



The Possible Mechanism of Physiological Adaptation to the Low-Se Diet and Its Health Risk in the Traditional Endemic Areas of Keshan Diseases

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Received: 28 May 2021 / Accepted: 23 July 2021 / Published online: 8 August 2021

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Abstract

Selenium is an essential trace element for humans and animals. As with oxygen and sulfur, etc., it belongs to the sixth main group of the periodic table of elements. Therefore, the corresponding amino acids, such as selenocysteine (Sec), serine (Ser), and cysteine (Cys), have similar spatial structure, physical, and chemical properties. In this review, we focus on the neglected but key role of serine in a possible mechanism of the physiological adaptation to Se-deficiency in human beings with an adequate intake of dietary protein: the insertion of Cys in place of Sec during the translation of selenoproteins dependent on the Sec insertion sequence element in the 3'UTR of mRNA at the UGA codon through a novel serine-dependent pathway for the de novo synthesis of the Cys-tRNA^{[Ser]Sec}, similar to Sec-tRNA^{[Ser]Sec}. We also discuss the important roles of serine in the metabolism of selenium directly or indirectly via GSH, and the maintenance of selenium homostasis regulated through the methylation modification of Sec-tRNA^{[Ser]Sec} at the position 34U by SAM. Finally, we propose a hypothesis to explain why Keshan disease has gradually disappeared in China and predict the potential health risk of the human body in the physiological adaptation state of low selenium based on the results of animal experiments.

Keywords Serine · Selenium metabolism · Sec-tRNA^{[Ser]Sec} · Selenium deficiency · Physical adaptation

Introduction

Selenium (Se) is an essential trace element for humans and animals due to its antioxidant and anti-inflammatory superiorities. Among the 25 selenoproteins that contain

selenocysteine (the twenty-first amino acid, or Sec for short), Se takes the active site. Some selenoproteins have enzymatic activity, such as glutathione peroxidases, thioredoxin reductases, and deiodinase.

Se is located in the sixth main group (VIA) of the periodic table of elements, as with oxygen (O), sulfur (S), tellurium (Te), polonium (Po), and livermorium (Lv). Therefore, serine (Ser), cysteine (Cys), and selenocysteine (Sec) have similar chemical structures, as shown in Fig. 1. These amino acids can transform into each other [1, 2].

Here, we firstly introduce the sources and major metabolic pathways of serine and describe how serine participates in the metabolism of amino acids with sulfur in the biosyntheses of SAM and GSH. Next, we focus on the neglected but crucial roles of serine involving in the metabolism of selenium-containing amino acids, as well as in the biosynthesis of 25 selenoproteins. Finally, we suggest a novel hypothesis to explain the gradual disappearance of Keshan disease without Se-supplementation and its latent health risk in China presently.

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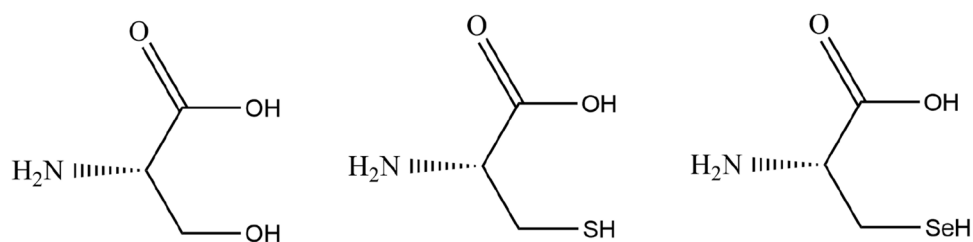
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Fig. 1 The chemical structures of L-serine, L-cysteine, and L-selenocysteine. With the exception of oxygen, sulfur, and selenium at one specific site, the three amino acids have the same elements, arrangement, and three-dimensional structure



The L-Serine and Its Major Metabolic Pathways

Serine is a “nutritionally non-essential amino acid” (NNAA), being synthesized sufficiently in the human body. It can meet the needs for maximal growth and optimal health.

Exogenous Serine

The serine level is normally sufficient in a diet with any adequate source of protein. It may include Fungi (mushroom, yeast), plants (vegetables, fruits, nuts), eggs, meat like freshwater products or seafood (fish, shrimp shells), livestock (beef, mutton, pork), and poultry (chicken, duck, turkey).

Dietary proteins are ingested and absorbed in the gastrointestinal tract. The majority of exogenous serine is hydrolyzed by several digestive enzymes, e.g., epsins from the stomach and pancreatic proteases from the pancreas. These are first broken down into oligopeptides then hydrolyzed at the apical membrane of the small intestine wall [3–7] and that of the large intestine [8], where the oligopeptides are further digested into di- and tripeptides, as well as free AAs including free serine from diet. These are then transported into the enterocyte across the basolateral membrane and

enter the portal circulation for utilization [8, 9]. It is noticeable that there are different characteristics of protein digestion, absorption, and amino acid transported in vulnerable groups as in the newborns and the elderly [10–12].

Two Pathways for Biosynthesis of Endogenous Serine

Moreover, serine can also be endogenously derived from various metabolic pathways in the human body. The *de novo synthesis* of serine comes from the bypassing of glycolysis by three enzymes, namely, the 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and phosphoserine phosphatase (PSPH). Serine can also be directly transformed from glycine in one step by the enzyme SHMT1/2 (Fig. 2).

