptotic proteins Bax and Caspase-3; and regulating the PI3K/AKT/mTOR pathway [207–209]. In addition, GPX4 is a key molecule in ferroptosis, and selenium supplementation inhibits ferroptosis [180,210].

In a multinational, prospective, observational cohort study, selenium deficiency was found to be associated with impaired exercise tolerance and a 50% increase in mortality in patients with HF. Researchers have found that selenium is independently associated with impaired mitochondrial function in human cardiomyocytes in vitro [211]. When the case of a patient who died due to cardiomyopathy and ventricular fibrillation was analysed, fatal cardiomyopathy was found to be caused by selenium deficiency. In particular, replacement fibrosis and widespread myocytolysis were observed in the heart [212].

Although few studies found no significant association between selenium and cardiovascular disease [213,214] (for example, an analysis of American physicians found no significant association between plasma levels of the antioxidant selenium and the risk of myocardial infarction [215]), the mainstream notion is that selenium can protect against CVDs and maintain normal cardiovascular function.

4.5. Cancer

Based on increasing studies, selenium affects the incidence of cancer. Many cancer cells are selenophilic; however, the selenide, an intermediate product of Sec synthesis, is poisonous. Selenide in cancer cells must be detoxed by selenophosphate synthetase 2 (SEPHS2) [216]. Of note, this process is not required in normal cells. Therefore, when selenium supplementation exceeds a certain dose, selenide accumulates in cancer cells and impairs their growth.

Clinical trials have supported the above conclusion. Early observational studies revealed that individuals with adequate selenium levels in their diet or body tissues have a lower risk of cancer, and plasma selenium levels can decline before some cancers develop [217,218]. However, in a 1973 clinical trial, selenium levels in serum samples collected from 111 patients who developed cancer within the following five years were compared with those from 210 cancer-free individuals matched based on sex, age, and living environment. The findings revealed that the risk of cancer for individuals in the

highest quintile of serum selenium was half that of individuals in the lowest quintile [219]. However, some clinical trials have concluded that selenium supplementation does not reduce the overall incidence of cancers, such as lung, bladder, and prostate cancers, with liver cancer as the exception [220–222].

We speculate that selenium may confer resistance against cancers when the dosage is appropriate. An eight-year intervention trial was conducted in a general population of 130,471. The incidence of primary liver cancer (PLC) was 35.1% lower in the selenium-supplemented salt group (15 mg sodium selenite per kg) than in the non-supplemented population. After selenium was removed from the treatment group, PLC incidence began to rebound [223]. Selenium protects against breast cancer [224], which has the highest incidence worldwide. A total of 974 men with a history of basal cell carcinoma or squamous cell carcinoma were enrolled in a randomised, double-blind, placebo-controlled trial, receiving 200 µg per day of selenium supplementation or placebo for an average of 4.5 years. At the 6.5 years follow-up, a significant reduction (63%) in the secondary endpoint of prostate cancer incidence was found for men treated with selenium [225]. Similarly, selenium was found to be inversely associated with adenoma and colorectal cancer [226].

The chemical form and bioavailability of selenium, and the stage and type of cancer influence the above results. Most studies on the relationship between selenium and cancer are currently observational studies. As there are still many conflicting conclusions in related studies, further studies are needed to clarify the relevance of selenium in cancer.

4.6. Type 2 Diabetes

Insulin resistance is a characteristic of type 2 diabetes [227]. The relationship between serum selenium levels and type 2 diabetes mellitus has long been a topic of discussion. Selenium has been shown to affect T2DM through multiple pathways (Figure 5). Most experimental results support a positive correlation between serum selenium levels and T2DM. For example, in a randomised, double-blind, placebo-controlled trial averaging 7.7 years, individuals who took 200 µg/d selenium orally had a higher incidence of T2DM than those who took the placebo [228]. Another dose-response meta-analysis revealed that selenium exposure increased the risk of T2DM as supplementation increased the hepatic production of Sepp1, which is a proven inducer of insulin resistance [229–231]. Sepp1 can reduce tyrosine phosphorylation of insulin receptors in hepatocytes, and decrease serine phosphorylation in myocytes, thus impairing their insulin signaling and glucose metabolism [230].

Primary hyperinsulinemia is another pathogenesis of T2DM. Under physiological conditions, the islet β-cells express particularly low amounts of some antioxidant enzymes such as GPXs, catalase and superoxide dismutases; while express moderate to high levels of Sepp1 which exhibits low reactivity with H₂O₂; this results in the susceptibility of islet β-cells to ROS. Selenium intake enhances the expression and activity of GPX1. Based on the antioxidant effect of selenium, the upregulation of GPX1 could reduce intracellular H₂O₂ production and inhibit islet inflammation and oxidative stress, thereby playing a protective role in islet β-cells [232–234]. The formation of insulin is accompanied by the constant formation of disulphide bonds, a process that is susceptible to the redox state. In addition, GPX1 upregulates the transcription factors involved in insulin synthesis, such as MAFA and NKX-6.1. However, these changes are not necessarily beneficial. The overexpression of GPX1 caused by a high selenium status causes the dysregulation of PDX1 and UCP2, and can easily develop into hyperinsulinaemia, decrease insulin sensitivity, and induce the development of a T2DM-like phenotype. Insulin-like effects of high doses of sodium selenomethionine and sodium selenite have been observed in diabetic animals, as in [235,236]. The symptoms of type 2 diabetes were found to be relieved in GPX1 knockout and dietary selenium-deficient mice.

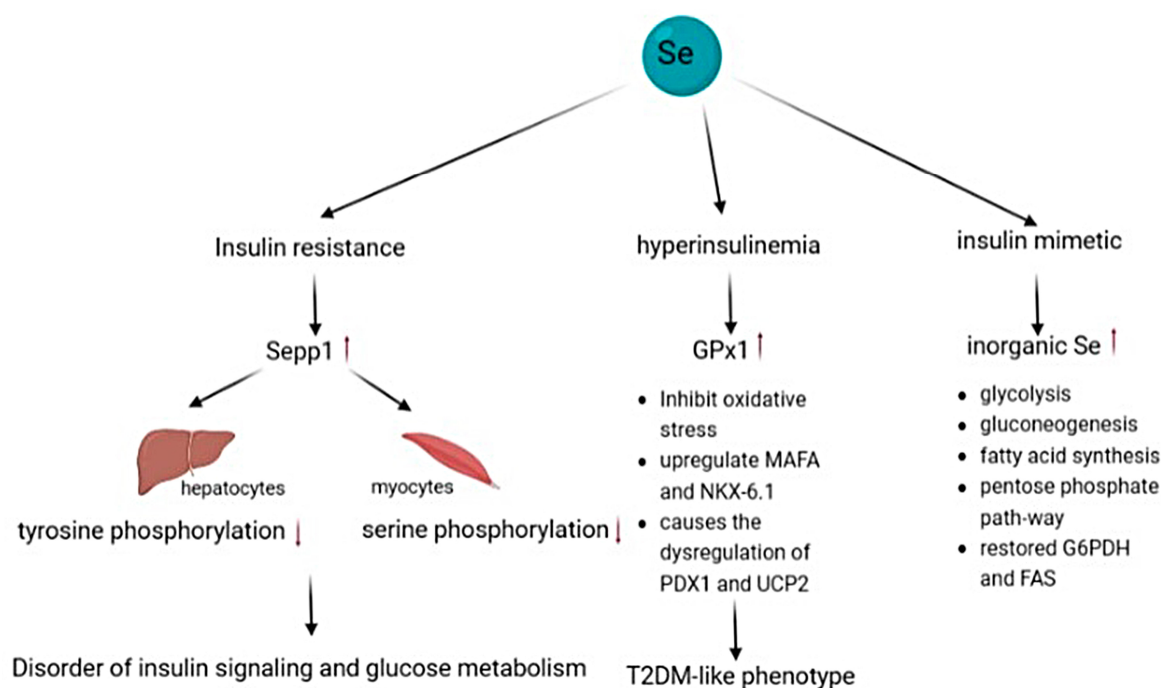


Figure 5. Mechanisms of selenium effects on T2DM. High concentration of Sepp1 induced by high selenium levels impairs insulin signaling and glucose metabolism; and high GPX1 induces T2DM-like phenotype. Inorganic selenium as an insulin analogue aggravates T2DM.

Early studies found that inorganic selenium can act as an insulin mimetic. Selenate was efficient in stimulating glucose ingestion both in vitro and in vivo [237,238] it mimics insulin in glycolysis, gluconeogenesis, fatty acid synthesis, and the pentose phosphate pathway. The expression of glucose-6-phosphate dehydrogenase (G6PDH) and fatty acid synthase (FAS) in rats' hepatocytes or diabetic animals was restored under the treatment of selenate, suggesting that selenate can stimulate adipogenesis in the liver [239,240]. In 1990, high doses of selenate were found to enhance insulin-stimulated phosphorylation of tyrosine phosphoprotein and insulin receptor kinase activity in rat adipocytes [237].

A meta-analysis of 13,460 individuals revealed that people with relatively lower serum selenium levels (<97.5 µg/L) and relatively higher serum selenium levels (>132.5 µg/L) had a higher prevalence of T2DM. However, the increase in incidence was more obvious in individuals with high selenium levels. In a few other studies, plasma selenium concentration was found to be significantly lower in patients with diabetes than in controls. Such findings suggest that a simple linear relationship does not exist between T2DM and selenium levels, and both high and low selenium levels are potential risk factors for T2DM [241].

4.7. Heavy Metal-Based Illness

Selenium has been shown to impact oxidation resistance and chelation to inhibit heavy metal toxicity (Figure 6) such as mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Tl), lead (Pb), and silver (Ag). Metal ions exist in numerous proteins and are required for electron transfer, oxygen transport, catalysis, and other biological processes. However, the accumulation of heavy metals in organisms will induce multiple adverse effects in vivo such as hepatorenal and renal toxicity, neurotoxicity, reproductive toxicity, and immunotoxicity and lead to serious health problems [242,243]. Oxidative stress is the primary toxic mechanism of heavy metals. It is reported that H₂O₂ and superoxide anion were dose-dependently increased in mercury-treated erythrocytes [244]. ROS induced by mercury results in both cell necrosis and apoptosis [245]. The liver and kidneys are extremely sensitive to the toxic effects of cadmium. Cadmium is unable to generate ROS by itself; however, it can replace the iron and copper from cytoplasmic and membrane proteins, contributing to the increasing concentration of unbound iron and free copper [246]. They

participate in causing oxidative stress via Fenton reactions and impair the mitochondrial electron transport chain and the function of NADPH oxidase [247]. Cadmium atoms can also combine with selenium atoms and lead to a decrease in the synthesis of selenoenzymes. ROS generation and DNA damage induced by arsenic cause a shift in the cell cycle [248]. Chromium causes oxidative damage and a wide range of DNA lesions in the presence of cellular reductants. Mitochondrial dysfunction and cellular deregulation were reported in hippocampal neurons treated with thallium [249]. The results of a meta-analysis manifested that lead treatment causes severe oxidative stress and testicular tissue was more sensitive to lead than other tissues [250]. Silver-mediated dysfunction of the respiratory chain increases the production of ROS [251].

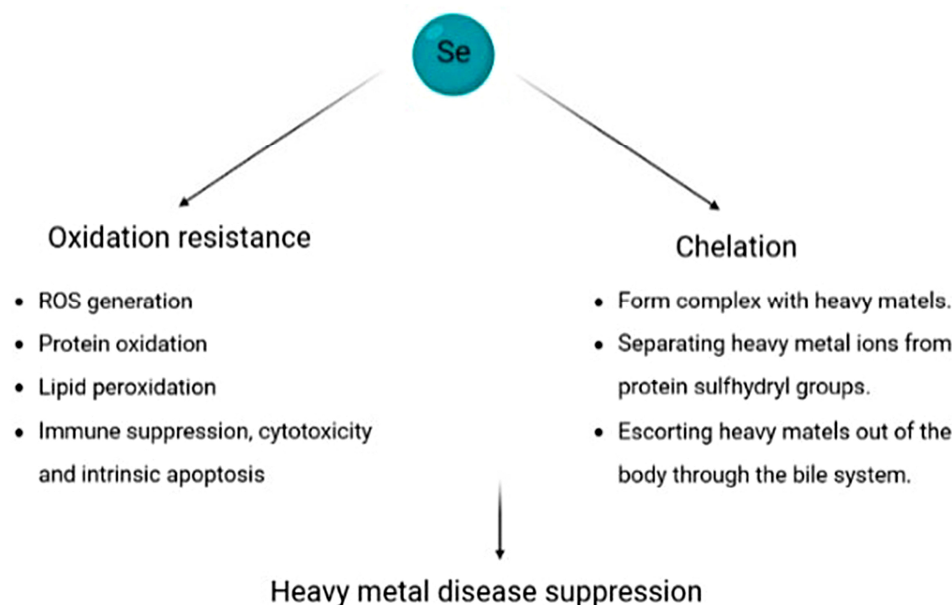


Figure 6. Mechanisms of selenium effects on heavy-metal-based illness. Oxidative stress is the primary toxic mechanism of heavy metals. Selenium detoxifies heavy metal ions by reducing the production of ROS; it can also compete directly with protein sulfhydryl groups for heavy metal ions and excrete them out of the body.

