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Systems Biology of Selenium and Complex Disease

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Abstract
Selenium is an essential trace element for maintenance of overall health, whose deficiency and dyshomeostasis have been linked to a variety of diseases and disorders. The majority of previous researches focused on characterization of genes encoding selenoproteins or proteins involved in selenium metabolism as well as their functions. Many studies in humans also investigated the relationship between selenium and complex diseases, but their results have been inconsistent. In recent years, systems biology and "-omics" approaches have been widely used to study complex and global variations of selenium metabolism and function in physiological and different pathological conditions. The present paper reviews recent progress in large-scale and systematic analyses of the relationship between selenium status or selenoproteins and several complex diseases, mainly including population-based cohort studies and meta-analyses, genetic association studies, and some other omics-based studies. Advances in ionomics and its application in studying the interaction between selenium and other trace elements in human health and diseases are also discussed.

Keywords Selenium · Selenoprotein · Systems biology · Complex disease · Ionome

Introduction

Selenium (Se) is an important trace element for optimal health and development of humans and other mammals. This micronutrient is best known for its unique biological functions in redox balance and may become a promising chemopreventive agent against several cancers [1, 2]. It also has a role in antiinflammatory and antiviral activities, in preventing heart disease, and in delaying the progression of neurodegenerative diseases and AIDS [3–5].

In mammals, Se is mostly present in the form of selenocysteine (Sec), a non-standard amino acid which is found in a minor fraction of proteins, named selenoproteins [6, 7]. These selenoproteins participate in a wide range of cellular physiological processes, such as redox signaling and antioxidant defense, thyroid hormone metabolism, immune responses, as well as cardiovascular and brain function maintenance [8–11]. As an essential nutrient for humans, Se has a narrow range between deficiency and toxicity. Se deficiency is directly related to several endemic diseases, such as Keshan disease (KD), which typically occur in populations living in the Se-poor regions [10, 12, 13]. On the other hand, excessive Se can be toxic and may result in a condition called selenosis [10, 14, 15].

Complex diseases are thought to be caused by genetic variations, environmental factors, and their interactions, such as diabetes, cancer, and a variety of cardiovascular, neurodegenerative, and psychological diseases [16–19]. Relationships between Se and complex diseases had been discovered a long time before, which then raised great interests in both exploration of biochemical function of Se and utilization of Se supplements for prevention and therapy of these diseases [10, 20–22]. Previously, numerous studies have been performed to evaluate Se status and to characterize selenoproteins, Se metabolic components and their functions in physiological and different pathological conditions; however, some of the findings are controversial. For example, inconsistent results were indicated among studies aimed at assessing the associations between Se supplementation and incident diabetes [20]. It is still unclear how disruptions of Se homeostasis and selenoprotein functions are involved in the development and progression of complex diseases. Therefore, a more complete

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understanding of metabolism, regulation, and function of this micronutrient is urgently needed.

In the recent decade, with the rapid growth in the amount of biological data available (such as genome, transcriptome, proteome), systematic and "-omics" approaches have become more and more important in investigating the relationship between trace elements (such as Se) and health or complex diseases. Systems biology of Se represents systematic and integrated studies of Se status as well as its metabolism and function taking into account the variations and interactions of different components such as genes, proteins, compounds, and other elements (Fig. 1). For example, a series of meta-analyses and genome/proteome-wide studies have been carried out in either patients or related animal models, which may help to improve our understanding of the utilization and function of Se and their variations or dyshomeostasis in various diseases or disorders [23–29]. In addition, the concept of ionome (all minerals and trace elements in a cell, tissue, or organism) was also introduced [30, 31]. Ionomic studies have revealed new interactions between Se and other elements in several complex diseases [31–33]. These contributions may not only provide mechanistic insights into the metabolism of Se but also facilitate development of new Se-related drugs and therapeutic strategies against complex diseases.

In this review, we focus on the metabolism and homeostasis of Se in humans as well as the relationship between Se imbalance or selenoprotein gene variants and several complex diseases (such as diabetes, cancer, and neurodegenerative diseases) based on recent systems biology researches, including population-based cohort studies and meta-analysis, genetic association studies, and some other omics-based analyses. Such information may achieve a more integrated and system-level picture of the critical roles Se plays in physiological and pathological conditions. We also discuss recent developments in Se-related ionomic studies for certain diseases.