Major Pathways for Well-Known Physiological Roles of Serine

Physiologically, serine plays a variety of roles, most importantly as a phosphorylation site in proteins. Besides its role in protein synthesis, serine plays a vital role in multiple cellular reactions, as the NNAA is a precursor of many important metabolites (Fig. 3). These include a one-carbon unit of the essence for the *de novo* synthesis of nucleotides

Fig. 2 The uptake or biosynthesis of serine via cells. This schematic diagram illustrates the transporters for exogenous serine or the pathways for synthesis of endogenous serine in mammalian cells, where the serine is a biosynthetic precursor. Modified from Ref. [13]

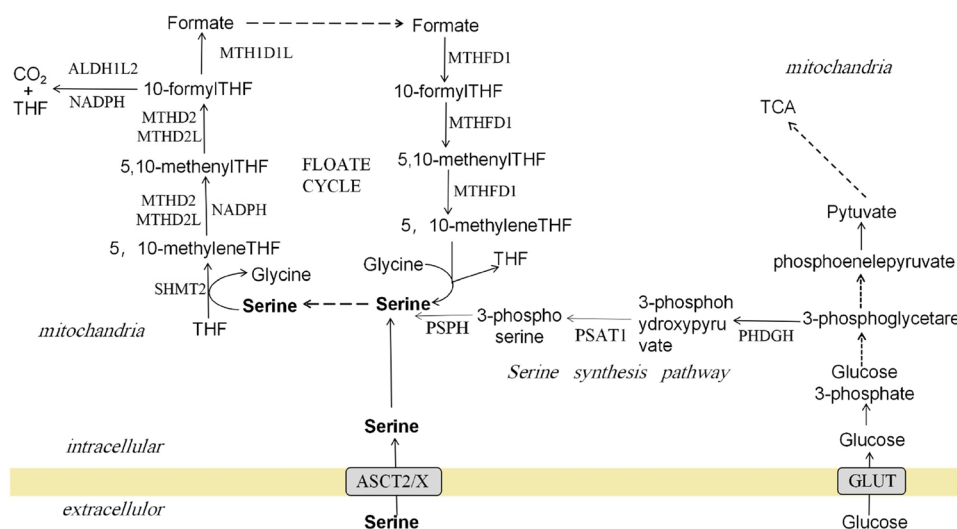
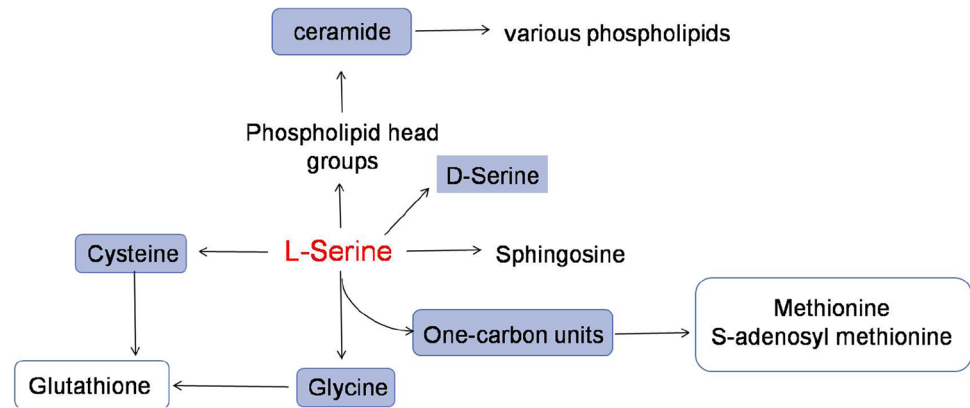


Fig. 3 The metabolic fates of serine. This schematic illustrates the products in mammalian cells where serine is a biosynthetic precursor. Modified from Ref. [14]



ceramide these are crucial for phospholipids and neurotransmitters, such as phosphatidylserine, D-serine, L-glycine, and L-cysteine for glutathione (GSH).

D-Serine

In the human central nervous system (CNS), D-serine is an important neurotransmitter and main endogenous co-agonist of glutamate at the glycine site of *N*-methyl-D-aspartate receptor (NMDAR) that is essential to NMDAR activation [15–18]. Not merely modulates various crucial physiological functions, it also participates in a variety of pathological processes, as NMDAR transmission, synaptic plasticity, and neurotoxicity. Endogenous D-serine is directly transformed from L-serine by serine racemase (SR) in most neural cells [19, 20].

It is well-documented that serine has difficulty passing through the blood–brain barrier. The brain needs to synthesize endogenous serine. In the human CNS, L-serine is predominantly biosynthesized in astrocytes from 3-phosphoglycerate through the *de novo* synthetic pathway and serves as a precursor for the synthesis of D-serine. The case of L-serine as well as that of L-glycine, another important neurotransmitter, is described, discussing the roles of GSH, selenite, and selenite.

Astrocytes express the enzymes available for the *de novo* synthesis of L-serine through the glycolysis bypass. An efficient L-serine shuttle mechanism has been found between glia and neurons for the generation of the NMDAR co-agonist D-serine. Neurons were found to be the main site for the newly synthesized D-serine [21, 22].

One-Carbon Units Including SAM

There is a broader set of transformations among folate-mediated one-carbon units, known as the metabolism of one-carbon units, and these make them available for the syntheses of purine, thymidine, and the remethylation of homocysteine (hCys).