As previously mentioned, selenium functions in the form of selenoproteins, which contribute for antioxidant defense. Both the GPXs and Trx system, which are most important to oxidative defense, are the targets of heavy metal compounds. Selenium supplementation diminished ROS generation, protein oxidation, and lipid peroxidation induced by heavy metals through maintaining the activities of selenoenzymes. Furthermore, it also protects cells from immune suppression, cytotoxicity, and intrinsic apoptosis [150,252–254]. The latter probably much relies on its scavenging effect on ROS.

Chelation therapy remains a main treatment for heavy metal poisoning in clinic. Selenium can also interact directly with heavy metals, especially mercury, cadmium, and arsenic, which are usually highly affiliative for sulfhydryl groups and can result in the structural distortion of proteins. However, selenium seems to have higher affinity with heavy metals and can sequester metal ions to reduce their biological availability. It is confirmed that the affinity of mercury for selenium is up to one million times higher than that for sulphur in analogous forms. Selenium was found to form a complex with cadmium or arsenic and escort them out of the body through the bile system [255]. However, cadmium can also undermine the anticarcinogenic effects of selenium (such as liver cancer, renal carcinoma, and prostate cancer) at higher exposures [256–258].

5. Discussion

The effects of selenium on health are complex. While many novel selenoproteins been identified, their associations with diseases need to be defined. However, to date, no

fully unified conclusions have been reached. In this review, we focus on the functions and mechanisms of selenium and selenoproteins as well as their roles in systemic diseases. By summarizing the effects of selenium and selenoproteins on a variety of different diseases, it is not difficult to conclude that selenium supplementation may play a dual role as it exerts anti-inflammatory and antioxidant effects at nutritional doses but reverses these effects at supnutritional doses.

In the future, more specific studies are needed to clarify the mechanisms underlying the effects of selenium on various systemic diseases to determine the appropriate level of supplementation. As the baseline selenium levels of individuals in different populations are not the same, separate studies are required for different populations, in addition to different diseases. The specific molecular mechanisms underlying the effect of selenium supplementation on a particular disease should also be clarified considering the differences between different forms of selenium supplementation. More relevant basic and clinical studies are expected to maximise the benefits and reduce the potential risks of the trace element selenium.

Author Contributions: F.Z. and X.L. devised and wrote the manuscript. Y.W. funded the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by grants of the National Natural Science Foundation of China (Grant number: 82070376 and 81873491).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Figures have been created with BioRender.com (accessed on 1 February 2023).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mertz, W. The Essential Trace Elements. *Science* **1981**, *213*, 1332–1338. [[CrossRef](#)] [[PubMed](#)]
2. Rayman, M.P. Food-chain selenium and human health: Emphasis on intake. *Br. J. Nutr.* **2008**, *100*, 254–268. [[CrossRef](#)] [[PubMed](#)]
3. Schwarz, K.; Foltz, C.M. Factor 3 activity of selenium compounds. *J. Biol. Chem.* **1958**, *233*, 245–251. [[CrossRef](#)] [[PubMed](#)]
4. Stadtman, T.C. Selenocysteine. *Annu. Rev. Biochem.* **1996**, *65*, 83–100. [[CrossRef](#)] [[PubMed](#)]
5. Arnér, E.S.; Holmgren, A. The thioredoxin system in cancer. *Semin. Cancer Biol.* **2006**, *16*, 420–426. [[CrossRef](#)] [[PubMed](#)]
6. Kang, D.; Lee, J.; Jung, J.; Carlson, B.A.; Chang, M.J.; Chang, C.B.; Kang, S.-B.; Lee, B.C.; Gladyshev, V.N.; Hatfield, D.L.; et al. Selenophosphate synthetase 1 deficiency exacerbates osteoarthritis by dysregulating redox homeostasis. *Nat. Commun.* **2022**, *13*, 779. [[CrossRef](#)]
7. Xie, M.; Sun, X.; Li, P.; Shen, X.; Fang, Y. Selenium in cereals: Insight into species of the element from total amount. *Compr. Rev. Food Sci. Food Saf.* **2021**, *20*, 2914–2940. [[CrossRef](#)]
8. Alcântara, D.B.; Dionísio, A.P.; Artur, A.G.; Silveira, B.K.; Lopes, A.F.; Guedes, J.A.; Luz, L.R.; Nascimento, R.F.; Lopes, G.S.; Hermsdorff, H.H.; et al. Selenium in Brazil nuts: An overview of agronomical aspects, recent trends in analytical chemistry, and health outcomes. *Food Chem.* **2022**, *372*, 131207. [[CrossRef](#)]
9. Yang, H.; Yang, X.; Ning, Z.; Kwon, S.Y.; Li, M.-L.; Tack, F.M.; Kwon, E.E.; Rinklebe, J.; Yin, R. The beneficial and hazardous effects of selenium on the health of the soil-plant-human system: An overview. *J. Hazard. Mater.* **2022**, *422*, 126876. [[CrossRef](#)]
10. Pyrzynska, K.; Sentkowska, A. Selenium in plant foods: Speciation analysis, bioavailability, and factors affecting composition. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 1340–1352. [[CrossRef](#)]
11. Finley, J.W. Bioavailability of selenium from foods. *Nutr. Rev.* **2006**, *64*, 146–151. [[CrossRef](#)] [[PubMed](#)]
12. Ip, C.; Hayes, C.; Budnick, R.M.; Ganther, H.E. Chemical form of selenium, critical metabolites, and cancer prevention. *Cancer Res.* **1991**, *51*, 595–600.
13. Klimaszewska, M.; Górská, S.; Dawidowski, M.; Podsadni, P.; Turło, J. Biosynthesis of Se-methyl-seleno-l-cysteine in Basidiomycetes fungus *Lentinula edodes* (Berk.) Pegler. *Springerplus* **2016**, *5*, 733. [[CrossRef](#)]
14. Burk, R.F.; Hill, K.E. Regulation of Selenium Metabolism and Transport. *Annu. Rev. Nutr.* **2015**, *35*, 109–134. [[CrossRef](#)] [[PubMed](#)]
15. Adadi, P.; Barakova, N.V.; Muravyov, K.Y.; Krivoschapkina, E.F. Designing selenium functional foods and beverages: A review. *Food Res. Int.* **2019**, *120*, 708–725. [[CrossRef](#)] [[PubMed](#)]
16. Mistry, H.D.; Pipkin, F.B.; Redman, C.W.; Poston, L. Selenium in reproductive health. *Am. J. Obstet. Gynecol.* **2012**, *206*, 21–30. [[CrossRef](#)] [[PubMed](#)]

17. Leiter, O.; Zhuo, Z.; Rust, R.; Wasielewska, J.M.; Grönnert, L.; Kowal, S.; Overall, R.W.; Adusumilli, V.S.; Blackmore, D.G.; Southon, A.; et al. Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging. *Cell Metab.* **2022**, *34*, 408–423. [\[CrossRef\]](#)
18. Gharipour, M.; Ouguerram, K.; Nazih, E.; Salehi, M.; Behmanesh, M.; Roohafza, H.; Hosseini, S.M.; Nezafati, P.; Dianatkah, M.; Gharipour, A.; et al. Effects of selenium supplementation on expression of SEPP1 in mRNA and protein levels in subjects with and without metabolic syndrome suffering from coronary artery disease: Selenegene study a double-blind randomized controlled trial. *J. Cell Biochem.* **2018**, *119*, 8282–8289. [\[CrossRef\]](#)
19. Hill, K.E.; Wu, S.; Motley, A.K.; Stevenson, T.D.; Winfrey, V.P.; Capecchi, M.R.; Atkins, J.; Burk, R.F. Production of selenoprotein P (Sepp1) by hepatocytes is central to selenium homeostasis. *J. Biol. Chem.* **2012**, *287*, 40414–40424. [\[CrossRef\]](#)
20. Labunsky, V.M.; Hatfield, D.L.; Gladyshev, V.N. Selenoproteins: Molecular pathways and physiological roles. *Physiol. Rev.* **2014**, *94*, 739–777. [\[CrossRef\]](#)
21. Zhang, Y.; Romero, H.; Salinas, G.; Gladyshev, V.N. Dynamic evolution of selenocysteine utilization in bacteria: A balance between selenoprotein loss and evolution of selenocysteine from redox active cysteine residues. *Genome. Biol.* **2006**, *7*, R94. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Castellano, S.; Andrés, A.M.; Bosch, E.; Bayes, M.; Guigó, R.; Clark, A.G. Low exchangeability of selenocysteine, the 21st amino acid, in vertebrate proteins. *Mol. Biol. Evol.* **2009**, *26*, 2031–2040. [\[CrossRef\]](#)
23. Shu, N.; Cheng, Q.; Arnér, E.S.; Davies, M.J. Inhibition and crosslinking of the selenoprotein thioredoxin reductase-1 by p-benzoquinone. *Redox Biol.* **2020**, *28*, 101335. [\[CrossRef\]](#)
24. Zeida, A.; Trujillo, M.; Ferrer-Sueta, G.; Denicola, A.; Estrin, D.A.; Radi, R. Catalysis of Peroxide Reduction by Fast Reacting Protein Thiols. *Chem. Rev.* **2019**, *119*, 10829–10855. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Mobli, M.; Morgenstern, D.; King, G.F.; Alewood, P.F.; Muttenthaler, M. Site-specific pK(a) determination of selenocysteine residues in selenovasopressin by using ⁷⁷Se NMR spectroscopy. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 11952–11955. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Mousa, R.; Dardashti, R.N.; Metanis, N. Selenium and Selenocysteine in Protein Chemistry. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 15818–15827. [\[CrossRef\]](#)
27. Sheppard, K.; Yuan, J.; Hohn, M.J.; Jester, B.; Devine, K.M.; Söll, D. From one amino acid to another: tRNA-dependent amino acid biosynthesis. *Nucleic Acids. Res.* **2008**, *36*, 1813–1825. [\[CrossRef\]](#)
28. Arnér, E.S. Common modifications of selenocysteine in selenoproteins. *Essays Biochem.* **2020**, *64*, 45–53. [\[CrossRef\]](#)
29. Commans, S.; Böck, A. Selenocysteine inserting tRNAs: An overview. *FEMS Microbiol. Rev.* **1999**, *23*, 335–351. [\[CrossRef\]](#)
30. Wang, C.; Guo, Y.; Tian, Q.; Jia, Q.; Gao, Y.; Zhang, Q.; Zhou, C.; Xie, W. SerRS-tRNA^{Sec} complex structures reveal mechanism of the first step in selenocysteine biosynthesis. *Nucleic Acids. Res.* **2015**, *43*, 10534–10545.
31. Fischer, N.; Neumann, P.; Bock, L.V.; Maracci, C.; Wang, Z.; Paleskava, A.; Konevega, A.L.; Schröder, G.F.; Grubmüller, H.; Ficner, R.; et al. The pathway to GTPase activation of elongation factor SelB on the ribosome. *Nature* **2016**, *540*, 80–85. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Schoenmakers, E.; Agostini, M.; Mitchell, C.; Schoenmakers, N.; Papp, L.; Rajanayagam, O.; Padidela, R.; Ceron-Gutierrez, L.; Doffinger, R.; Prevosto, C.; et al. Mutations in the selenocysteine insertion sequence-binding protein 2 gene lead to a multisystem selenoprotein deficiency disorder in humans. *J. Clin. Invest.* **2010**, *120*, 4220–4235. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Dumitrescu, A.M.; Liao, X.-H.; Abdullah, M.S.Y.; Lado-Abeal, J.; Majed, F.A.; Moeller, L.; Boran, G.; Schomburg, L.; Weiss, R.E.; Refetoff, S. Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. *Nat. Genet.* **2005**, *37*, 1247–1252. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Chavatte, L.; Ii, B.A.B.; Driscoll, D.M. Ribosomal protein L30 is a component of the UGA-selenocysteine recoding machinery in eukaryotes. *Nat. Struct. Mol. Biol.* **2005**, *12*, 408–416. [\[CrossRef\]](#)
35. Papp, L.V.; Wang, J.; Kennedy, D.; Boucher, D.; Zhang, Y.; Gladyshev, V.N.; Singh, R.N.; Khanna, K.K. Functional characterization of alternatively spliced human SECISBP2 transcript variants. *Nucleic Acids. Res.* **2008**, *36*, 7192–7206. [\[CrossRef\]](#)
36. Peeler, J.C.; Weerapana, E. Chemical Biology Approaches to Interrogate the Selenoproteome. *Acc. Chem. Res.* **2019**, *52*, 2832–2840. [\[CrossRef\]](#)
37. Stadtman, T.C. Selenium biochemistry. *Annu. Rev. Biochem.* **1990**, *59*, 111–127. [\[CrossRef\]](#)
38. Spallholz, J.E.; Boylan, L.M.; Larsen, H.S. Advances in understanding selenium's role in the immune system. *Ann. N. Y. Acad. Sci.* **1990**, *587*, 123–139. [\[CrossRef\]](#)
39. Allan, C.B.; Lacourciere, G.M.; Stadtman, T.C. Responsiveness of selenoproteins to dietary selenium. *Annu. Rev. Nutr.* **1999**, *19*, 1–16. [\[CrossRef\]](#)
40. Schomburg, L.; Köhrle, J. On the importance of selenium and iodine metabolism for thyroid hormone biosynthesis and human health. *Mol. Nutr. Food Res.* **2008**, *52*, 1235–1246. [\[CrossRef\]](#)
41. Olson, G.E.; Winfrey, V.P.; Hill, K.E.; Burk, R.F. Megalin mediates selenoprotein P uptake by kidney proximal tubule epithelial cells. *J. Biol. Chem.* **2008**, *283*, 6854–6860. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Curran, J.E.; Jowett, J.B.M.; Elliott, K.S.; Gao, Y.; Gluschenko, K.; Wang, J.; Azim, D.M.A.; Cai, G.; Mahaney, M.C.; Comuzzie, A.G.; et al. Genetic variation in selenoprotein S influences inflammatory response. *Nat. Genet.* **2005**, *37*, 1234–1241. [\[CrossRef\]](#) [\[PubMed\]](#)