Selenocysteine Biosynthesis, Selenoproteins, and Selenoproteomes

The biosynthesis of Sec and its specific insertion into selenoproteins require a complex machinery that translates UGA stop codon as Sec. In mammals, this process needs a stem-loop structure in the 3′-untranslated region of selenoprotein mRNAs, named Sec insertion sequence (SECIS) element, a unique $tRNA^{[Ser]Sec}$, and some other proteins and enzymes dedicated to Sec incorporation [6, 34–36]. In general, $tRNA^{[Ser]Sec}$ is first charged with serine by seryl-tRNA synthetase and phosphorylated by a specific O-phosphoseryl-$tRNA^{[Ser]Sec}$ kinase. After that, the phosphate moiety of O-phosphoserine of the $tRNA^{[Ser]Sec}$ is replaced by Se (derived from selenophosphate) to form Sec-$tRNA^{[Ser]Sec}$ by Sec synthase. Selenophosphate is synthesized by selenophosphate synthetase 2 (SEPHS2). The eukaryotic Sec-specific elongation factor eEFSec binds Sec-$tRNA^{[Ser]Sec}$ and is critical for Sec insertion into proteins. Additional factors have been identified to be involved in selenoprotein biosynthesis, such as SECIS binding protein 2 (SBP2), ribosomal protein L30, and Secp43.

Sec is usually present in the active site of selenoproteins, being essential for their catalytic activity. A list of mammalian and other eukaryotic selenoproteins is shown in Table 1. To date, 25 and 24 selenoprotein genes have been discovered in human and mouse, respectively [7, 37]. The major selenoprotein families include glutathione peroxidases (GPXs) that have oxidoreductase functions and regulate immune response, thioredoxin reductases (TXNRDs) that provide an important defense against oxidative damage, iodothyronine deiodinases (DIOs) that participate in normal thyroid hormone metabolism, selenoprotein F (SELENOF), selenoprotein K (SELENOK), selenoprotein N (SELENON), selenoprotein P (SELENOP), selenoprotein S (SELENOS),

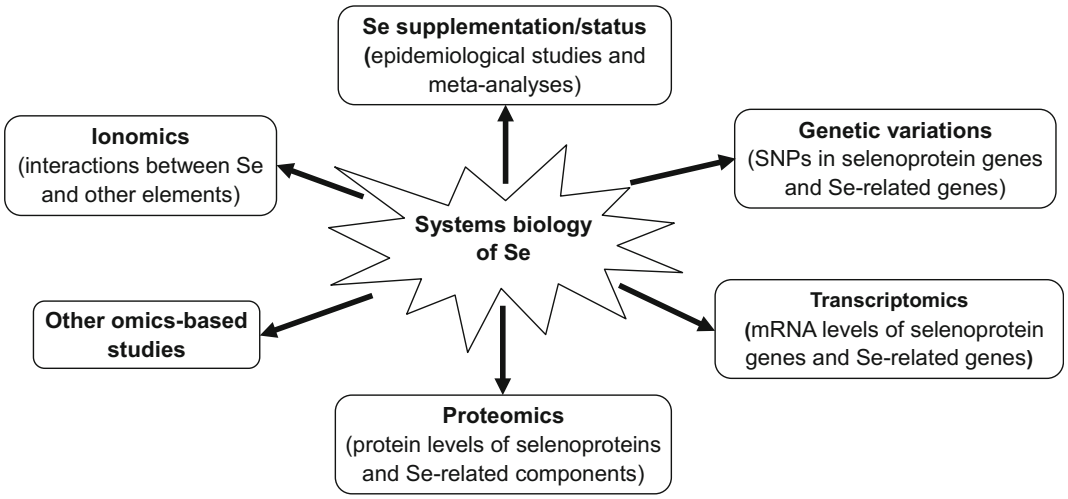

Fig. 1 A diagram illustrating the main research contents of systems biology of Se

Table 1 Selenoprotein families detected in mammals and other eukaryotes

Mammalian selenoproteins	Selenoproteins detected in other eukaryotes
Iodothyronine deiodinase (DIO) family: DIO1, DIO2 and DIO3	Methionine sulfoxide reductase A
Glutathione peroxidase (GPX) family: GPX1, GPX2, GPX3, GPX4 and GPX6	Protein disulfide isomerase
Thioredoxin reductase (TXNRD) family: TXNRD1, TXNRD2 and TXNRD3	Selenoprotein J
Selenoprotein F	Selenoprotein U
Selenoprotein H	Selenoprotein L
Selenoprotein I	Selenoprotein E
Selenoprotein K	SAM-dependent methyltransferase
Selenoprotein M	AhpC-like protein
Selenoprotein N	Peroxiredoxin-like protein
Selenoprotein O	Thioredoxin-fold protein
Selenoprotein P	Membrane selenoprotein
Selenoprotein S	Other hypothetical proteins
Selenoprotein T	
Selenoprotein V	
Selenoprotein W	
Methionine sulfoxide reductase B1	
Selenophosphate synthetase 2	

selenoprotein W (SELENOW), SEPHS2, and methionine sulfoxide reductase B1. However, the precise functions of many eukaryotic selenoproteins are still unknown.