In the folate cycle in mammal cells, serine can be broken into L-glycine and 5, 10-methylenetetrahydro-folate (5,10-meTHF; a one-carbon unit), either in the reactions of the cytosol catalyzed by SHMT1 or in the mitochondria by SHMT2 [23–28]. Following this, the (5,10-meTHF) is used for the synthesis of dTMP, and 5-mTHF for hCys remethylation to reproduce Met and then SAM in the Met cycle.

Phospholipids Derived from Ceramide

De novo synthesis of ceramide occurs in the endoplasmic reticulum (ER) in mammalian cells and starts with the condensation of the active C16 fatty acid palmitoyl-CoA and L-serine by serine palmitoyltransferase (SPT) [29–32]. Ceramide is the metabolic center for sphingolipids, serving as a precursor to sphingomyelins, which are ubiquitous building blocks of mammal cell membranes [33–39].

Phospholipids constitute the main components of the cellular membrane. They are often classified into two groups: sphingolipids and phosphoglycerides, respectively containing sphingosine and glycerol. Among the later phosphoglycerides on the cellular plasma membrane, i.e., phosphatidylserine with a negatively charged head-group, abbreviated as PS, is preferentially found on the cytoplasmic leaflet and is mainly required for nerve cell membranes and myelin (especially as a neurotransmitter) [40–45]. PS is synthesized in mammalian cells by two distinct PS synthases that exchange L-serine for choline in phosphatidylcholine (PC) or ethanolamine in phosphatidylethanolamine (PE), respectively. Because of its strong lipophilicity, PS can quickly enter the brain through the blood–brain barrier to improve the function of nerve cells, regulate the conduction of nerve impulses, and enhance the memory function of the brain [46–51].

De Novo Synthesis of Glutathione

There are several pathways to producing the endogenous GSH, the reduced form of glutathione [52–54]. It can be

quickly synthesized from GSSG through the GSH salvage pathway. This can occur intracellularly via the reduction of GSSG by glutathione reductase (GR) and extracellularly via γ -glutamyl transferase (γ -GT)–mediated degradation of exogenous GSH, which provides L-glutamic acid, L-cysteine, and L-glycine [52, 53]. Endogenous GSH can also be slowly de novo synthesized in a two-step reaction in the cytosol of all mammalian cells [54]. L-Glutamate and L-cysteine are catalyzed by γ -glutamylcysteine ligase (also referred to as γ -glutamylcysteine synthetase), first in an ATP-dependent manner. Following this, L-glycine is added by glutathione synthase (Fig. 4).

Exogenous or endogenous serine might be utilized for the syntheses of two endogenous AAs (L-glycine and L-cysteine) [13, 55, 56] which are essential for the de novo biosynthesis of GSH[54]. L-Serine can be converted directly into L-glycine by the enzyme SHMT[55] or utilized to produce L-cysteine through the transsulfuration metabolic pathway [13, 56].

The Transformation of Serine into Cysteine Through Two Different Pathways

De Novo Biosynthesis of Cysteine

It is well-known that cysteine (Cys) is not an essential amino acid since it can be synthesized from the essential amino acid methionine (Met) ingested from the diet [57–59]. The first step is the transfer of an adenosine group from ATP

to Met by methionine adenosyltransferase (MAT), resulting in the formation of S-adenosylmethionine (SAM). In the second step, SAM, as the methyl donor, donates a methyl group to many molecules (such as DNA, RNA, proteins, and neurotransmitters) and is transformed into S-adenosyl homocysteine (SAH). SAH is subsequently broken down into adenosine and homocysteine (Hcy) via a reversible reaction by S-adenosyl homocysteine hydrolase (SAHH). In the transsulfuration process, with the help of vitamin B₆, Hcy transfers the sulfate group to Ser catalyzed successively by cystathionine β -synthase (CBS) and cystathionine γ -lyase (CSE) and the latter is transformed into Cys (Fig. 4). Cys is one of the 20 amino acids and is commonly used in protein synthesis. Cys-tRNA can be aminoacylated directly with Cys and its genetic codons are UGU/UGC for its insertion into proteins, especially in the active cores of various important enzymes.

De Novo Biosynthesis of Cys-tRNA^{[Ser]^{Sec} (Fig. 6 with Green Markers)}

Most aminoacyl-tRNAs are formed by the aminoacylation of tRNA catalyzed by aminoacyl-tRNA synthetases directly one-for-one. However, Cys-tRNA^{[Ser]^{Sec}, a non-canonical Cys-tRNA, is now found to be formed through a novel pathway by a series of enzymes used in the biosynthesis of Sec-tRNA^{[Ser]^{Sec}. Cysteine carried by Cys-tRNA^{[Ser]^{Sec} comes from two parts, the carbon backbone directly provided from serine and the sulfate element from hydrogen sulfide, which}}}