43. Reeves, M.A.; Hoffmann, P.R. The human selenoproteome: Recent insights into functions and regulation. *Cell Mol. Life. Sci.* **2009**, *66*, 2457–2478. [[CrossRef](#)] [[PubMed](#)]
44. Beilstein, M.; Vendeland, S.; Barofsky, E.; Jensen, O.; Whanger, P. Selenoprotein W of rat muscle binds glutathione and an unknown small molecular weight moiety. *J. Inorg. Biochem.* **1996**, *61*, 117–124. [[CrossRef](#)] [[PubMed](#)]
45. Muntoni, F.; Brockington, M.; Godfrey, C.; Ackroyd, M.; Robb, S.; Manzur, A.; Kinali, M.; Mercuri, E.; Kaluarachchi, M.; Feng, L.; et al. Muscular dystrophies due to defective glycosylation of dystroglycan. *Acta Myol.* **2007**, *26*, 129–135. [[PubMed](#)]
46. Zhao, Y.; Wang, H.; Zhou, J.; Shao, Q. Glutathione Peroxidase GPX1 and its Dichotomous Roles in Cancer. *Cancers* **2022**, *14*, 2560. [[CrossRef](#)] [[PubMed](#)]
47. Yan, J.; Guo, Y.; Fei, Y.; Zhang, R.; Han, Y.; Lu, S. GPx1 knockdown suppresses chondrogenic differentiation of ATDC5 cells through induction of reductive stress. *Acta Biochim. Biophys. Sin.* **2017**, *49*, 110–118. [[CrossRef](#)]
48. Kafeel, S.; Hashim, Z.; Fawwad, A.; Nawab, S.N. Predisposition of SOD1, GPX1, CAT genetic variants and their haplotypes in cataractogenesis of type 2 diabetes mellitus in Pakistan. *Acta Diabetol.* **2022**, *59*, 623–632. [[CrossRef](#)]
49. Johnson, L.A.; Phillips, J.A.; Mauer, C.; Edwards, M.; Balldin, V.H.; Hall, J.R.; Barber, R.; Conger, T.L.; Ho, E.J.; O'bryant, S.E. The impact of GPX1 on the association of groundwater selenium and depression: A Project FRONTIER study. *BMC. Psychiatry* **2013**, *13*, 7. [[CrossRef](#)]
50. Pei, J.; Fu, W.; Yang, L.; Zhang, Z.; Liu, Y. Oxidative stress is involved in the pathogenesis of Keshan disease (an endemic dilated cardiomyopathy) in China. *Oxid. Med. Cell Longev.* **2013**, *2013*, 474203. [[CrossRef](#)]
51. Orhan, H.; Marol, S.; Hepşen, I.F.; Şahin, G. Effects of some probable antioxidants on selenite-induced cataract formation and oxidative stress-related parameters in rats. *Toxicology* **1999**, *139*, 219–232. [[CrossRef](#)] [[PubMed](#)]
52. Sun, Y.; Zheng, Y.; Wang, C.; Liu, Y. Glutathione depletion induces ferroptosis, autophagy, and premature cell senescence in retinal pigment epithelial cells. *Cell Death Dis.* **2018**, *9*, 753. [[CrossRef](#)] [[PubMed](#)]
53. Brigelius-Flohé, R.; Kipp, A.P. Physiological functions of GPx2 and its role in inflammation-triggered carcinogenesis. *Ann. N. Y. Acad. Sci.* **2012**, *1259*, 19–25. [[CrossRef](#)] [[PubMed](#)]
54. Esworthy, R.S.; Yang, L.; Frankel, P.H.; Chu, F.-F. Epithelium-specific glutathione peroxidase, Gpx2, is involved in the prevention of intestinal inflammation in selenium-deficient mice. *J. Nutr.* **2005**, *135*, 740–745. [[CrossRef](#)] [[PubMed](#)]
55. Chang, C.; Worley, B.L.; Phaëton, R.; Hempel, N. Extracellular Glutathione Peroxidase GPx3 and its Role in Cancer. *Cancers* **2020**, *12*, 2197. [[CrossRef](#)] [[PubMed](#)]
56. Li, G.; Qin, Y.; Cheng, Z.; Cheng, X.; Wang, R.; Luo, X.; Zhao, Y.; Zhang, D.; Li, G. Gpx3 and Egr1 Are Involved in Regulating the Differentiation Fate of Cardiac Fibroblasts under Pressure Overload. *Oxid. Med. Cell Longev.* **2022**, *2022*, 3235250. [[CrossRef](#)]
57. Covington, T.A.; Pilz, P.M.; Mulhern, R.M.; Ngoy, S.; Loscalzo, A.; Liu, J.; Fisch, S.; Grune, J. GPx3 deficiency exacerbates maladaptive right ventricular remodeling in experimental pulmonary artery banding. *Am. J. Physiol. Lung. Cell Mol. Physiol.* **2023**, *324*, L550–L556. [[CrossRef](#)]
58. Hangauer, M.J.; Viswanathan, V.S.; Ryan, M.J.; Bole, D.; Eaton, J.K.; Matov, A.; Galeas, J.; Dhruv, H.D.; Berens, M.E.; Schreiber, S.L.; et al. Contribution of ferroptosis and GPX4's dual functions to osteoarthritis progression. *EBioMedicine* **2022**, *76*, 103847.
59. Hangauer, M.J.; Viswanathan, V.S.; Ryan, M.J.; Bole, D.; Eaton, J.K.; Matov, A.; Galeas, J.; Dhruv, H.D.; Berens, M.E.; Schreiber, S.L.; et al. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. *Nature* **2017**, *551*, 247–250. [[CrossRef](#)]
60. Wang, Y.; Yan, S.; Liu, X.; Deng, F.; Wang, P.; Yang, L.; Hu, L.; Huang, K.; He, J. PRMT4 promotes ferroptosis to aggravate doxorubicin-induced cardiomyopathy via inhibition of the Nrf2/GPX4 pathway. *Cell Death Differ.* **2022**, *29*, 1982–1995. [[CrossRef](#)]
61. Zhang, J.; Bi, J.; Ren, Y.; Du, Z.; Li, T.; Wang, T.; Zhang, L.; Wang, M.; Wei, S.; Lv, Y.; et al. Involvement of GPX4 in irisin's protection against ischemia reperfusion-induced acute kidney injury. *J. Cell Physiol.* **2021**, *236*, 931–945. [[CrossRef](#)]
62. Reichert, C.O.; de Freitas, F.A.; Sampaio-Silva, J.; Rokita-Rosa, L.; Barros, P.d.L.; Levy, D.; Bydlowski, S.P. Ferroptosis Mechanisms Involved in Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 8765. [[CrossRef](#)] [[PubMed](#)]
63. 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. USA* **2015**, *112*, 268–272. [[CrossRef](#)]
64. Lin, W.; Tang, Y.; Zhang, M.; Liang, B.; Wang, M.; Zha, L.; Yu, Z. Integrated Bioinformatic Analysis Reveals TXNRD1 as a Novel Biomarker and Potential Therapeutic Target in Idiopathic Pulmonary Arterial Hypertension. *Front. Med.* **2022**, *9*, 894584. [[CrossRef](#)] [[PubMed](#)]
65. Fu, B.; Meng, W.; Zeng, X.; Zhao, H.; Liu, W.; Zhang, T. TXNRD1 Is an Unfavorable Prognostic Factor for Patients with Hepatocellular Carcinoma. *Biomed. Res. Int.* **2017**, *2017*, 4698167. [[CrossRef](#)]
66. Liang, J.; Wang, S.; Hu, J.; Hong, X.; Zhu, M.; Liu, X.; Alswadeh, M.; Mo, F.; Dai, M. Targeted inhibition of TXNRD1 prevents cartilage extracellular matrix degeneration by activating Nrf2 pathway in osteoarthritis. *Biochem. Biophys. Res. Commun.* **2022**, *635*, 267–276. [[CrossRef](#)]
67. Kudin, A.P.; Baron, G.; Zsurka, G.; Hampel, K.G.; Elger, C.E.; Grote, A.; Weber, Y.; Lerche, H.; Thiele, H.; Nürnberg, P.; et al. Homozygous mutation in TXNRD1 is associated with genetic generalized epilepsy. *Free Radic. Biol. Med.* **2017**, *106*, 270–277. [[CrossRef](#)] [[PubMed](#)]
68. Bailey, J.N.C.; ANZRAG Consortium; Loomis, S.J.; Kang, J.H.; Allingham, R.R.; Gharahkhani, P.; Khor, C.C.; Burdon, K.P.; Aschard, H.; Chasman, D.I.; et al. Genome-wide association analysis identifies TXNRD2, ATXN2 and FOXC1 as susceptibility loci for primary open-angle glaucoma. *Nat. Genet.* **2016**, *48*, 189–194. [[CrossRef](#)]