Several comparative genomic analyses of mammalian and other eukaryotic selenoproteomes have reported significant differences in the composition of selenoproteomes among different organisms [38–41]. The number of selenoproteins varied from zero (plants, fungi, and some protists) to 56 (*Aureococcus anophagefferens*) [42]. SELENOK and SELENOW appeared to be the most widespread selenoprotein families which are present in most eukaryotes that utilize Sec. The origin of many mammalian selenoproteins can be traced back to the ancestral, unicellular eukaryotes [39]. These ancient selenoproteins were preserved during evolution and remain in mammals, whereas many other species, including land plants, fungi, nematodes, insects, and protists, manifested numerous, independent selenoprotein loss events [38]. Very recently, it was reported that Sec could also be used by early-branching fungal phyla, which provides new evidence for the function and evolution of Se in fungi [43].

Recent Advances in Selenium and Complex Diseases: a Systems Biology Perspective

As an essential micronutrient, Se is involved in a lot of metabolic activities such as modulating redox balance and mimicking insulin function. Low Se intake has been linked to a variety of developmental defects and disease states and high Se results in cellular toxicity. Several Se supplementation trials, such as the Selenium and Vitamin E Cancer Prevention Trial, have revealed that moderately higher Se intake may influence redox status through selenoprotein synthesis and cause an increased risk of type 2 diabetes (T2D) [44, 45]. Therefore, Se homeostasis and intrinsic physiological roles need to be well maintained for human health and preventing various diseases. Moreover, identification of associations between genetic variations (such as single nucleotide polymorphisms, SNPs) in either selenoprotein genes or Se-related genes and diseases has also shed light on how these diseases or disorders may be caused. In the following sections, we will focus on several complex diseases and discuss recent advances in systematic analyses of the relationship between Se and these diseases.

Diabetes

Diabetes mellitus is a complex metabolic disease characterized by hyperglycemia and impaired glucose homeostasis, which may lead to long-term damage, dysfunction, and failure of various organs [46]. It comprises several forms, such as type 1 diabetes (T1D), T2D, and gestational diabetes (GD). Among them, T2D makes up over 90% of the cases, which is caused by the disruption of the insulin signaling pathway (also known as insulin resistance). The connection between Se and the onset or progression of diabetes is uncertain and controversial. As both hyperglycemia and insulin abnormality have been associated with excess levels of reactive oxygen species,

Se had been considered to be helpful in the prevention and therapy of T2D [47, 48]. However, in recent years, an increasing number of studies have shown that Se might be a risk factor for diabetes, which is opposite to the previous expectation. Such conflicting results are probably due to individual Se status and genetic factors.

Several large-scale, population-based epidemiological studies have been carried out to investigate Se levels in the blood of T2D patients [13, 49–54]. For example, an early study examined the relationship between serum Se levels and the prevalence of diabetes based on a cross-sectional analysis of 8876 US adults [49]. After multivariable adjustment, high Se concentrations were found to be positively associated with incidence of diabetes, implying that Se intake should not be recommended for the prevention of diabetes in individuals and populations with adequate Se status. Similar results were observed in some other studies using different populations of subjects, which raised additional concerns about the association of high Se dietary intake with T2D [28, 50–54]. Recently, several comprehensive reviews and meta-analyses based on a large number of previously published articles have been performed to investigate the complex relationship between Se and T2D, most of which suggest that Se may increase the risk of T2D across a wide range of exposure levels [20, 55–58]. However, results from a very recent randomized, clinical trial do not support a significant adverse effect of daily Se supplementation (200 μg/day of selenized yeast, six months of intervention) on pancreatic β cell function or insulin sensitivity as an explanation for associations between Se and T2D [59]. This may suggest that different doses and/or forms of Se may have different effects on the development of diabetes. On the other hand, the results of previous studies about the association between blood Se level and GD are also inconsistent [33]. Two recent meta-analyses systematically evaluated the relationship between serum Se level and GD [60, 61]. Se level was found to be significantly lower in women with GD than those with normal glucose tolerance, implying that Se deficiency is related to an increased risk of GD.