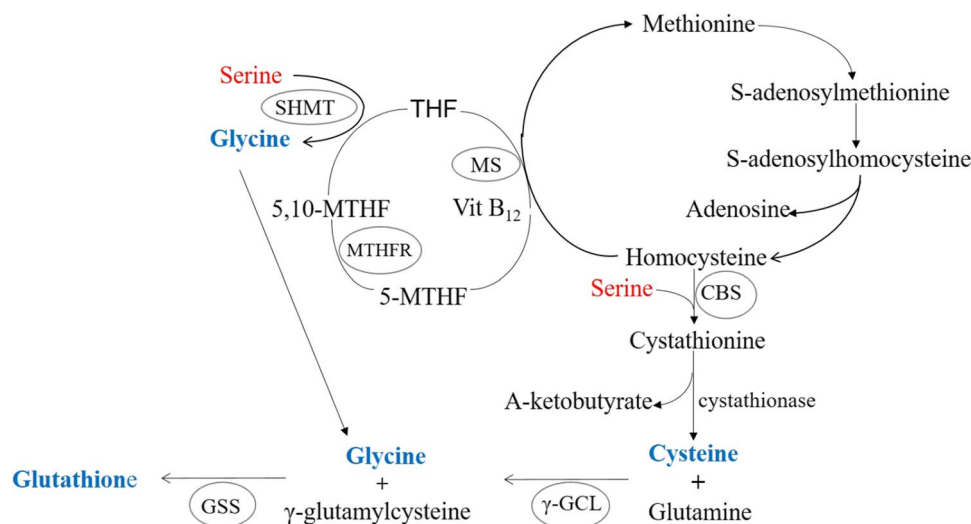


Fig. 4 The indirect role of serine in the synthesis of glutathione and cysteine. This schematic illustrates that serine is the biosynthetic precursor for the endogenous synthesis of glycine or cysteine which are essential for GSH. Cysteine can be produced by cystine rapidly and also be de novo biosynthesized by the transsulfuration process.

Modified from reference [60]. Abbreviations: *SHMT* serine hydroxymethyltransferase, *5-MTHF* 5-methyltetrahydrofolate, *5,10-MTHF* 5,10-methyltetrahydrofolate, *MS* methionine synthase, *MTHFR* methylenetetrahydrofolate reductase, *CBS* cystathionine beta-synthase, γ -*GCL* γ -glutamylcysteine ligase, *GSS* glutathione synthetase

is degenerated from several sulfur-containing compounds, including cysteine itself from protein breakdown.

The Transformation of Serine into Selenocysteine Through a tRNA-Dependent Pathway

Generation of Hydrogen Selenide and H₂SePO₃

There are different types of Se species in the human diet. Generally, the principal component of selenium compounds in plant foods is mainly selenomethionine (SeMet), the major selenium form in animal foods is selenocysteine (Sec), and some fungi (such as yeast) and nuts are rich in methylselenol-producing selenocompounds [61, 62]. Selenate and selenite are often used as nutritional supplements in infant formula and clinic parenteral nutritional formulae [63–65]. Any form of Se-containing compounds ingested by the human body can be metabolized to the same intermediate, HSe⁻ directly or through methylselenol (CH₃SeH) indirectly (Fig. 5). Among these Se species, serine was found to be essential during the generation of HSe⁻ from SeMet directly or from selenate and selenite indirectly.

SeMet

As we know, SeMet and Met share the same metabolic pathways: Met cycle and transsulfuration process. The metabolism of methionine (Met) starts with the Met cycle and then enters the transsulfuration pathway where Se is transferred from homocysteine (hCys) to serine, and the

latter is transformed into Sec, with the help of vitamin B₆ [68]. However, unlike cysteine (Cys), selenocysteine (Sec) cannot be utilized directly for the aminoacylation of tRNA to produce the Sec-tRNA for the expression of selenoproteins. Sec needs to be broken down by the specific enzyme selenocysteine lyase (Scly) into L-alanine and HSe⁻ (SeMet → Sec → HSe⁻) [69–71]. Historically, more attention has been paid to the effect of vitamin B₆ on the catalyzation in the Scly step [72–76] rather than the essential role of serine [77].