69. Sibbing, D.; Pfeufer, A.; Perisic, T.; Mannes, A.M.; Fritz-Wolf, K.; Unwin, S.; Sinner, M.F.; Gieger, C.; Gloeckner, C.J.; Wichmann, H.-E.; et al. Mutations in the mitochondrial thioredoxin reductase gene TXNRD2 cause dilated cardiomyopathy. *Eur. Heart J.* **2011**, *32*, 1121–1133. [\[CrossRef\]](#)
70. Kariž, S.; Mankoč, S.; Petrovič, D. Association of thioredoxin reductase 2 (TXNRD2) gene polymorphisms with myocardial infarction in Slovene patients with type 2 diabetes mellitus. *Diabetes Res. Clin. Pract.* **2015**, *108*, 323–328. [\[CrossRef\]](#)
71. Gencheva, R.; Arnér, E.S.J. Thioredoxin Reductase Inhibition for Cancer Therapy. *Annu. Rev. Pharmacol. Toxicol.* **2022**, *62*, 177–196. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Aboobakar, I.F.; Kinzy, T.G.; Zhao, Y.; Fan, B.; Pasquale, L.R.; Qassim, A.; Kolovos, A.; Schmidt, J.M.; Craig, J.E.; Bailey, J.N.C.; et al. Mitochondrial TXNRD2 and ME3 genetic risk scores are associated with specific primary open-angle glaucoma phenotypes. *Ophthalmology* **2023**, in press. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Dou, Q.; Turanov, A.A.; Mariotti, M.; Hwang, J.Y.; Lee, S.-G.; Paulo, J.A.; Yim, S.H.; Gygi, S.P.; Chung, J.-J.; Gladyshev, V.N. Selenoprotein TXNRD3 supports male fertility via the redox regulation of spermatogenesis. *J. Biol. Chem.* **2022**, *298*, 102183. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Liu, Q.; Du, P.; Zhu, Y.; Zhang, X.; Cai, J.; Zhang, Z. Thioredoxin reductase 3 suppression promotes colitis and carcinogenesis via activating pyroptosis and necrosis. *Cell Mol. Life Sci.* **2022**, *79*, 106. [\[CrossRef\]](#)
75. França, M.M.; German, A.; Fernandes, G.W.; Liao, X.-H.; Bianco, A.C.; Refetoff, S.; Dumitrescu, A.M. Human Type 1 Iodothyronine Deiodinase (DIO1) Mutations Cause Abnormal Thyroid Hormone Metabolism. *Thyroid* **2021**, *31*, 202–207. [\[CrossRef\]](#)
76. Bruinstroop, E.; Zhou, J.; Tripathi, M.; Yau, W.W.; Boelen, A.; Singh, B.K.; Yen, P.M. Early induction of hepatic deiodinase type 1 inhibits hepatosteatosis during NAFLD progression. *Mol. Metab.* **2021**, *53*, 101266. [\[CrossRef\]](#)
77. Poplawski, P.; Rybicka, B.; Boguslawska, J.; Rodzik, K.; Visser, T.J.; Nauman, A.; Piekliko-Witkowska, A. Induction of type 1 iodothyronine deiodinase expression inhibits proliferation and migration of renal cancer cells. *Mol. Cell Endocrinol.* **2017**, *442*, 58–67. [\[CrossRef\]](#)
78. Bomer, N.; Hollander, W.D.; Ramos, Y.F.M.; Bos, S.D.; van der Breggen, R.; Lakenberg, N.; Pepers, B.A.; van Eeden, A.E.; Darvishan, A.; Tobi, E.W.; et al. Underlying molecular mechanisms of DIO2 susceptibility in symptomatic osteoarthritis. *Ann. Rheum. Dis.* **2015**, *74*, 1571–1579. [\[CrossRef\]](#)
79. Bradley, D.; Liu, J.; Blaszcak, A.; Wright, V.; Jalilvand, A.; Needleman, B.; Noria, S.; Renton, D.; Hsueh, W. Adipocyte DIO2 Expression Increases in Human Obesity but Is Not Related to Systemic Insulin Sensitivity. *J. Diabetes Res.* **2018**, *2018*, 2464652. [\[CrossRef\]](#)
80. Guo, T.-W.; Zhang, F.-C.; Yang, M.-S.; Gao, X.-C.; Bian, L.; Duan, S.-W.; Zheng, Z.-J.; Gao, J.-J.; Wang, H.; Li, R.-L.; et al. Positive association of the DIO2 (deiodinase type 2) gene with mental retardation in the iodine-deficient areas of China. *J. Med. Genet.* **2004**, *41*, 585–590. [\[CrossRef\]](#)
81. Meulenbelt, I.; Bos, S.D.; Chapman, K.; van der Breggen, R.; Houwing-Duistermaat, J.J.; Kremer, D.; Kloppenburg, M.; Carr, A.; Tsezou, A.; González, A.; et al. Meta-analyses of genes modulating intracellular T3 bio-availability reveal a possible role for the DIO3 gene in osteoarthritis susceptibility. *Ann. Rheum. Dis.* **2011**, *70*, 164–167. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Liu, Y.Y.; Brent, G.A. Thyroid hormone and the brain: Mechanisms of action in development and role in protection and promotion of recovery after brain injury. *Pharmacol. Ther.* **2018**, *186*, 176–185. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Vidart, J.; Axelrud, L.; Braun, A.C.; Marschner, R.A.; Wajner, S.M. Relationship among Low T3 Levels, Type 3 Deiodinase, Oxidative Stress, and Mortality in Sepsis and Septic Shock: Defining Patient Outcomes. *Int. J. Mol. Sci.* **2023**, *24*, 3935. [\[CrossRef\]](#) [\[PubMed\]](#)
84. 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. [\[CrossRef\]](#)
85. Lee, H.-J.; Park, J.S.; Yoo, H.J.; Lee, H.M.; Lee, B.C.; Kim, J.H. The Selenoprotein MsrB1 Instructs Dendritic Cells to Induce T-Helper 1 Immune Responses. *Antioxidants* **2020**, *9*, 1021. [\[CrossRef\]](#)
86. Carlisle, A.E.; Lee, N.; Matthew-Onabanjo, A.N.; Spears, M.E.; Park, S.J.; Youkana, D.; Doshi, M.B.; Peppers, A.; Li, R.; Joseph, A.B.; et al. Selenium detoxification is required for cancer-cell survival. *Nat. Metab.* **2020**, *2*, 603–611. [\[CrossRef\]](#)
87. Flowers, B.; Bochnacka, O.; Poles, A.; Diamond, A.M.; Kastrati, I. Distinct Roles of SELENOF in Different Human Cancers. *Biomolecules* **2023**, *13*, 486. [\[CrossRef\]](#)
88. Li, M.; Zhang, Y.; Zhou, J.; Liu, H. Selenoprotein F Knockout Caused Glucose Metabolism Disorder in Young Mice by Disrupting Redox Homeostasis. *Antioxidants* **2022**, *11*, 2105. [\[CrossRef\]](#)
89. Bertz, M.; Kühn, K.; Koeberle, S.C.; Müller, M.F.; Hoelzer, D.; Thies, K.; Deubel, S.; Thierbach, R.; Kipp, A.P. Selenoprotein H controls cell cycle progression and proliferation of human colorectal cancer cells. *Free Radic. Biol. Med.* **2018**, *127*, 98–107. [\[CrossRef\]](#)
90. Sarma, A.S.; Siddardha, B.; Pragna Lakshmi, T.; Ranganath, P.; Dalal, A. A novel homozygous synonymous splicing variant in SELENOI gene causes spastic paraplegia 81. *J. Gene Med.* **2023**, *2023*, e3501. [\[CrossRef\]](#)
91. Zhang, Z.H.; Song, G.L. Roles of Selenoproteins in Brain Function and the Potential Mechanism of Selenium in Alzheimer's Disease. *Front. Neurosci.* **2021**, *15*, 646518. [\[CrossRef\]](#) [\[PubMed\]](#)

92. Abdurahman, A.; Li, Y.; Jia, S.-Z.; Xu, X.-W.; Lin, S.-J.; Ouyang, P.; He, Z.J.; Zhang, Z.-H.; Liu, Q.; Xu, Y.; et al. Knockdown of the SELENOK gene induces ferroptosis in cervical cancer cells. *Metallomics* **2023**, *15*, mfa019. [[CrossRef](#)] [[PubMed](#)]
93. Rogachev, V.V.; Goltyshev, M.V.; Varlamova, E.G.; Turovsky, E.A. Turovsky. Molecular Mechanisms of the Cytotoxic Effect of Recombinant Selenoprotein SELENOM on Human Glioblastoma Cells. *Int. J. Mol. Sci.* **2023**, *24*, 6469. [[CrossRef](#)] [[PubMed](#)]
94. Cai, J.; Huang, J.; Yang, J.; Chen, X.; Zhang, H.; Zhu, Y.; Liu, Q.; Zhang, Z. The protective effect of selenoprotein M on non-alcoholic fatty liver disease: The role of the AMPK α 1-MFN2 pathway and Parkin mitophagy. *Cell Mol. Life Sci.* **2022**, *79*, 354. [[CrossRef](#)] [[PubMed](#)]
95. Lin, S.; Chen, C.; Ouyang, P.; Cai, Z.; Liu, X.; Abdurahman, A.; Peng, J.; Li, Y.; Zhang, Z.; Song, G.-L. SELENOM Knockout Induces Synaptic Deficits and Cognitive Dysfunction by Influencing Brain Glucose Metabolism. *J. Agric. Food Chem.* **2023**, *71*, 1607–1619. [[CrossRef](#)]
96. Pozzer, D.; Varone, E.; Chernorudskiy, A.; Schiarea, S.; Missiroli, S.; Giorgi, C.; Pinton, P.; Canato, M.; Germinario, E.; Nogara, L.; et al. A maladaptive ER stress response triggers dysfunction in highly active muscles of mice with SELENON loss. *Redox Biol.* **2019**, *20*, 354–366. [[CrossRef](#)]
97. Zhao, Y.; Chen, P.; Lv, H.-J.; Wu, Y.; Liu, S.; Deng, X.; Shi, B.; Fu, J. Comprehensive Analysis of Expression and Prognostic Value of Selenoprotein Genes in Thyroid Cancer. *Genet. Test. Mol. Biomarkers* **2022**, *26*, 159–173. [[CrossRef](#)]
98. Wang, C.; Yu, Q.; Song, T.; Wang, Z.; Song, L.; Yang, Y.; Shao, J.; Li, J.; Ni, Y.; Chao, N.; et al. The heterogeneous immune landscape between lung adenocarcinoma and squamous carcinoma revealed by single-cell RNA sequencing. *Signal. Transduct. Target. Ther.* **2022**, *7*, 289. [[CrossRef](#)]
99. Short, S.P.; Pilat, J.M.; Barrett, C.W.; Reddy, V.K.; Haberman, Y.; Hendren, J.R.; Marsh, B.J.; Keating, C.E.; Motley, A.K.; Hill, K.E.; et al. Colonic Epithelial-Derived Selenoprotein P Is the Source for Antioxidant-Mediated Protection in Colitis-Associated Cancer. *Gastroenterology* **2021**, *160*, 1694–1708. [[CrossRef](#)]
100. Ekoue, D.N.; Ansong, E.; Liu, L.; Macias, V.; Deaton, R.; Lacher, C.; Picklo, M.; Nonn, L.; Gann, P.H.; Kajdacsy-Balla, A.; et al. Correlations of SELENOF and SELENOP genotypes with serum selenium levels and prostate cancer. *Prostate* **2018**, *78*, 279–288. [[CrossRef](#)]
101. Schweizer, U.; Wirth, E.K.; Klopstock, T.; Höltzer, S.M.; Becker, L.; Moskovitz, J.; Grune, T.; Fuchs, H.; Gailus-Durner, V.; de Angelis, M.H.; et al. Seizures, ataxia and parvalbumin-expressing interneurons respond to selenium supply in Selenop-deficient mice. *Redox Biol.* **2022**, *57*, 102490. [[CrossRef](#)] [[PubMed](#)]
102. Schomburg, L.; Orho-Melander, M.; Struck, J.; Bergmann, A.; Melander, O. Selenoprotein-P Deficiency Predicts Cardiovascular Disease and Death. *Nutrients* **2019**, *11*, 1852. [[CrossRef](#)] [[PubMed](#)]
103. Santos, L.R.; Durães, C.; Ziros, P.G.; Pestana, A.; Esteves, C.; Neves, C.; Carvalho, D.; Bongiovanni, M.; Renaud, C.O.; Char-toumpekis, D.V.; et al. Interaction of Genetic Variations in NFE2L2 and SELENOS Modulates the Risk of Hashimoto's Thyroiditis. *Thyroid* **2019**, *29*, 1302–1315. [[CrossRef](#)] [[PubMed](#)]
104. Strauss, E.; Tomczak, J.; Staniszewski, R.; Oszkinis, G. Associations and interactions between variants in selenoprotein genes, selenoprotein levels and the development of abdominal aortic aneurysm, peripheral arterial disease, and heart failure. *PLoS ONE* **2018**, *13*, e0203350. [[CrossRef](#)]
105. Varlamova, E.G.; Goltyshev, M.V.; Turovsky, E.A. The Role of Selenoproteins SELENOM and SELENOT in the Regulation of Apoptosis, ER Stress, and Calcium Homeostasis in the A-172 Human Glioblastoma Cell Line. *Biology* **2022**, *11*, 811. [[CrossRef](#)]
106. Alsharif, I.; Boukhzar, L.; Lefranc, B.; Godefroy, D.; Aury-Landas, J.; Rego, J.D.; Rego, J.D.; Naudet, F.; Arabo, A.; Chagraoui, A.; et al. Cell-penetrating, antioxidant SELENOT mimetic protects dopaminergic neurons and ameliorates motor dysfunction in Parkinson's disease animal models. *Redox Biol.* **2021**, *40*, 101839. [[CrossRef](#)]
107. Rocca, C.; Pasqua, T.; Boukhzar, L.; Anouar, Y.; Angelone, T. Progress in the emerging role of selenoproteins in cardiovascular disease: Focus on endoplasmic reticulum-resident selenoproteins. *Cell Mol. Life Sci.* **2019**, *76*, 3969–3985. [[CrossRef](#)]
108. Kim, H.; Lee, K.; Kim, J.M.; Kim, M.Y.; Kim, J.-R.; Lee, H.-W.; Chung, Y.W.; Shin, H.-I.; Kim, T.; Park, E.-S.; et al. Selenoprotein W ensures physiological bone remodeling by preventing hyperactivity of osteoclasts. *Nat. Commun.* **2021**, *12*, 2258. [[CrossRef](#)]
109. Liao, C.; Hardison, R.C.; Kennett, M.J.; Carlson, B.A.; Paulson, R.F.; Prabhu, K.S. Selenoproteins regulate stress erythroid progenitors and spleen microenvironment during stress erythropoiesis. *Blood* **2018**, *131*, 2568–2580. [[CrossRef](#)]
110. Shengyu, C.; Yinhu, L.; Yuanhong, L.; Jinbo, Z.; Can, F.; Hao, X.; Changjiang, Z. Selenium alleviates heart remodeling through Sirt1/AKT/GSK-3 β pathway. *Int. Immunopharmacol.* **2022**, *111*, 109158. [[CrossRef](#)]
111. Wang, Y.; Liu, B.; Wu, P.; Chu, Y.; Gui, S.; Zheng, Y.; Chen, X. Dietary Selenium Alleviated Mouse Liver Oxidative Stress and NAFLD Induced by Obesity by Regulating the KEAP1/NRF2 Pathway. *Antioxidants* **2022**, *11*, 349. [[CrossRef](#)]
112. Zhang, X.; Wang, Q.; Zhang, J.; Song, M.; Shao, B.; Han, Y.; Yang, X.; Li, Y. The Protective Effect of Selenium on T-2-Induced Nephrotoxicity Is Related to the Inhibition of ROS-Mediated Apoptosis in Mice Kidney. *Biol. Trace Elem. Res.* **2022**, *200*, 206–216. [[CrossRef](#)] [[PubMed](#)]
113. Marcocci, C.; Leo, M.; Altea, M.A. Oxidative stress in graves' disease. *Eur. Thyroid. J.* **2012**, *1*, 80–87. [[CrossRef](#)] [[PubMed](#)]
114. Maraldi, T.; Riccio, M.; Zamboni, L.; Vinceti, M.; De Pol, A.; Hakim, G. Low levels of selenium compounds are selectively toxic for a human neuron cell line through ROS/RNS increase and apoptotic process activation. *Neurotoxicology* **2011**, *32*, 180–187. [[CrossRef](#)] [[PubMed](#)]
115. Tosatto, S.C.; Bosello, V.; Fogolari, F.; Mauri, P.; Roveri, A.; Toppo, S.; Flohé, L.; Ursini, F.; Maiorino, M. The catalytic site of glutathione peroxidases. *Antioxid. Redox Signal.* **2008**, *10*, 1515–1526. [[CrossRef](#)] [[PubMed](#)]