In addition to the epidemiological results about Se dietary intake, imbalance of Se can also result from impaired function of either selenoproteins or proteins involved in Se metabolism. In recent years, several SNPs in a small number of selenoprotein genes have been reported to be associated with different types of diabetes (Table 2). For example, previous studies have shown that some SELENOS gene polymorphisms are closely associated with the risk for diabetes [62]. Moreover, certain SNPs in SELENOS gene might also play a role in the development of cardiovascular disease (CVD) risk in European Americans enriched for T2D [63]. SELENOP is often regarded as a biochemical marker of Se status. Previous studies revealed that some of the SNPs in SELENOP gene might be associated with fasting insulin and the acute insulin response, suggesting a potential role of SELENOP in glucose homeostasis [79]. Very recently, it was reported that one polymorphism (rs13154178) in SELENOP gene may lead to GD in the Turkish society [64]. These human genetic studies highlight the relationship between Se and glucose homeostasis and diabetes. Future research is necessary to clearly understand the

Table 2 Genetic association between selenoprotein genes and several complex diseases

Disease	Selenoprotein gene	Reference
Diabetes		
Type 2 diabetes	SELENOS	[62, 63]
Gestational diabetes	SELENOP	[64]
Cancer		
Prostate cancer	GPX1, GPX3, SELENOF, SELENOK, SELENOP, TXNRD1, TXNRD2	[65–69]
Colorectal cancer	GPX2, GPX3, GPX4, SELENOF, SELENOP, SELENOS, TXNRD1, TXNRD2	[24, 65, 70]
Breast cancer	GPX1, SELENOF, SELENOP	[65, 71]
Cardiovascular disease (CVD)		
Ischemic stroke and atherosclerotic CVD	SELENOS	[63, 72, 73]
Peripheral arterial disease	GPX4, SELENOP, SELENOS	[74, 75]
Abdominal aortic aneurysm	SELENOP	[75]
Dilated cardiomyopathy	TXNRD2	[27]
Some other diseases		
Kashin-Beck disease	GPX1, SELENOF, SELENOS	[76, 77]
Hashimoto's thyroiditis	SELENOS	[78]
Congenital rigid spine muscular dystrophy	SELENON	[27]
Familial glucocorticoid deficiency	TXNRD2	[27]

biologic effects of Se while considering the basal Se levels, polymorphisms in selenoprotein genes, and the major clinical outcomes.

Cancer

The relationship between Se and cancer, particularly prostate, gastrointestinal, and breast cancers, has been investigated extensively by many researchers over the last decades [2, 65, 80, 81]. Early epidemiological studies suggested an inverse relation between Se exposure and risk of various cancers [80]. However, the results of several large-scale supplementation trials have been confusing, which show that Se supplementation could not reduce the risk of cancer and may even increase it for several types, such as high-grade prostate cancer [65, 80, 82–84]. Therefore, it is important to use more advanced and systematic approaches to further explore the link between Se metabolism and function and different cancers. In recent years, a large number of population-based prospective studies and meta-analyses have been carried out to study the relationship between Se and different cancer types. For example, a very recent meta-analysis systematically evaluated the association between dietary Se intake and incidence of different cancers, which revealed a significant inverse relationship between Se intake (≥ 55 μg/day) and overall cancer risk [85]. Another study applied meta-analysis, meta-regression and dose-response approaches to investigate the associations between Se exposure and cancer risk based on 69 published studies [86]. High serum/plasma/toenail Se levels had different effects on specific types of cancer, which may decrease the risk of breast, lung, esophageal, gastric, and prostate cancers. In spite that genetic variations in several selenoprotein genes (such as GPXs, TXNRDs, SELENOF, SELENOP, and SELENOS) have been reported to influence risk of several cancers including prostate, colorectal, and breast cancers (Table 2) [65], mechanistic links between these genes and carcinogenesis are not clear. Additionally, transcriptomic studies have identified novel selenoprotein biomarkers of Se status and novel Se-targeted pathways involved in different cancers [65].