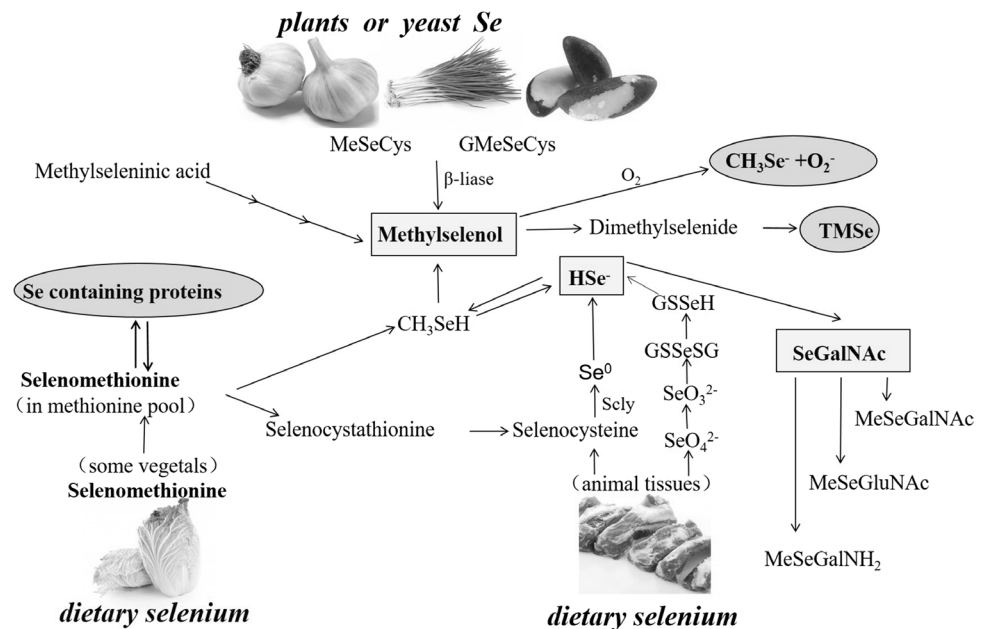
Selenate and Selenite

In general, the content of selenate and selenite in foods is very low and the proportion is small. Selenate and selenite are usually used as nutritional supplements, or as enhancers in Se-enriched salt, for population-based intervention targeting individuals in selenium-deficient areas [78, 79]. Most of all, the authorized forms of selenium in infant formula and clinic parenteral formulae are still inorganic, including selenate and selenite. In the human body, selenate must first be reduced to selenite. Selenite then requires a large amount of GSH to produce HSe⁻ [80–82]. In the above-mentioned GSH section, we have discussed that the two amino acids used in the synthesis of GSH, glycine, and cysteine, are often derived from serine.

CH₃SeH-Producing Selenocompounds

These selenocompounds include SeMet, methylselenocysteine (MeSec), and methylselenic acid (MSA), and γ-glutamyl-Se-methylselenocysteine (γ-GMeSec). These

Fig. 5 Major sources of selenium and their metabolism in the human body. Both organic selenium (SeMet, Sec, and methyl-Sec) and inorganic selenium (selenate and selenite) from the diet or supplement are supposed to generate HSe⁻ in the cell before the biosynthesis of selenoproteins. Modified from Ref. [67]



selenocompounds, except for SeMet, often produce CH_3SeH by various pathways firstly: SeMet can generate CH_3SeH by γ -lyase; MeSec and γ -GMeSec are transformed into CH_3SeH by β -lyase; MSA is reduced to CH_3SeH by GSH. And then CH_3SeH is demethylated into HSe^- by demethylase.

Before HSe^- is used for de novo Sec synthesis, it must be phosphorylated to produce an active metabolite, seleophosphate ($\text{H}_2\text{SePO}_3^-$), with ATP by seleophosphate synthetase (SEPHS2).

De Novo Biosynthesis of Sec-tRNA^{[Ser]Sec} (Fig. 6 with Yellow Markers)

Initially, Sec-tRNA, also called Sec-tRNA^{[Ser]Sec}, is not directly loaded with the Sec amino acid but with L-serine by seryl-tRNA synthetase (SerRS) with the presence of ATP, resulting in an intermediate Ser-tRNA^{[Ser]Sec}. Then, the Ser residue in Ser-tRNA^{[Ser]Sec} is phosphorylated by PSTK with the presence of ATP too, resulting in another intermediate O-phosphoseryl-tRNA^{[Ser]Sec}, abbreviated as pSer-tRNA^{[Ser]Sec}. Finally, O-phosphoseryl-tRNA^{[Ser]Sec} selenium transferase (SepSecS or SecS, a PLP-dependent enzyme) performs the transformation between Ser and Sec on tRNA, resulting in the generation of Sec-tRNA^{[Ser]Sec}.

Mature of Sec-tRNA^{[Ser]Sec}

The modification of bases occurs at several positions on Sec-tRNA^{[Ser]Sec} to generate the mature Sec-tRNA^{[Ser]Sec}, especially in the single 2'-O-hydroxymethyl group at position 34 (Um34) in the wobble position of this tRNA [83–86]. In mammal animal models, the base modification in Sec-tRNA^{[Ser]Sec} at position 34U can be catalyzed by the specific enzyme ALKBH8 dependent on SAM (Fig. 6), which is a most specialized final step in the maturation of Sec-tRNA^{[Ser]Sec}

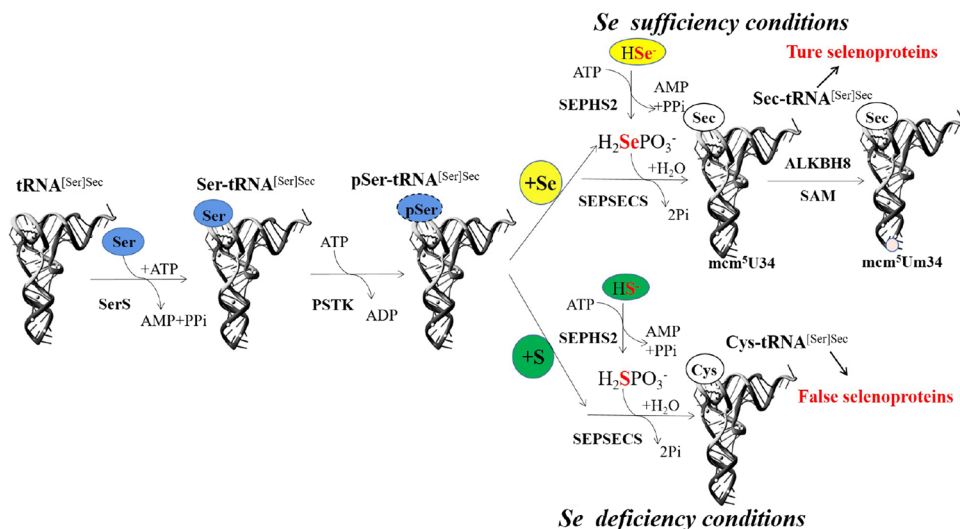
Sec, and increases the efficiency of codon reading [84–89]. Even though the molecular mechanism by which mcm5U and mcm5Um at position 34 influence the efficient recoding of UGA is presently not elucidated, the importance of this modification in selenoprotein synthesis has been inferred from the genetically modified mice [84]. Interestingly, the expression of housekeeping selenoprotein genes, such as TrxR₁ and TrxR₃, is dependent on mcm5U-Sec-tRNA^{[Ser]Sec} isoform, while the stress-related selenoproteins including GPX1, GPX3, SelW, SELENOW, and MSR1 are generally synthesized by the mcm5Um-Sec-tRNA^{[Ser]Sec} isoform. However, some selenoproteins including GPX4 and SELENOP can be synthesized by the two isoforms. In other words, the expressions of 25 selenoproteins are dependent on the form of Sec-tRNA^{[Ser]Sec} in response to Se-deficiency or the ROS/RNS stress in a different order of priority [83, 84, 90–94].