116. Masuda, R.; Kimura, R.; Karasaki, T.; Sase, S.; Goto, K. Modeling the Catalytic Cycle of Glutathione Peroxidase by Nuclear Magnetic Resonance Spectroscopic Analysis of Selenocysteine Selenenic Acids. *J. Am. Chem. Soc.* **2021**, *143*, 6345–6350. [\[CrossRef\]](#)
117. Chu, F.; Doroshov, J.; Esworthy, R. Expression, characterization, and tissue distribution of a new cellular selenium-dependent glutathione peroxidase, GSHPx-GI. *J. Biol. Chem.* **1993**, *268*, 2571–2576. [\[CrossRef\]](#)
118. Wingler, K.; Böcher, M.; Flohé, L.; Kollmus, H.; Brigelius-Flohé, R. mRNA stability and selenocysteine insertion sequence efficiency rank gastrointestinal glutathione peroxidase high in the hierarchy of selenoproteins. *Eur. J. Biochem.* **1999**, *259*, 149–157. [\[CrossRef\]](#)
119. Björnstedt, M.; Xue, J.; Huang, W.; Akesson, B.; Holmgren, A. The thioredoxin and glutaredoxin systems are efficient electron donors to human plasma glutathione peroxidase. *J. Biol. Chem.* **1994**, *269*, 29382–29384. [\[CrossRef\]](#)
120. Schwarz, M.; Löser, A.; Cheng, Q.; Wichmann-Costaganna, M.; Schädel, P.; Werz, O.; Arnér, E.S.; Kipp, A.P. Side-by-side comparison of recombinant human glutathione peroxidases identifies overlapping substrate specificities for soluble hydroperoxides. *Redox Biol.* **2023**, *59*, 102593. [\[CrossRef\]](#)
121. Chi, Q.; Zhang, Q.; Lu, Y.; Zhang, Y.; Xu, S.; Li, S. Roles of selenoprotein S in reactive oxygen species-dependent neutrophil extracellular trap formation induced by selenium-deficient arteritis. *Redox Biol.* **2021**, *44*, 102003. [\[CrossRef\]](#)
122. Serfass, R.E.; Ganther, H.E. Defective microbicidal activity in glutathione peroxidase-deficient neutrophils of selenium-deficient rats. *Nature* **1975**, *255*, 640–641. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Pagmantidis, V.; Méplan, C.; van Schothorst, E.M.; Keijzer, J.; Hesketh, J.E. Supplementation of healthy volunteers with nutritionally relevant amounts of selenium increases the expression of lymphocyte protein biosynthesis genes. *Am. J. Clin. Nutr.* **2008**, *87*, 181–189. [\[CrossRef\]](#)
124. Pan, S.; Li, T.; Tan, Y.; Xu, H. Selenium-containing nanoparticles synergistically enhance Pemetrexed&NK cell-based chemotherapeutic. *Biomaterials* **2022**, *280*, 121321. [\[PubMed\]](#)
125. Gong, D.; Sun, K.; Yin, K.; Wang, X. Selenium mitigates the inhibitory effect of TBBPA on NETs release by regulating ROS/MAPK pathways-induced carp neutrophil apoptosis and necroptosis. *Fish Shellfish Immunol.* **2023**, *132*, 108501. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Huang, L.-J.; Mao, X.-T.; Li, Y.-Y.; Liu, D.-D.; Fan, K.-Q.; Liu, R.-B.; Wu, T.-T.; Wang, H.-L.; Zhang, Y.; Yang, B.; et al. Multiomics analyses reveal a critical role of selenium in controlling T cell differentiation in Crohn's disease. *Immunity* **2021**, *54*, 1728–1744.e7. [\[CrossRef\]](#)
127. Kiremidjian-Schumacher, L.; Roy, M.; Wishe, H.I.; Cohen, M.W.; Stotzky, G. Supplementation with selenium and human immune cell functions. II. Effect on cytotoxic lymphocytes and natural killer cells. *Biol. Trace Elem. Res.* **1994**, *41*, 115–127. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Enqvist, M.; Nilsson, G.; Hammarfjord, O.; Wallin, R.P.; Björkstöm, N.K.; Björnstedt, M.; Hjerpe, A.; Ljunggren, H.G.; Dobra, K.; Malmberg, K.J.; et al. Selenite induces posttranscriptional blockade of HLA-E expression and sensitizes tumor cells to CD94/NKG2A-positive NK cells. *J. Immunol.* **2011**, *187*, 3546–3554. [\[CrossRef\]](#)
129. Kiremidjian-Schumacher, L.; Roy, M.; Wishe, H.I.; Cohen, M.W.; Stotzky, G. Supplementation with selenium and human immune cell functions. I. Effect on lymphocyte proliferation and interleukin 2 receptor expression. *Biol. Trace Elem. Res.* **1994**, *41*, 103–114. [\[CrossRef\]](#)
130. Nelson, S.M.; Lei, X.; Prabhu, K.S. Selenium levels affect the IL-4-induced expression of alternative activation markers in murine macrophages. *J. Nutr.* **2011**, *141*, 1754–1761. [\[CrossRef\]](#)
131. de Toledo, J.; Fraga-Silva, T.F.; Borim, P.A.; de Oliveira, L.R.; Oliveira, E.D.; Périco, L.L.; Hiruma-Lima, C.A.; de Souza, A.A.L.; de Oliveira, C.A.F.; Padilha, P.M.; et al. Organic Selenium Reaches the Central Nervous System and Downmodulates Local Inflammation: A Complementary Therapy for Multiple Sclerosis? *Front. Immunol.* **2020**, *11*, 571844. [\[CrossRef\]](#)
132. Winterbourn, C.C.; Kettle, A.J.; Hampton, M.B. Reactive Oxygen Species and Neutrophil Function. *Annu. Rev. Biochem.* **2016**, *85*, 765–792. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Boyne, R.; Arthur, J.R. The response of selenium-deficient mice to *Candida albicans* infection. *J. Nutr.* **1986**, *116*, 816–822. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Miller, A.L. The etiologies, pathophysiology, and alternative/complementary treatment of asthma. *Altern. Med. Rev.* **2001**, *6*, 20–47.
135. Gholami, M.; Zendedel, A.; Khayat, Z.K.; Ghanad, K.; Nazari, A.; Pirhadi, A. Selenium effect on ischemia-reperfusion injury of gastrocnemius muscle in adult rats. *Biol. Trace Elem. Res.* **2015**, *164*, 205–211. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Zendejdel, A.; Gharibi, Z.; Anbari, K.; Abbaszadeh, A.; Khayat, Z.K.; Khorramabadi, R.M.; Soleymaninejad, M.; Gholami, M. Ameliorate Peripheral Nerve Ischemic-Reperfusion Injury via Decreased TNF- α . *Biol. Trace Elem. Res.* **2017**, *176*, 328–337. [\[CrossRef\]](#)
137. Safaralizadeh, R.; Nourizadeh, M.; Zare, A.; Kardar, G.A.; Pourpak, Z. Influence of selenium on mast cell mediator release. *Biol. Trace Elem. Res.* **2013**, *154*, 299–303. [\[CrossRef\]](#) [\[PubMed\]](#)
138. Hong, C.; Chow, C. Induction of eosinophilic enteritis and eosinophilia in rats by vitamin E and selenium deficiency. *Exp. Mol. Pathol.* **1988**, *48*, 182–192. [\[CrossRef\]](#)
139. Weitzel, F.; Wendel, A. Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide tone. *J. Biol. Chem.* **1993**, *268*, 6288–6292. [\[CrossRef\]](#)
140. Dalla Puppa, L.; Savaskan, N.E.; Bräuer, A.U.; Behne, D.; Kyriakopoulos, A. The role of selenite on microglial migration. *Ann. N. Y. Acad. Sci.* **2007**, *1096*, 179–183. [\[CrossRef\]](#)