Prostate cancer is the most common type of cancer among men worldwide. Although a lot of studies have attempted to investigate the relation between Se and prostate cancer, their conclusions show inconsistency [87]. In recent years, evidences from a series of meta-analyses of prospective epidemiological data suggest a strong association between Se levels and this type of cancer. An early study analyzed the relation between plasma/serum Se and prostate cancer based on 13,254 participants and 5007 cases of prostate cancer from twelve studies, which showed a decreased cancer risk with increasing plasma/serum Se levels [88]. Such an inverse correlation was also confirmed by two other meta-analyses performed very recently, implying that Se has a protective role against development of prostate cancer and its progression to advanced stages [89, 90]. Thus, it seems that Se supplementation can be proposed for prevention of prostate cancer based on more systematic researches. Significant correlation between SNPs in several selenoprotein genes (e.g., SELENOP, GPX1, SELENOF, SELENOK, TXNRD1, and TXNRD2) and risk of prostate cancer (especially high-grade or advanced-stage prostate cancer) has been reported in different cohorts [65–68]. Recently, the impact of selenoprotein gene variations on plasma Se levels and prostate cancer aggressiveness was analyzed [69]. Polymorphisms in a small number of selenoprotein genes may either influence plasma Se levels (such as TXNRD2 and SELENOP) or be associated with the risk of presenting with aggressive prostate cancer (such as TXNRD2). These findings may contribute to explaining the biological effects of Se in prostate cancer development and highlight potential roles of certain selenoproteins in tumor progression. Using microarray-based transcriptome analysis, a clinical trial examined the effects of a short-term intervention with Se (300 μg per day for five weeks) on gene expression in human prostate tissue and found that Se could affect expression of genes implicated in epithelial-to-mesenchymal transition and inflammation, suggesting a preventive effect of Se on prostate cancer progression [91].

The relationship between Se and most subtypes of gastrointestinal cancer (especially colorectal, gastric, and esophageal cancers) has been evaluated by a number of prospective trials, which highlight a protective effect of this micronutrient against these cancers [84–86, 92]. In recent years, several meta-analyses of published epidemiologic studies have been carried out [84, 86, 93–96]. One study examined the association between Se level in blood and risk of colorectal cancer and found a significant inverse correlation between Se level and risk of colorectal adenoma [93]. Another meta-analysis found that high Se exposure may have different effects on specific subtypes of gastrointestinal cancer [86]. To study the potential effects of Se level on the risk of gastric cancer and its mortality, a systematic review was performed based on eight studies including 17,834 subjects, which implies that Se is inversely associated with the risk and mortality of gastric cancer [94]. Interestingly, a recent meta-analysis of the relationship between Se and risk of esophageal adenocarcinoma reported that higher Se level is not significantly associated with the risk of this cancer [95]. Several genetic variants in selenoproteins abundantly expressed in the colon (such as GPX4, SELENOS, SELENOP, SELENOF, TXNRD1, and TXNRD2) have been found to be related to colorectal cancer in different populations, indicating that metabolic functions of these selenoproteins may affect colorectal cancer risk [24, 65, 70]. One study integrated transcriptomic and proteomic approaches to describe the impact of differences in Se status on colorectal expression patterns [97]. A number of genes (including SELENOW and SELENOK) and related pathways

(such as inflammatory signaling, cytoskeleton, and cancer pathways) correlated significantly with suboptimal Se status, which may further influence colorectal cancer risk.

Breast cancer is the most invasive cancer in women. Some clinical studies revealed a correlation between Se deficiency and the incidence of breast cancer; however, findings of some other reports are inconsistent. Based on a meta-analytic method, one study combined previous results and found significant correlation between serum Se concentration and breast cancer [98]. Similar trends were observed in more recent meta-analyses [84, 86]. The relationship between SNPs in selenoprotein genes and breast cancer risk has also been examined in population-based studies. Several polymorphisms in GPX1, SELENOF, and SELENOP were found to be associated with a significant increase in breast cancer risk in different populations, suggesting a potential tumor suppressor role of these selenoproteins in breast cancer etiology [65, 71]. In order to identify novel markers for diagnosis and prognosis of breast cancer, a recent study performed a global analysis of the selenotranscriptome expression in human breast cancer cell lines [99]. Differentially expressed selenoprotein genes (such as GPX1–4 and DIO2) were found, and putative key nodes (including TP53, estrogen receptor 1, and catenin-β1) that may control the selenoprotein gene networks in breast cancer cells were also identified.

Associations of Se intake, homeostasis and function with some other types of cancer, such as lung, thyroid and skin cancers, have also been examined. However, there is no sufficient evidence to support a significant correlation between Se levels and those cancers and that increasing Se intake prevents cancer in humans. More effort is needed to assess whether Se may alter the risk of cancer in individuals with a specific genetic background or nutritional status and to investigate the mechanisms underlying such effects.

Neurodegenerative Diseases

Se has been found to play a role in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders [100–102]. Although the exact function of this micronutrient in disease process remains unclear, deficiencies in the activity of antioxidant selenoproteins (such as SELENOW, GPXs, and TXNRDs) might possibly be a critical upstream event in the pathogenesis of these diseases [100].