The Underlying Mechanism of the Outbreak or Disappearance of Keshan Disease in China

A fatal unknown disease was firstly found in the winter of 1935 in Keshan county of Heilongjiang province. It was thus renamed Keshan disease (KD). KD continued to prevail during the war. Later on, it was prevalent again in Se-deficient regions of China in the 1960s and 1970s. The acute case was characterized by a diminished heart ability to pump blood because of the enlarged and weakened left ventricle, affecting young children and women in particular [95–99].

As early as 1965, clinic researchers at Xian Medical University in China began to use selenium supplementation as a way to treat patients during the outbreak of Keshan disease. Then, Se-supplementation was demonstrated as an effective

Fig. 6 The replacement of Sec or Cys by a de novo synthesis dependent on a unique Ser-tRNA. This schematic illustrates the de novo synthesis of Sec or Cys from Ser on tRNA with the presence of ATP. Modified from Ref. [122]



way to prevent the occurrence of KD in the Se-deficient areas around the world subsequently [100–104].

Up to now, it is well-known that KD appeared only under extremely poor Se status accompanied by environmental or host stress. The biological functions of Se are mainly exerted by selenoproteins (encoded by 25 genes in humans) [79, 105–108]. The outbreak of Keshan disease might be due to the level of Se (less than 20 µg/day) in the human body, which is too low to meet the minimum expression of some housekeeping selenoprotein genes (thioredoxin reductases, including TrxR₁ and TrxR₃).

Nowadays in the Se-deficient regions in China, the amount is still less than the recommended by the Chinese Nutrition Society, though the dietary selenium intake of local residents is slowly rising. The population-based intervention strategies including the supplement of selenium-enriched salt or oral sodium selenite tablets have already been terminated since 2014, but new cases of severe diseases directly related to selenium deficiency (such as Keshan disease and Kashin Beck disease) have been rarely reported, or even disappeared [79, 109–111].

Why and how? There are two existing hypotheses. One is that the genetics of residents living in the Se-deficient areas for a long time has changed, and then they gradually adapt to their low-Se or Se-deficient diets [112]. It is known that some populations do show genetic adaptations to low selenium levels, but this cannot be expected to explain the recent reduction of selenium-related diseases. Another more likely hypothesis is that the dietary selenium intake of residents living in these Se-deficient areas is sufficient following with enough dietary protein intake or the consumption of imported Se-enriched foods [78, 113]. However, with the development of logistics, people eat a wide range of food, so timely supplement of selenium. At the same time, the animal husbandry feed has been strengthened with selenium. This might also be the main reason for the near disappearance of selenium deficiency. Therefore, relevant questions deserve further investigation in the near future.

Here, we provide a novel hypothesis about the disappearance of Keshan disease in China that there may be a physiological adaptation to the suboptimal Se status for the local residents living in the classical Se-deficient areas due to the replacement of Sec by Cys, accompanied by the daily intake of adequate dietary protein.

The Dietary Se Intake of Local Residents Is More Than 17 µg/Day

From previous studies reported by a national Keshan disease research group from China in the 1970s, Keshan disease often occurred if the average dietary Se intake daily from local foods ingested by residents was less than 17 µg/day and not enough to guarantee the expression of

housekeeping selenoprotein genes (thioredoxin reductases, including TXNRD1 and TXNRD3) and led to the outbreak of this acute heart disease and even death [79, 107]. At present, the average dietary Se intake daily reported is increasing gradually up to more than 17 µg/day followed by the daily intake of adequate dietary protein [114–116], which is at least sufficient for the minimum expression of housekeeping genes in the human body, but is still much lower than the RNIs recommended by the Chinese Nutrition Society [117].

The Replacement of Sec by Cys Via a Unique Ser-tRNA-Dependent Pathway at a Low-Se Status

From above, we have learned that the transformation between Ser and Cys or Sec can often occur usually through the transsulfuration process or the tRNA-dependent pathway. Naturally, Cys is often found to replace Sec in prokaryotic cells and eukaryotic cells to synthesize similar proteins. Through genetic engineering, the Sec residue in mammal selenoenzymes (thioredoxin reductase and GPX4) was specifically replaced by Cys to generate the pseudo-selenoenzymes. It was found that these artificial enzymes still had catalytic activity, which was decreased dramatically [118]. Then, Cys was found to recode the same genetic code UGA usually for Sec and be incorporated into the corresponding position of Sec in the peptide chain of selenoproteins by the unique Cys-tRNA^{[Ser]Sec}, biosynthesized through the Ser-tRNA-dependent pathway, to generate the pseudoselenoproteins naturally in rats at the suboptimal intake of Se (Fig. 6) [119–121]. However, this replacement of Sec by Cys in the peptide chain of selenoproteins needs to be confirmed directly in local residents living in the classical Se-deficient areas in China in further studies.