141. Branco, V.; Coppo, L.; Aschner, M.; Carvalho, C. N-Acetylcysteine or Sodium Selenite Prevent the p38-Mediated Production of Proinflammatory Cytokines by Microglia during Exposure to Mercury (II). *Toxics* **2022**, *10*, 433. [\[CrossRef\]](#) [\[PubMed\]](#)
142. Shrimali, R.K.; Irons, R.D.; Carlson, B.A.; Sano, Y.; Gladyshev, V.N.; Park, J.M.; Hatfield, D.L. Hatfield. Selenoproteins mediate T cell immunity through an antioxidant mechanism. *J. Biol. Chem.* **2008**, *283*, 20181–20185. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Smith-Garvin, J.E.; Koretzky, G.A.; Jordan, M.S. T cell activation. *Annu. Rev. Immunol.* **2009**, *27*, 591–619. [\[CrossRef\]](#) [\[PubMed\]](#)
144. Kuhns, M.S.; Davis, M.M.; Garcia, K.C. Deconstructing the form and function of the TCR/CD3 complex. *Immunity* **2006**, *24*, 133–139. [\[CrossRef\]](#)
145. Yue, T.; Zhan, X.; Zhang, D.; Jain, R.; Wang, K.-W.; Choi, J.H.; Misawa, T.; Su, L.; Quan, J.; Hildebrand, S.; et al. SLFN2 protection of tRNAs from stress-induced cleavage is essential for T cell-mediated immunity. *Science* **2021**, *372*, eaba4220. [\[CrossRef\]](#)
146. Sena, L.A.; Li, S.; Jairaman, A.; Prakriya, M.; Ezponda, T.; Hildeman, D.A.; Wang, C.-R.; Schumacker, P.T.; Licht, J.D.; Perlman, H.; et al. Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. *Immunity* **2013**, *38*, 225–236. [\[CrossRef\]](#)
147. Roy, M.; Kiremidjian-Schumacher, L.; Wishe, H.I.; Cohen, M.W.; Stotzky, G. Selenium supplementation enhances the expression of interleukin 2 receptor subunits and internalization of interleukin 2. *Proc. Soc. Exp. Biol. Med.* **1993**, *202*, 295–301. [\[CrossRef\]](#)
148. Thikkurissy, S.; Pavone, A.; Rega, A.; Bae, R.; Roy, M.; Wishe, H.I.; Kiremidjian-Schumacher, L. Effect of interleukin-2 and selenium on the growth of squamous cell carcinoma cells. *Otolaryngol. Head. Neck. Surg.* **2001**, *124*, 142–149. [\[CrossRef\]](#)
149. Verma, S.; Hoffmann, F.W.; Kumar, M.; Huang, Z.; Roe, K.; Nguyen-Wu, E.; Hashimoto, A.S.; Hoffmann, P.R. Selenoprotein K knock-out mice exhibit deficient calcium flux in immune cells and impaired immune responses. *J. Immunol.* **2011**, *186*, 2127–2137. [\[CrossRef\]](#)
150. Ren, X.; Wang, S.; Zhang, C.; Hu, X.; Zhou, L.; Li, Y.; Xu, L. Selenium ameliorates cadmium-induced mouse leydig TM3 cell apoptosis via inhibiting the ROS/JNK/c-jun signaling pathway. *Ecotoxicol. Environ. Saf.* **2020**, *192*, 110266. [\[CrossRef\]](#)
151. Dehghani, M.; Shokrgozar, N.; Ramzi, M.; Kalani, M.; Golmoghaddam, H.; Arandi, N. The impact of selenium on regulatory T cell frequency and immune checkpoint receptor expression in patients with diffuse large B cell lymphoma (DLBCL). *Cancer Immunol. Immunother.* **2021**, *70*, 2961–2969. [\[CrossRef\]](#) [\[PubMed\]](#)
152. McCarty, M. Promotion of interleukin-2 activity as a strategy for ‘rejuvenating’ geriatric immune function. *Med. Hypotheses* **1997**, *48*, 47–54. [\[CrossRef\]](#)
153. Peretz, A.A.; Nève, J.; Desmedt, J.; Duchateau, J.; Dramaix, M.; Famaey, J.P. Lymphocyte response is enhanced by supplementation of elderly subjects with selenium-enriched yeast. *Am. J. Clin. Nutr.* **1991**, *53*, 1323–1328. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Hoffmann, F.W.; Hashimoto, A.C.; Shafer, L.A.; Dow, S.; Berry, M.J.; Hoffmann, P.R. Dietary selenium modulates activation and differentiation of CD4+ T cells in mice through a mechanism involving cellular free thiols. *J. Nutr.* **2010**, *140*, 1155–1161. [\[CrossRef\]](#) [\[PubMed\]](#)
155. Fu, J.; Yang, T.; Wang, W.; Xu, S. Effect of selenium antagonist lead-induced damage on Th1/Th2 imbalance in the peripheral blood lymphocytes of chickens. *Ecotoxicol. Environ. Saf.* **2019**, *175*, 74–82. [\[CrossRef\]](#) [\[PubMed\]](#)
156. Romagnani, S. Th1 and Th2 in human diseases. *Clin. Immunol. Immunopathol.* **1996**, *80*, 225–235. [\[CrossRef\]](#)
157. Hawkes, W.C.; Hwang, A.; Alkan, Z. The effect of selenium supplementation on DTH skin responses in healthy North American men. *J. Trace Elem. Med. Biol.* **2009**, *23*, 272–280. [\[CrossRef\]](#)
158. Hasselmark, L.; Malmgren, R.; Zetterström, O.; Unge, G. Selenium supplementation in intrinsic asthma. *Allergy* **1993**, *48*, 30–36.
159. Yao, Y.; Chen, Z.; Zhang, H.; Chen, C.; Zeng, M.; Yunis, J.; Wei, Y.; Wan, Y.; Wang, N.; Zhou, M.; et al. Selenium-GPX4 axis protects follicular helper T cells from ferroptosis. *Nat. Immunol.* **2021**, *22*, 1127–1139. [\[CrossRef\]](#)
160. Werz, O.; Steinhilber, D. Selenium-dependent peroxidases suppress 5-lipoxygenase activity in B-lymphocytes and immature myeloid cells. The presence of peroxidase-insensitive 5-lipoxygenase activity in differentiated myeloid cells. *Eur. J. Biochem.* **1996**, *242*, 90–97. [\[CrossRef\]](#)
161. Vega, L.; Rodríguez-Sosa, M.; García-Montalvo, E.A.; Del Razo, L.M.; Elizondo, G. Non-optimal levels of dietary selenomethionine alter splenocyte response and modify oxidative stress markers in female mice. *Food Chem. Toxicol.* **2007**, *45*, 1147–1153. [\[CrossRef\]](#) [\[PubMed\]](#)
162. Cheng, W.-H.; Holmström, A.; Li, X.; Wu, R.T.Y.; Zeng, H.; Xiao, Z. Effect of dietary selenium and cancer cell xenograft on peripheral T and B lymphocytes in adult nude mice. *Biol. Trace Elem. Res.* **2012**, *146*, 230–235. [\[CrossRef\]](#) [\[PubMed\]](#)
163. Gao, S.; Jin, Y.; Hall, K.S.; Liang, C.; Unverzagt, F.W.; Ji, R.; Murrell, J.R.; Cao, J.; Shen, J.; Ma, F.; et al. Selenium level and cognitive function in rural elderly Chinese. *Am. J. Epidemiol.* **2007**, *165*, 955–965. [\[CrossRef\]](#) [\[PubMed\]](#)
164. Cardoso, B.R.; Roberts, B.R.; Malpas, C.B.; Vivash, L.; Genc, S.; Saling, M.M.; Desmond, P.; Steward, C.; Hicks, R.J.; Callahan, J.; et al. Supranutritional Sodium Selenate Supplementation Delivers Selenium to the Central Nervous System: Results from a Randomized Controlled Pilot Trial in Alzheimer’s Disease. *Neurotherapeutics* **2019**, *16*, 192–202. [\[CrossRef\]](#)
165. Corcoran, N.M.; Martin, D.; Hutter-Paier, B.; Windisch, M.; Nguyen, T.; Nheu, L.; Sundstrom, L.E.; Costello, A.J.; Hovens, C.M. Sodium selenate specifically activates PP2A phosphatase, dephosphorylates tau and reverses memory deficits in an Alzheimer’s disease model. *J. Clin. Neurosci.* **2010**, *17*, 1025–1033. [\[CrossRef\]](#)
166. van Eersel, J.; Ke, Y.D.; Liu, X.; Delerue, F.; Kril, J.J.; Götz, J.; Ittner, L.M. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer’s disease models. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 13888–13893. [\[CrossRef\]](#)
167. Sun, C.; Du, Z.; Liu, X.; Yang, Y.; Zhou, S.; Li, C.; Cao, X.; Zhao, Q.; Wong, K.; Chen, W.; et al. Selenium Forms and Dosages Determined Their Biological Actions in Mouse Models of Parkinson’s Disease. *Nutrients* **2022**, *15*, 11. [\[CrossRef\]](#)

168. Sophiabadi, M.; Rastgoo, N.; Haghdooost-Yazdi, H. Dopaminergic Neuronal Death in Substantia Nigra Associates with Serum Levels of Total Bilirubin, Selenium, and Zinc: Evidences from 6-Hydroxydopamine Animal Model of Parkinson's Disease. *Biol. Trace Elem. Res.* **2022**, *200*, 4058–4067. [\[CrossRef\]](#)
169. Ellwanger, J.H.; Molz, P.; Dallemole, D.R.; dos Santos, A.P.; Müller, T.E.; Cappelletti, L.; da Silva, M.G.; Franke, S.I.R.; Prá, D.; Henriques, J.A.P. Selenium reduces bradykinesia and DNA damage in a rat model of Parkinson's disease. *Nutrition* **2015**, *31*, 359–365. [\[CrossRef\]](#)
170. Tawfik, K.M.; Moustafa, Y.M.; El-Azab, M.F. Neuroprotective mechanisms of sildenafil and selenium in PTZ-kindling model: Implications in epilepsy. *Eur. J. Pharmacol.* **2018**, *833*, 131–144. [\[CrossRef\]](#)
171. Nazıroğlu, M. Role of selenium on calcium signaling and oxidative stress-induced molecular pathways in epilepsy. *Neurochem. Res.* **2009**, *34*, 2181–2191. [\[CrossRef\]](#)
172. Schibler, U. Selenium cysteine and epileptic seizures. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 753. [\[CrossRef\]](#)
173. Burk, R.F.; Hill, K.E.; Motley, A.K.; Winfrey, V.P.; Kurokawa, S.; Mitchell, S.L.; Zhang, W. Selenoprotein P and apolipoprotein E receptor-2 interact at the blood-brain barrier and also within the brain to maintain an essential selenium pool that protects against neurodegeneration. *FASEB J.* **2014**, *28*, 3579–3588. [\[CrossRef\]](#) [\[PubMed\]](#)
174. Burk, R.F.; Hill, K.E.; Olson, G.E.; Weeber, E.J.; Motley, A.K.; Winfrey, V.P.; Austin, L.M. Deletion of apolipoprotein E receptor-2 in mice lowers brain selenium and causes severe neurological dysfunction and death when a low-selenium diet is fed. *J. Neurosci.* **2007**, *27*, 6207–6211. [\[CrossRef\]](#)
175. Schweizer, U.; Streckfuss, F.; Pelt, P.; Carlson, B.A.; Hatfield, D.L.; Köhrle, J.; Schomburg, L. Hepatically derived selenoprotein P is a key factor for kidney but not for brain selenium supply. *Biochem. J.* **2005**, *386*, 221–226. [\[CrossRef\]](#) [\[PubMed\]](#)
176. Schomburg, L.; Schweizer, U.; Holtmann, B.; Flohé, L.; Sendtner, M.; Köhrle, J. Gene disruption discloses role of selenoprotein P in selenium delivery to target tissues. *Biochem. J.* **2003**, *370*, 397–402. [\[CrossRef\]](#) [\[PubMed\]](#)
177. Sasuclark, A.R.; Khadka, V.S.; Pitts, M.W. Cell-Type Specific Analysis of Selenium-Related Genes in Brain. *Antioxidants* **2019**, *8*, 120. [\[CrossRef\]](#) [\[PubMed\]](#)
178. Scharpf, M.; Schweizer, U.; Arzberger, T.; Roggendorf, W.; Schomburg, L.; Köhrle, J. Neuronal and ependymal expression of selenoprotein P in the human brain. *J. Neural. Transm.* **2007**, *114*, 877–884. [\[CrossRef\]](#)
179. Caito, S.W.; Milatovic, D.; Hill, K.E.; Aschner, M.; Burk, R.F.; Valentine, W.M. Progression of neurodegeneration and morphologic changes in the brains of juvenile mice with selenoprotein P deleted. *Brain Res.* **2011**, *1398*, 1–12. [\[CrossRef\]](#)
180. Yang, W.S.; SriRamaratnam, R.; Welsch, M.E.; Shimada, K.; Skouta, R.; Viswanathan, V.S.; Cheah, J.H.; Clemons, P.A.; Shamji, A.F.; Clish, C.B.; et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell* **2014**, *156*, 317–331. [\[CrossRef\]](#)
181. Ingold, I.; Berndt, C.; Schmitt, S.; Doll, S.; Poschmann, G.; Buday, K.; Roveri, A.; Peng, X.; Porto Freitas, F.P.; Seibt, T.; et al. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. *Cell* **2018**, *172*, 409–422.e21. [\[CrossRef\]](#) [\[PubMed\]](#)
182. Yant, L.J.; Ran, Q.; Rao, L.; Van Remmen, H.; Shibata, T.; Belter, J.G.; Motta, L.; Richardson, A.; Prolla, T.A. The selenoprotein GPX4 is essential for mouse development and protects from radiation and oxidative damage insults. *Free Radic. Biol. Med.* **2003**, *34*, 496–502. [\[CrossRef\]](#) [\[PubMed\]](#)
183. Yoo, S.-E.; Chen, L.; Na, R.; Liu, Y.; Rios, C.; Van Remmen, H.; Richardson, A.; Ran, Q. Gpx4 ablation in adult mice results in a lethal phenotype accompanied by neuronal loss in brain. *Free Radic. Biol. Med.* **2012**, *52*, 1820–1827. [\[CrossRef\]](#)
184. Wirth, E.K.; Conrad, M.; Winterer, J.; Wozny, C.; Carlson, B.A.; Roth, S.; Schmitz, D.; Bornkamm, G.W.; Coppola, V.; Tessarollo, L.; et al. Neuronal selenoprotein expression is required for interneuron development and prevents seizures and neurodegeneration. *FASEB J.* **2010**, *24*, 844–852. [\[CrossRef\]](#) [\[PubMed\]](#)
185. Chen, S.; Chen, Y.; Zhang, Y.; Kuang, X.; Liu, Y.; Guo, M.; Ma, L.; Zhang, D.; Li, Q. Iron Metabolism and Ferroptosis in Epilepsy. *Front. Neurosci.* **2020**, *14*, 601193. [\[CrossRef\]](#) [\[PubMed\]](#)
186. Kahn-Kirby, A.H.; Amagata, A.; Maeder, C.I.; Mei, J.J.; Sideris, S.; Kosaka, Y.; Hinman, A.; Malone, S.A.; Bruegger, J.J.; Wang, L.; et al. Targeting ferroptosis: A novel therapeutic strategy for the treatment of mitochondrial disease-related epilepsy. *PLoS ONE* **2019**, *14*, e0214250. [\[CrossRef\]](#)
187. Yoo, M.H.; Gu, X.; Xu, X.M.; Kim, J.Y.; Carlson, B.A.; Patterson, A.D.; Cai, H.; Gladyshev, V.N.; Hatfield, D.L. Delineating the role of glutathione peroxidase 4 in protecting cells against lipid hydroperoxide damage and in Alzheimer's disease. *Antioxid. Redox Signal* **2010**, *12*, 819–827. [\[CrossRef\]](#)
188. Bellinger, F.P.; Bellinger, M.T.; Seale, L.A.; Takemoto, A.S.; Raman, A.V.; Miki, T.; Manning-Boğ, A.B.; Berry, M.J.; White, L.R.; Ross, G.W. Glutathione Peroxidase 4 is associated with Neuromelanin in Substantia Nigra and Dystrophic Axons in Putamen of Parkinson's brain. *Mol. Neurodegener.* **2011**, *6*, 8. [\[CrossRef\]](#)
189. 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 Biol.* **2017**, *12*, 8–17. [\[CrossRef\]](#)
190. Chung, Y.W.; Jeong, D.; Noh, O.J.; Park, Y.H.; Kang, S.I.; Lee, M.G.; Lee, T.-H.; Bin Yim, M.; Kim, I.Y. Antioxidative role of selenoprotein W in oxidant-induced mouse embryonic neuronal cell death. *Mol. Cells* **2009**, *27*, 609–613. [\[CrossRef\]](#)
191. Zhang, Y.; Zhou, Y.; Schweizer, U.; Savaskan, N.E.; Hua, D.; Kipnis, J.; Hatfield, D.L.; Gladyshev, V.N. Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals. *J. Biol. Chem.* **2008**, *283*, 2427–2438. [\[CrossRef\]](#) [\[PubMed\]](#)