AD is a socially significant neurodegenerative disease characterized by progressive impairment of memory and cognitive abilities. The neuropathological hallmarks of AD include the deposition of extracellular amyloid plaques, intracellular neurofibrillary tangles and the loss of neurons and synapses in the hippocampus and the cerebral cortex [103, 104]. Previously, several longitudinal and cross-sectional studies have demonstrated a negative correlation between Se concentrations in blood/hair and cognitive decline in both mild cognitive impairment (MCI) and AD patients [105–108]. However, some other studies did not show significant difference in blood Se level between AD patients and controls in certain cohorts [109, 110]. To give a systematic evaluation of the relationship between Se status and AD, several meta-analyses have been conducted very recently [111–113]. One study analyzed Se levels in circulation (plasma/serum, blood), erythrocytes, and cerebrospinal fluid (CSF) of AD patients and controls based on twelve case–control studies [111]. Circulatory Se concentration was found to be significantly lower in AD patients, and such a decrease is correlated with GPX levels in AD. Another meta-analysis used 116 selected publications to analyze the blood and brain/CSF levels of multiple trace elements and minerals in AD patients versus controls, which also suggests lower circulatory levels of Se in AD patients [113]. These results imply that patients with AD have specific Se requirements. Selenoproteins are often hypothesized to have some involvement in the pathology of MCI and AD; however, the relationship between polymorphisms in some selenoprotein genes (such as GPX1 and SELENOP) and AD risk has not been identified [114]. It was only reported that certain SNPs in GPX1 gene may differentially affect the Se status and GPX activity in MCI and AD patients [115]. Although current knowledge could not provide strong evidence for a role of Se in the development and treatment of AD, it allows speculation on a potential preventive relevance. Recent animal model studies have shown that supplementation with Se-containing compounds could improve cognitive and motor performance of AD transgenic mice while preventing neurodegeneration [114, 116]. Further omics studies (such as proteome and transcriptome) provide new insights into the mechanism of the action of these compounds on AD therapy and intervention, which suggest a complex, multicomponent network including many other genes/proteins involved in a wide range of biological pathways [117, 118].

PD is a chronic neurodegenerative movement disorder and is characterized by a progressive loss of dopaminergic neurons together with the presence of Lewy bodies in substantia nigra pars compacta [102]. It has been proposed that cellular oxidative damage is one of the leading causes of this disease [119]. As Se is involved in antioxidant defense system, it is likely to play a special role in the pathogenesis of PD. To date, only few population-based studies have investigated the relationship between Se and PD, which lead to contradictory and ambiguous results. An early study investigated the association between plasma Se levels and the presence of neurological signs related to PD in 1012 Italian participants [120]. Although no association could be identified between plasma Se and PD, a positive correlation was observed between plasma Se and performance in neurological tasks assessing coordination and motor speed. In some other smaller PD cohorts (less than

100 patients), no difference in circulating Se levels compared to controls has been identified [121]. However, a large cohort study (238 PD, 302 controls) from eastern China reported that plasma Se (and iron) concentrations were significantly increased in patients with PD, implying that lower plasma Se levels may reduce the risk for PD [32]. Very recently, the CSF samples from a group of PD patients and controls were analyzed for the quantification of multiple elements [122]. The level of Se was significantly higher in the PD group than the control group. Moreover, Se was identified as one of the elements (with the highest impact) for sample discrimination, which could be used as independent biomarker for the diagnosis of PD. It is possible that both very high and very low body levels of Se may result in increased levels of oxidative stress and contribute to the pathogenesis of PD [102]. Some selenoproteins, such as SELENOP and GPX4, have been reported to be involved in the physiopathology of PD [100, 102]. However, the underlying reasons for these observations have not been systematically analyzed using omics-based approaches. Further analyses of genetic variations in selenoprotein genes and genes involved in Se metabolism and their associations with PD may provide another avenue to understand specific Se functionality in the progression of PD.

Population-based or omics studies on the relationship between Se status or selenoproteins and other neurodegenerative diseases, such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), are limited and with somewhat conflicting results. Both Se concentration and GPX activity tend to be decreased in MS patients, as observed in the cohorts from Iran and Poland [123, 124]. However, a recent cross-sectional study showed that there was no significant difference between MS patients and healthy controls in Se levels [125]. Although the cause of ALS is unknown, previous epidemiological studies suggest a link between prevalence of ALS and excessive exposure to Se [100]. One study examined levels of different Se species in CSF samples of Italian ALS patients, which revealed that excess selenite and human serum albumin-bound Se and low concentrations of SELENOP-bound Se in the central nervous system might be associated with increased ALS risk [126]. Analysis of Se species in the CSF of ALS patients carrying different ALS-associated gene mutations suggests that there is an interaction between different types of Se species and genetic mutations in triggering the onset of this disease [127]. However, another case–control study of 163 ALS patients and 229 controls from USA showed that blood Se (and zinc) levels were inversely associated with ALS, particularly among those with worse function, indicating that deficiencies of Se and zinc may have a role in ALS etiology [128]. Large-scale prospective cohort studies are encouraged to reveal the mechanisms underlying the varied roles of Se in neurodegenerative diseases.