The Dietary Protein Intake Sufficient for the Basic Requirement of Local Residents

As an essential element, Se exerted the important biological functions mainly by selenoproteins. Therefore, in addition to selenocysteine, like other structural and functional proteins in the human body, these selenoproteins need all 20 kinds of amino acids, including essential and non-essential amino acids. More than that, some Se-containing enzymes, such as GPXs and TrxRs still require the participation of GSH and Thioredoxin (Trx) to perform their biological functions. Most of all, several amino acids themselves play a very important role in the metabolism of Se, the replacement of Sec by Cys through the de novo biosynthesis of Sec-tRNA^{[Ser]Sec} and Cys-tRNA^{[Ser]Sec}, and the expression of false or true selenoprotein.

Serine

Firstly, serine is neglected for its crucial role in the expression of true or false selenoproteins directly through the de novo biosynthesis of Sec-tRNA^[Ser]Sec or Cys-tRNA^[Ser]Sec. It was reported that serine had a synergistic effect with selenocompounds on the expression of selenoproteins in cells [122, 123] and improved the selenium nutritional status in sows and their offspring [124]. Dietary serine and sulfate-containing amino acids are related to the nutritional status of selenium in lactating Chinese women [125]. Also, serine can promote the generation of HSe⁻ from homocysteine through the transsulfuration pathway. Then, serine can be used as the donor of one-carbon units carried on tetrahydrofolate for the methionine cycle to produce SAM. Finally, serine can be transformed into cysteine and glycine utilized for the de novo synthesis of GSH, which is necessary for the biological function of GPXs and the metabolism of inorganic Se.

Methionine

In addition to the de novo biosynthesis of cysteine and generation of SH⁻, methionine is essential for the production of the unique one-carbon unit SAM. As a reactive methyl carrier, SAM is the second common enzymatic cofactor except for ATP and is well-known for its major role in epigenetics and many biosynthetic processes. More than that, SAM is crucial for the maturation of Sec-tRNA^[Ser]Sec and the efficiency of codon reading. Also, SAM takes part in the metabolism and is used to generate CH₃SeH, dimethylselenide (DMSe, (CH₃)₂Se) and trimethylselenium ion (TMSe, (CH₃)₃Se) or Se-methyl-N-acetyl-selenohexosamine (selenosugar, SeSUG) (Fig. 7) [126–128].

Cysteine

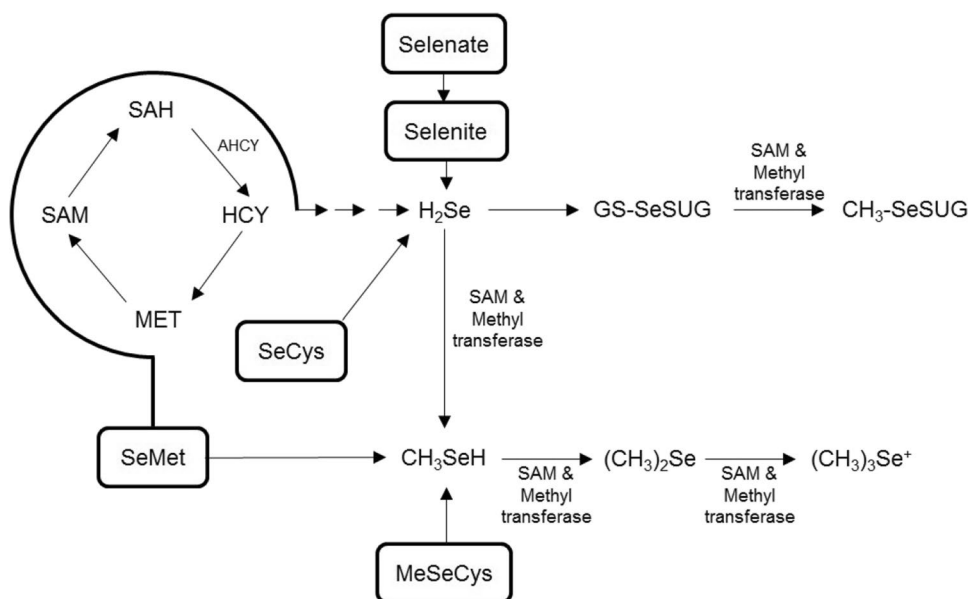
In addition to the direct participation in the de novo biosynthesis of GSH, cysteine can replace selenocysteine in the expression of selenoproteins through degeneration into SH⁻ for the de novo biosynthesis of Cys-tRNA^[Ser]Sec.

Glycine, Glutamine, and Glutamate

Both glycine and glutamine can be used to generate endogenous serine. Glycine can be transformed into serine in one step by the enzyme SHMT1/2, while glutamine participates in the second step in the metabolic bypass of glycolysis for the de novo synthesis of serine providing the amino group in the presence of vitamin B₆ by the enzyme PSAT1 [129, 130]. Glutamine and glutamate can be converted to each other, and glutamate is essential to generate GSH together with glycine and cysteine in the cell.