192. Loscalzo, J. Keshan disease, selenium deficiency, and the selenoproteome. *N. Engl. J. Med.* **2014**, *370*, 1756–1760. [[CrossRef](#)] [[PubMed](#)]
193. Liu, X.; Wang, Y.; Han, S.; Zhang, Y.; Zou, Y.; Su, S.; Zhou, H.; Zhang, X.; Liang, H.; Hou, J.; et al. A Spatial Ecological Study on Serum Selenium and Keshan Disease in Heilongjiang Province, China. *Biol. Trace Elem. Res.* **2021**, *199*, 3253–3261. [[CrossRef](#)] [[PubMed](#)]
194. Moore, J.A.; Noiva, R.; Wells, I.C. Selenium concentrations in plasma of patients with arteriographically defined coronary atherosclerosis. *Clin. Chem.* **1984**, *30*, 1171–1173. [[CrossRef](#)]
195. Krohn, R.M.; Lemaire, M.; Silva, L.F.N.; Lemarié, C.; Bolt, A.; Mann, K.K.; Smits, J. High-selenium lentil diet protects against arsenic-induced atherosclerosis in a mouse model. *J. Nutr. Biochem.* **2016**, *27*, 9–15. [[CrossRef](#)] [[PubMed](#)]
196. Schwenke, D.C.; Behr, S.R. Vitamin E combined with selenium inhibits atherosclerosis in hypercholesterolemic rabbits independently of effects on plasma cholesterol concentrations. *Circ. Res.* **1998**, *83*, 366–377. [[CrossRef](#)]
197. Zhang, Y.; Cartland, S.P.; Henriquez, R.; Patel, S.; Gammelgaard, B.; Flouda, K.; Hawkins, C.L.; Rayner, B.S. Selenomethionine supplementation reduces lesion burden, improves vessel function and modulates the inflammatory response within the setting of atherosclerosis. *Redox Biol.* **2020**, *29*, 101409. [[CrossRef](#)]
198. Luoma, P.V.; Sotaniemi, E.A.; Korpela, H.; Kumpulainen, J. Serum selenium, glutathione peroxidase activity and high-density lipoprotein cholesterol—Effect of selenium supplementation. *Res. Commun. Chem. Pathol. Pharmacol.* **1984**, *46*, 469–472.
199. Maiorino, M.; Conrad, M.; Ursini, F. GPx4, Lipid Peroxidation, and Cell Death: Discoveries, Rediscoveries, and Open Issues. *Antioxid. Redox Signal* **2018**, *29*, 61–74. [[CrossRef](#)]
200. Leitinger, N. Cholesteryl ester oxidation products in atherosclerosis. *Mol. Aspects. Med.* **2003**, *24*, 239–250. [[CrossRef](#)]
201. Hussein, O.; Rosenblat, M.; Refael, G.; Aviram, M. Dietary selenium increases cellular glutathione peroxidase activity and reduces the enhanced susceptibility to lipid peroxidation of plasma and low-density lipoprotein in kidney transplant recipients. *Transplantation* **1997**, *63*, 679–685. [[CrossRef](#)] [[PubMed](#)]
202. Toivanen, J.L. Effects of selenium, vitamin E and vitamin C on human prostacyclin and thromboxane synthesis in vitro. *Prostaglandins. Leukot. Med.* **1987**, *26*, 265–280. [[CrossRef](#)] [[PubMed](#)]
203. Luoma, P.V.; Stengård, J.; Korpela, H.; Rautio, A.; Sotaniemi, E.A.; Suvanto, E.; Marniemi, J. Lipid peroxides, glutathione peroxidase, high density lipoprotein subfractions and apolipoproteins in young adults. *J. Intern. Med.* **1990**, *227*, 287–289. [[CrossRef](#)] [[PubMed](#)]
204. Sies, H.; Jones, D.P. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 363–383. [[CrossRef](#)]
205. Choi, A.M.; Ryter, S.W.; Levine, B. Autophagy in human health and disease. *N. Engl. J. Med.* **2013**, *368*, 651–662. [[CrossRef](#)]
206. Blankenberg, S.; Rupprecht, H.J.; Bickel, C.; Torzewski, M.; Hafner, G.; Tiret, L.; Smieja, M.; Cambien, F.; Meyer, J.; Lackner, K.J. Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. *N. Engl. J. Med.* **2003**, *349*, 1605–1613. [[CrossRef](#)]
207. Sordillo, L.M.; Streicher, K.L.; Mullarky, I.K.; Gandy, J.C.; Trigona, W.; Corl, C.M. Selenium inhibits 15-hydroperoxyoctadecadienoic acid-induced intracellular adhesion molecule expression in aortic endothelial cells. *Free Radic. Biol. Med.* **2008**, *44*, 34–43. [[CrossRef](#)]
208. Gao, J.; Tian, X.; Yan, X.; Wang, Y.; Wei, J.; Wang, X.; Yan, X.; Song, G. Selenium Exerts Protective Effects Against Fluoride-Induced Apoptosis and Oxidative Stress and Altered the Expression of Bcl-2/Caspase Family. *Biol. Trace Elem. Res.* **2021**, *199*, 682–692. [[CrossRef](#)]
209. Han, Q.; Wang, A.; Fu, Q.; Zhou, S.; Bao, J.; Xing, H. Protective role of selenium on ammonia-mediated nephrotoxicity via PI3K/AKT/mTOR pathway: Crosstalk between autophagy and cytokine release. *Ecotoxicol. Environ. Saf.* **2022**, *242*, 113918. [[CrossRef](#)]
210. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. *Cell* **2012**, *149*, 1060–1072. [[CrossRef](#)]
211. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Selenium and outcome in heart failure. *Eur. J. Heart Fail* **2020**, *22*, 1415–1423.
212. Fleming, C.R.; Lie, J.; McCall, J.; O'Brien, J.; Baillie, E.E.; Thistle, J.L. Selenium deficiency and fatal cardiomyopathy in a patient on home parenteral nutrition. *Gastroenterology* **1982**, *83*, 689–693. [[CrossRef](#)]
213. Jenkins, D.J.A.; Spence, J.D.; Giovannucci, E.L.; Kim, Y.-I.; Josse, R.; Vieth, R.; Blanco Mejia, S.; Viguiliouk, E.; Nishi, S.; Sahye-Pudaruth, S.; et al. Supplemental Vitamins and Minerals for CVD Prevention and Treatment. *J. Am. Coll. Cardiol.* **2018**, *71*, 2570–2584. [[CrossRef](#)] [[PubMed](#)]
214. Virtamo, J.; Valkeila, E.; Alfthan, G.; Punsar, S.; Huttunen, J.K.; Karvonen, M.J. Serum selenium and the risk of coronary heart disease and stroke. *Am. J. Epidemiol.* **1985**, *122*, 276–282. [[CrossRef](#)]
215. Salvini, S.; Hennekens, C.H.; Morris, J.; Willett, W.C.; Stampfer, M.J. Plasma levels of the antioxidant selenium and risk of myocardial infarction among U.S. physicians. *Am. J. Cardiol.* **1995**, *76*, 1218–1221. [[CrossRef](#)] [[PubMed](#)]
216. Eagle, K.; Jiang, Y.; Shi, X.; Li, M.; Obholzer, N.P.; Hu, T.; Perez, M.W.; Koren, J.V.; Kitano, A.; Yi, J.S.; et al. An oncogenic enhancer encodes selective selenium dependency in AML. *Cell Stem. Cell* **2022**, *29*, 386–399.e7. [[CrossRef](#)]