Cardiovascular Diseases

In the recent decade, an increasing amount of evidence suggests that Se is important for proper functioning of the cardiovascular system [11, 129]. Se deficiency is considered as a potential risk factor for several types of CVDs [48]. Although numerous studies have investigated the relationship between Se and CVD, the exact role of this micronutrient in the development of these diseases remains only partly understood. Many observational studies and randomized controlled trials have shown inconsistent associations between Se intake and CVD risk. To give a systematic review of the effectiveness of Se supplementation for the primary prevention of CVD, several meta-analyses have been recently conducted [4, 130–132]. One study collected data from twelve trials and found that there was no statistically significant effect of Se supplementation on CVD mortality, non-fatal CVD events, or all CVD events, which does not support the use of Se supplements in the primary prevention of CVD [4]. Another systematic review focusing on the relation between Se and metabolic risk factors also suggests that Se supplementation should not be recommended for primary or secondary cardiometabolic risk prevention in those populations with adequate Se amount [130]. Based on sixteen eligible trials (43,998 participants), one recent study revealed that Se supplementation was not statistically associated with coronary heart disease mortality although it increased serum GPX level [131]. On the other hand, the association between circulating Se and the incidence of CVD is also somewhat controversial. A meta-analysis systematically assessed blood Se levels in CVD, which showed a significant inverse correlation between Se concentrations and CVD risk within a narrow Se range [132]. These findings demonstrate the importance of considering Se status when studying its involvement in the onset and progression of CVD.

KD is an endemic heart disease occurring in China [133]. Although the exact etiology of KD has not been clarified, it is considered that Se deficiency or low activity of certain selenoproteins (such as GPX1) is a major contributing factor of KD [14, 133, 134]. Previously, a lot of studies have shown that low Se concentrations are associated with the occurrence of KD [133–135]. Additionally, several population-based intervention trials showed that oral administration of selenocompounds (such as sodium selenite tablets) could significantly reduce the incidence of KD [135]. Very recently, a systematic review was carried out to evaluate the association between KD and Se deficiency based on a large amount of related studies from 1935 to 2017 [136]. Se supplements were found to significantly reduce the occurrence of KD in its endemic areas, suggesting that Se deficiency is a cause of KD and Se could be included in the KD surveillance program. However, the relationship between hair Se content and KD in children appeared to be different based on a large-scale

prospective cohort study, which showed a U-shaped association between Se status and this disease [137]. A recent serum proteomic analysis identified 19 Se-associated proteins that have quite different expression levels between KD patients and healthy controls [138]. Network analysis suggests that some of these proteins may play significant roles in the pathogenesis of KD.

Besides Se concentrations, genetic variations of several selenoprotein genes have also been reported to be associated with certain types of CVD (Table 2), such as SELENOS gene polymorphisms for ischemic stroke and atherosclerotic CVD [72, 73] and SELENOP variants in pathogenesis of peripheral arterial disease (PAD) [74]. Very recently, one study systematically examined the associations of SNPs of several selenoprotein genes and selenoprotein levels with the development of abdominal aortic aneurysm (AAA), PAD, and heart failure [75]. It appears that selenoprotein gene polymorphisms may constitute a risk factor for heart failure and peripheral atherosclerosis but prevent the development of AAA and that increased SELENOP concentrations might be a promising marker for heart failure. Thus, it seems that the functional role of Se and selenoproteins in the cardiovascular system and the relationships among Se intake/status, selenoproteins, and various CVDs are complicated. These issues need to be analyzed in depth in future research.

Other Diseases

Some other diseases have also been reported to be associated with severe Se deficiency and mutations in selenoprotein genes or Se-related genes, such as Kashin–Beck disease (KBD), thyroid diseases, and certain myopathies (Table 2). KBD is a chronic, endemic osteochondropathy accompanied by joint necrosis, which affects individuals in Se-deficient areas of China, southeast Siberia, and North Korea [139]. Systematic meta-analyses have been performed to analyze the association between Se status or Se supplementation and the incidence or treatment of KBD [140–142]. Low levels of Se in blood, hair, and urine were all found to be significant risk factors for KBD, and Se supplementation may be helpful for the treatment of patients with KBD. Several SNPs in certain selenoprotein genes, such as GPX1, SELENOF, and SELENOS, were reported to be associated with an increased risk of KBD [76, 77]. Moreover, microarray-based transcriptome analyses of the articular cartilages from KBD patients have revealed that a number of Se-related genes involved in a variety of biological processes and pathways may play important roles in the pathogenesis of KBD [143, 144].