Therefore, on the basis of adequate serine from diets, the transformation of glycine and even the de novo synthetic pathway from glycolysis, adequate dietary protein may provide a higher Se intake daily to guarantee the expression of housekeeping selenoprotein genes and also a small portion of stress-responsive selenoproteins and supply enough dietary S-containing amino acids to generate Cys-tRNA^[Ser]Sec for the biosynthesis of false selenoproteins instead of the corresponding stress-responsive selenoproteins in local inhabitants living in the classic Se-deficient areas. This might be an underlying mechanism for the disappearance of Keshan disease in China at present [79, 109–111].

Fig. 7 The SAM-dependent generation of CH₃SeH or final excretory forms of Se. This schematic illustrates the essential role in both of these metabolic pathways with the presence of ATP. Modified from Ref. [125]



The Latent Health Risk in a Case of Physiological Adaptation to a Low-Se Status

Optimal Se intake daily is quite important to human health. Se is an essential component of several enzymes involved in various crucial metabolic pathways, which are responsible for male reproduction, thyroid hormone metabolism, antioxidant defense systems, etc.

Male Subfertility

Previous studies involving different animal models had revealed the incredible importance of Se. Selenoproteins are essentially required for spermatogenesis, antioxidant defense, and other biological functions. Nowadays, more and more studies have focused on the elucidation of crucial roles played by the peculiar and canonical selenoproteins, i.e., glutathione peroxidase 4 (GPX4) and selenoprotein P (SELENOP) in male fertility. GPX4 plays an essential role in the disulfide bond formation for spermatogenesis [131–133]. SELENOP is biosynthesized in the liver, transported in the blood. SELENOP supplies Se for the biosynthesis of GPX4 via the apolipoprotein E receptor-2 [134]. The expression of inactive GPX4 or low-active GPX4 can lead to embryonic lethality and male subfertility [135–137]. Low-Se diet (0.15 mg/kg) reduced sperm quality and testicular glutathione peroxidase-4 activity in rats [138].

Hypothyroidism and Underdevelopment

During the metabolism of thyroid hormones, iodothyronine deiodinases (DIOs) are important enzymes that are responsible for the conversion of thyroxine (T4) to triiodothyronine (T3). There are three types of DIOs with different physiological functions: DIO1 is mainly responsible for the T3 level in blood; DIO2 participates in the conversion of T4 to T3, which is the only one composed of two Se atoms; DIO3 plays roles in the transformation of T4 to T3 and T3 to T2 protecting the brain when the plasma Se is lower than 67 µg/l, which have been connected with diminished peripheral capacity for the turning of T4 into T3. Se deficiency decreases the activity of DIOs and compromises thyroid function following by physiological and cognitive underdevelopment [139–143]. However, the results from a randomized controlled Se-supplement trial in UK elderly adults did not find the effect on thyroid function or on the ratio of T4/T3 [144, 145]. A small population survey of mothers and infants showed that the

growth and development of infants were correlated with dietary selenium intake of mothers or selenium content in breast milk [146].

Weak Immunobarrier

Selenium is believed to play several roles in some key biological processes to build up the immune barrier in the human body, including antioxidant defense, redox signaling, redox homeostasis, and the immune response including regulation of T cell proliferation, differentiation, and metabolism, achieved through activities of selenoproteins [147–149]. For instance, reactive oxygen species (ROS) are produced, usually removed from the body by a variety of selenium-containing enzymes; otherwise, the excess of ROS usually induces oxidative stress and causes health hazards during viral or bacterial infections [150, 151]. Recently, Se intake is sub-optimal or low and is considered one of the risk factors which might impact the outcome of SARS-CoV-2 infection [152].

Short Life Expectancy

Selenium is well known as one of the powerful antioxidants. A low level of plasma selenium was found to be associated with a higher incidence of esophageal and stomach cancer in a Chinese study [153]. Also, one study from Italy showed that the lowest quartile of plasma Se had higher mortality compared with the highest quartile of plasma Se in adults [154]. Up to now, studies on the correlation between oxidation damage and aging are still popular [155–157]. However, the results from the animal experiments are still inconsistent. Fortunately, the benefit of adequate Se intake on longevity was often confirmed in human studies [158–160].

Conclusions

Serine is a nonessential nutritional amino acid (NNAA) but its various biological functions are well known. Although selenium compounds and sulfur compounds share the same metabolic pathway, less research has focused on the key role of serine in the replacement of Sec by Cys to synthesize the pseudo-selenoproteins.

In this review, we propose several possible factors to explain why Keshan disease has gradually disappeared in China. Along with the adequate dietary proteins intake by local residents living in the classic Se-deficient areas, firstly, the low but more than 17 µg/day of selenium intake can guarantee the synthesis of housekeeping selenoproteins; secondly, the replacement of Sec by Cys is inclined to synthesize some stress-responsive selenoproteins; thirdly, enough AAs is uptaken for the synthesis of serine (from glycine),

GSH (glutamate, cysteine, and glycine), and SAM (from methionine).

We have reasons to predict the potential health risk for the human body in the physiological adaptation state of low selenium based on the results of animal experiments.

Author Contributions Respective contributions were as follows-QW and SZ: wrote the paper; FH and YQL: contributed to the conception of the work; HYW and ZWH: revised the paper critically for important content.

Funding The authors would like to thank the financial support of the National Natural Science Foundation of China under Grant Nos. 81973048, 81741032, and 81372989, the National Key Research and Development Program of China (grant number 2020YFC2006302), and the Chinese Nutrition Society Nutrition Scientific Research Fund (No. 2013-013).

Data Availability The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

Code Availability Not applicable.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors have read and approved the final manuscript.

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