217. Sundström, H.; Korpela, H.; Viinikka, L.; Kauppila, A. Serum selenium and glutathione peroxidase, and plasma lipid peroxides in uterine, ovarian or vulvar cancer, and their responses to antioxidants in patients with ovarian cancer. *Cancer Lett.* **1984**, *24*, 1–10. [\[CrossRef\]](#)
218. Schwartz, M.K. Role of trace elements in cancer. *Cancer Res.* **1975**, *35*, 3481–3487.
219. Willett, W.; Morris, J.S.; Pressel, S.; Taylor, J.; Polk, B.F.; Stampfer, M.; Rosner, B.; Schneider, K.; Hames, C. Prediagnostic serum selenium and risk of cancer. *Lancet* **1983**, *2*, 130–134. [\[CrossRef\]](#)
220. Lotan, Y.; Goodman, P.J.; Youssef, R.F.; Svatek, R.S.; Shariat, S.F.; Tangen, C.M.; Thompson, I.M.; Klein, E.A. Evaluation of vitamin E and selenium supplementation for the prevention of bladder cancer in SWOG coordinated SELECT. *J. Urol.* **2012**, *187*, 2005–2010. [\[CrossRef\]](#)
221. Reid, M.E.; Duffield-Lillico, A.J.; Garland, L.; Turnbull, B.W.; Clark, L.C.; Marshall, J.R. Selenium supplementation and lung cancer incidence: An update of the nutritional prevention of cancer trial. *Cancer Epidemiol. Biomarkers Prev.* **2002**, *11*, 1285–1291. [\[PubMed\]](#)
222. Lippman, S.M.; Klein, E.A.; Goodman, P.J.; Lucia, M.S.; Thompson, I.M.; Ford, L.G.; Parnes, H.L.; Minasian, L.M.; Gaziano, J.M.; Hartline, J.A.; et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* **2009**, *301*, 39–51. [\[CrossRef\]](#) [\[PubMed\]](#)
223. Yu, S.Y.; Zhu, Y.J.; Li, W.G. Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong. *Biol. Trace Elem. Res.* **1997**, *56*, 117–124. [\[CrossRef\]](#) [\[PubMed\]](#)
224. Flowers, B.; Poles, A.; Kastrati, I. Selenium and breast cancer—An update of clinical and epidemiological data. *Arch. Biochem. Biophys.* **2022**, *732*, 109465. [\[CrossRef\]](#)
225. Clark, L.C.; Dalkin, B.; Krongrad, A.; Combs, G.F., Jr.; Turnbull, B.W.; Slate, E.H.; Witherington, R.; Herlong, J.H.; Janosko, E.; Carpenter, D.; et al. Decreased incidence of prostate cancer with selenium supplementation: Results of a double-blind cancer prevention trial. *Br. J. Urol.* **1998**, *81*, 730–734. [\[CrossRef\]](#)
226. Mukhtar, M.; Ashfield, N.; Vodickova, L.; Vymetalkova, V.; Levy, M.; Liska, V.; Bruha, J.; Bendova, P.; O'sullivan, J.; Doherty, G.; et al. The Associations of Selenoprotein Genetic Variants with the Risks of Colorectal Adenoma and Colorectal Cancer: Case-Control Studies in Irish and Czech Populations. *Nutrients*. **2022**, *14*, 2718. [\[CrossRef\]](#)
227. Efendić, S.; Luft, R.; Wajngot, A. Aspects of the pathogenesis of type 2 diabetes. *Endocr. Rev.* **1984**, *5*, 395–410. [\[CrossRef\]](#)
228. Stranges, S.; Marshall, J.R.; Natarajan, R.; Donahue, R.P.; Trevisan, M.; Combs, G.F.; Cappuccio, F.P.; Ceriello, A.; Reid, M.E. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: A randomized trial. *Ann. Intern. Med.* **2007**, *147*, 217–223. [\[CrossRef\]](#)
229. Vinceti, M.; Filippini, T.; Rothman, K.J. Selenium exposure and the risk of type 2 diabetes: A systematic review and meta-analysis. *Eur. J. Epidemiol.* **2018**, *33*, 789–810. [\[CrossRef\]](#)
230. Misu, H.; Takamura, T.; Takayama, H.; Hayashi, H.; Matsuzawa-Nagata, N.; Kurita, S.; Ishikura, K.; Ando, H.; Takeshita, Y.; Ota, T.; et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. *Cell Metab.* **2010**, *12*, 483–495. [\[CrossRef\]](#)
231. Misu, H.; Takayama, H.; Saito, Y.; Mita, Y.; Kikuchi, A.; Ishii, K.-A.; Chikamoto, K.; Kanamori, T.; Tajima, N.; Lan, F.; et al. Deficiency of the hepatokine selenoprotein P increases responsiveness to exercise in mice through upregulation of reactive oxygen species and AMP-activated protein kinase in muscle. *Nat. Med.* **2017**, *23*, 508–516. [\[CrossRef\]](#) [\[PubMed\]](#)
232. Harmon, J.S.; Bogdani, M.; Parazzoli, S.D.; Mak, S.S.; Oseid, E.A.; Berghmans, M.; Leboeuf, R.C.; Robertson, R.P. beta-Cell-specific overexpression of glutathione peroxidase preserves intranuclear MafA and reverses diabetes in db/db mice. *Endocrinology* **2009**, *150*, 4855–4862. [\[CrossRef\]](#) [\[PubMed\]](#)
233. Guo, S.; Dai, C.; Guo, M.; Taylor, B.; Harmon, J.S.; Sander, M.; Robertson, R.P.; Powers, A.C.; Stein, R. Inactivation of specific β cell transcription factors in type 2 diabetes. *J. Clin. Invest.* **2013**, *123*, 3305–3316. [\[CrossRef\]](#) [\[PubMed\]](#)
234. Wang, X.D.; Vatamaniuk, M.Z.; Wang, S.K.; Roneker, C.A.; Simmons, R.A.; Lei, X.G. Molecular mechanisms for hyperinsulinaemia induced by overproduction of selenium-dependent glutathione peroxidase-1 in mice. *Diabetologia* **2008**, *51*, 1515–1524. [\[CrossRef\]](#)
235. Erbayraktar, Z.; Yılmaz, O.; Artmann, A.T.; Cehreli, R.; Coker, C. Effects of selenium supplementation on antioxidant defense and glucose homeostasis in experimental diabetes mellitus. *Biol. Trace Elem. Res.* **2007**, *118*, 217–226. [\[CrossRef\]](#)
236. Ayaz, M.; Can, B.; Ozdemir, S.; Turan, B. Protective effect of selenium treatment on diabetes-induced myocardial structural alterations. *Biol. Trace Elem. Res.* **2002**, *89*, 215–226. [\[CrossRef\]](#)
237. Ezaki, O. The insulin-like effects of selenate in rat adipocytes. *J. Biol. Chem.* **1990**, *265*, 1124–1128. [\[CrossRef\]](#)
238. McNeill, J.H.; Delgatty, H.L.; Battell, M.L. Insulinlike effects of sodium selenate in streptozocin-induced diabetic rats. *Diabetes* **1991**, *40*, 1675–1678. [\[CrossRef\]](#)
239. Ghosh, R.; Mukherjee, B.; Chatterjee, M. A novel effect of selenium on streptozotocin-induced diabetic mice. *Diabetes Res.* **1994**, *25*, 165–171.
240. Magnuson, M.A.; Andreone, T.L.; Printz, R.L.; Koch, S.; Granner, D.K. Rat glucokinase gene: Structure and regulation by insulin. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 4838–4842. [\[CrossRef\]](#)
241. Lv, Y.; Xie, L.; Dong, C.; Yang, R.; Long, T.; Yang, H.; Chen, L.; Zhang, L.; Chen, X.; Luo, X.; et al. Co-exposure of serum calcium, selenium and vanadium is nonlinearly associated with increased risk of type 2 diabetes mellitus in a Chinese population. *Chemosphere* **2021**, *263*, 128021. [\[CrossRef\]](#) [\[PubMed\]](#)
242. Yuan, W.; Yang, N.; Li, X. Advances in Understanding How Heavy Metal Pollution Triggers Gastric Cancer. *Biomed. Res. Int.* **2016**, *2016*, 7825432. [\[CrossRef\]](#) [\[PubMed\]](#)

243. Aaseth, J.; Alexander, J.; Alehagen, U.; Tinkov, A.; Skalny, A.; Larsson, A.; Crisponi, G.; Nurchi, V.M. The Aging Kidney-As Influenced by Heavy Metal Exposure and Selenium Supplementation. *Biomolecules* **2021**, *11*, 1078. [\[CrossRef\]](#) [\[PubMed\]](#)
244. Ahmad, S.; Mahmood, R. Mercury chloride toxicity in human erythrocytes: Enhanced generation of ROS and RNS, hemoglobin oxidation, impaired antioxidant power, and inhibition of plasma membrane redox system. *Environ. Sci. Pollut. Res. Int.* **2019**, *26*, 5645–5657. [\[CrossRef\]](#)
245. Kim, S.H.; Sharma, R.P. Mercury-induced apoptosis and necrosis in murine macrophages: Role of calcium-induced reactive oxygen species and p38 mitogen-activated protein kinase signaling. *Toxicol. Appl. Pharmacol.* **2004**, *196*, 47–57. [\[CrossRef\]](#)
246. Casolino, E.; Sblano, C.; Landriscina, C. Enzyme activity alteration by cadmium administration to rats: The possibility of iron involvement in lipid peroxidation. *Arch. Biochem. Biophys.* **1997**, *346*, 171–179. [\[CrossRef\]](#)
247. Cao, X.; Fu, M.; Bi, R.; Zheng, X.; Fu, B.; Tian, S.; Liu, C.; Li, Q.; Liu, J. Cadmium induced BEAS-2B cells apoptosis and mitochondria damage via MAPK signaling pathway. *Chemosphere* **2021**, *263*, 128346. [\[CrossRef\]](#)
248. Chayapong, J.; Madhyastha, H.; Madhyastha, R.; Nurrahmah, Q.I.; Nakajima, Y.; Choijookhuu, N.; Hishikawa, Y.; Maruyama, M. Arsenic trioxide induces ROS activity and DNA damage, leading to G0/G1 extension in skin fibroblasts through the ATM-ATR-associated Chk pathway. *Environ. Sci. Pollut. Res. Int.* **2017**, *24*, 5316–5325. [\[CrossRef\]](#)
249. Bramanti, E.; Onor, M.; Colombaioni, L. Neurotoxicity Induced by Low Thallium Doses in Living Hippocampal Neurons: Evidence of Early Onset Mitochondrial Dysfunction and Correlation with Ethanol Production. *ACS. Chem. Neurosci.* **2019**, *10*, 451–459. [\[CrossRef\]](#)
250. Fan, Y.; Zhao, X.; Yu, J.; Xie, J.; Li, C.; Liu, D.; Tang, C.; Wang, C. Lead-induced oxidative damage in rats/mice: A meta-analysis. *J. Trace Elem. Med. Biol.* **2020**, *58*, 126443. [\[CrossRef\]](#)
251. Park, H.-J.; Kim, J.Y.; Kim, J.; Lee, J.-H.; Hahn, J.-S.; Gu, M.B.; Yoon, J. Silver-ion-mediated reactive oxygen species generation affecting bactericidal activity. *Water Res.* **2009**, *43*, 1027–1032. [\[CrossRef\]](#)
252. Chitta, K.R.; Figueroa, J.A.L.; Caruso, J.A.; Merino, E.J. Selenium mediated arsenic toxicity modifies cytotoxicity, reactive oxygen species and phosphorylated proteins. *Metallomics* **2013**, *5*, 673–685. [\[CrossRef\]](#) [\[PubMed\]](#)
253. Saikiran, G.; Mitra, P.; Sharma, S.; Kumar, P.K.; Sharma, P. Selenium, oxidative stress and inflammatory markers in handicraft workers occupationally exposed to lead. *Arch. Environ. Occup. Health* **2022**, *77*, 561–567. [\[CrossRef\]](#) [\[PubMed\]](#)
254. Ganther, H.E. Interactions of vitamin E and selenium with mercury and silver. *Ann. N. Y. Acad. Sci.* **1980**, *355*, 212–226. [\[CrossRef\]](#)
255. Sun, H.-J.; Rathinasabapathi, B.; Wu, B.; Luo, J.; Pu, L.-P.; Ma, L.Q. Arsenic and selenium toxicity and their interactive effects in humans. *Environ. Int.* **2014**, *69*, 148–158. [\[CrossRef\]](#)
256. Schöpfer, J.; Drasch, G.; Schrauzer, G.N. Selenium and cadmium levels and ratios in prostates, livers, and kidneys of nonsmokers and smokers. *Biol. Trace Elem. Res.* **2010**, *134*, 180–187. [\[CrossRef\]](#)
257. Kazi, T.G.; Kolachi, N.F.; Afridi, H.I.; Kazi, N.G.; Sirajuddin; Naeemullah; Arain, S.S. Effects of mineral supplementation on liver cirrhotic/cancer male patients. *Biol. Trace Elem. Res.* **2012**, *150*, 81–90. [\[CrossRef\]](#) [\[PubMed\]](#)
258. Hsueh, Y.-M.; Lin, Y.-C.; Huang, Y.-L.; Shiue, H.-S.; Pu, Y.-S.; Huang, C.-Y.; Chung, C.-J. Effect of plasma selenium, red blood cell cadmium, total urinary arsenic levels, and eGFR on renal cell carcinoma. *Sci. Total Environ.* **2021**, *750*, 141547. [\[CrossRef\]](#)

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