In recent years, the relationship between Se supplementation or selenoprotein gene polymorphisms and several autoimmune thyroid diseases (such as Graves' disease and Hashimoto's thyroiditis) has been systematically examined [29, 78, 145, 146]. However, the efficacy of Se intake on thyroid function is complicated and controversial. Future well-powered studies are needed before determining the relevance of Se supplementation in these diseases.

Selenium and Disease Ionomics

The ionome is defined as the mineral nutrients and trace elements of an organism [31, 147]. Ionomics involves quantitative analysis of elemental composition in living systems using high-throughput elemental profiling techniques such as inductively coupled plasma mass spectrometry (ICP-MS) and X-ray fluorescence. In the recent decade, ionomics has been widely applied in yeast, plants, and mammals (including human), providing a powerful tool to identify new aspects of trace element metabolism and homeostasis in various physiological and pathological conditions [147–150]. For example, based on a genome-wide high-throughput siRNA/ionomics screen in human HeLa cells, novel mechanisms that regulate trace elements were characterized [151]. Specifically, it was found that Se levels could be controlled through several Sec machinery and selenoprotein genes such as SBP2 and TXNRD1. Moreover, new candidate genes that are involved in Se homeostasis and metabolic network are also identified, which opens new directions for studies of Se metabolism in humans [151]. Another ionomic study examined the distribution patterns of 18 elements in different organs of 26 mammalian species [152]. Some of the elements showed lineage-specific patterns, including reduced Se utilization in African mole rats, and positive correlation between the number of Sec residues in SELENOP and the Se levels in liver and kidney across mammals. In addition, species lifespan was found to be negatively linked with Se, providing new insights into the relationship between Se and organ physiology, lineage specialization, and longevity [152].

Before the concept of disease ionomics was introduced, ICP-MS had been used to quantify the levels of trace elements in samples of different diseases for years. With the rapid development of systems biology and computational approaches, advanced strategies have been developed for systematic analysis of the whole ionomic network, which improves our understanding of the complex interactions among different elements, including the relation between Se and other minerals [31, 153].

One study quantified the concentrations of several trace elements in plasma from a large number of patients with PD and controls, which suggests that lower plasma Se and iron levels may reduce the risk for this disease, whereas lower plasma zinc level is probably a PD risk factor [32]. Ratios between the concentrations of Se and other metals (such as iron, zinc, and copper) could be affected by both age and PD subtypes, implying complex interactions between them. A

computational model was also built to predict PD patients based on the concentrations of several elements (including Se) as well as other features such as sex and age, which achieved a good performance [32]. Recently, ionomic studies were conducted to investigate the potential mechanisms underlying the therapeutic effect of different selenocompounds in AD [154, 155]. One study investigated the brain ionomic profiles at multiple time points by using triple-transgenic AD (3×Tg-AD) mice with/without long-term high-dose sodium selenate supplementation [154]. Significant differences were observed at three levels: individual elements (especially reduced levels of iron and zinc), elemental correlation, and changes of such correlation, which demonstrate a highly dynamic and somewhat specific effect on brain ionome induced by selenate supplementation. Another study analyzed the brain ionome in 3×Tg-AD mice treated with Se-methylselenocysteine (SMC) using both ICP-MS and X-ray fluorescence approaches [155]. SMC supplementation can not only inhibit the over-accumulation of several AD risk metals (especially copper) but also influence element–element cross-links in the brain. Although there are still differences between the two kinds of selenocompounds, these results reveal that both organic and inorganic forms of Se play some significant roles in the regulation of metal homeostasis in the mouse brain and may be used for AD treatment. Future efforts are needed to investigate the interaction between Se and other elements in many other diseases.

Conclusions

Systems biology approaches have given strong support for studying the metabolism, homeostasis, and function of Se as well as its relationship with a variety of diseases. This review describes recent researches that used system-level strategies, such as large-scale population-based studies, meta-analyses, genetic association studies, and other omics-based analyses, to better understand the roles of Se in complex diseases. In addition, recent advances in disease ionomics have also provided new information about the interaction between Se and other trace elements in different conditions. Meanwhile, it should be admitted that the usage of systems biology approaches in the field of Se research is quite limited. In the future, with the rapid increase in the amount of genomic, transcriptomic, proteomic, and ionomic data that relate with Se, systematic and omics-based approaches will play a stronger role in studying the roles of Se in human health and disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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