Chapter

Synthesis and Types of Selenoproteins and Their Role in Regulating Inflammation and ER Stress Signaling Pathways: Overview

Volkan Gelen, Adem Kara and Abdulsamed Kükürt

Abstract

Selenium (Se) is one of the trace elements that play an important role in many biological processes in the living body. Selenium acts in the body mainly in its forms called selenoprotein. Selenoproteins play a role in various events such as oxidative stress, immunity, cancer, inflammation, and endoplasmic reticulum stress. In selenium deficiency, the expression of selenoproteins and thus their activity decrease. In this case, some reactions such as increased oxidative stress, weakened immunity, endoplasmic reticulum stress, and inflammation cannot be prevented. The main source of selenium is food, and a diet poor in selenium causes selenium and therefore selenoprotein deficiency. This chapter will present information about the synthesis of selenoproteins and their role, especially in inflammation and endoplasmic reticulum stress response.

Keywords: selenium, selenoproteins, ER stress, inflammation, oxidative stress

1. Introduction

Selenium (Se) is a trace element and must be taken from outside. Selenium was first discovered in 1817 [1]. Research on the effects of Se on the organism has gained momentum over time. Se has an important role in the regulation of many functions in the organism such as reproductive physiology, muscle functions, cardiovascular system, nervous system, and immune system [2]. Selenium is mainly found in many products such as soil, water, vegetables, fruits, meat, milk, eggs, and fish [3, 4]. Both excess and deficiency of selenium cause some problems [2]. Selenium deficiency causes a number of problems such as acute heart failure, arrhythmia, muscular dystrophy, short stature, and short extremities [5–7]. On the other hand, excessive intake of Se causes hair loss, deterioration in nail structure, and nervous system anomalies [1, 2]. In other words, as it can be understood, excess and deficiency of selenium cause a number of problems. Selenium can be taken into the body in organic Se and

inorganic forms. The inorganic forms of selenium are mostly selenate and selenite. Its organic form is selenomethionine (Se-Met) and selenocysteine (Sn) [8, 9]. Sec and Se-Met have many biological roles. The structures formed by proteins that combine with Se are called selenoproteins [10]. Selenoproteins are also involved in various biological functions such as maintaining homeostasis in the organism, oxidative stress, hormone release, regulation of the immune system, inflammation, and stress on the endoplasmic reticulum [11]. Selenium or selenoprotein deficiency is generally due to insufficient intake of foods [12]. The most common forms of Se are selenate, selenite, Sec, and Se-Met [13]. These forms are very active in homeostasis. In addition, it has been stated that they have many effects on cancer [14]. In line with this information, in this section, we aimed to explain the mechanism of action by discussing the synthesis of selenoprotein forms of Se, which is of such importance for the organism, their types, and their roles in inflammation and ER-stress.

2. Synthesis of selenoproteins

Selenium shows its effect on living things through selenoproteins. Its main biological form is selenocysteine, and its synthesis begins with the binding of the serine amino acid to tRNA [15]. Selenocysteine is similar to cysteine, but it has a selenium atom instead of sulfur in its structure and is ionized at physiological pH. In the study, replacing selenocysteine with cysteine dramatically reduces enzyme activity [16–19]. This supports the critical role of the ionized selenium atom [20]. Selenoproteins contain one or more selenocysteine residues in their primary structure [21]. According to current information, all selenoproteins, except Selenoprotein P, take part in redox reactions, are located in the catalytic regions of enzymes, and show enzymatic activity. Although selenoproteins have many similar functions in general, their amino acid sequences, tissue distributions of enzymatic activities, and interactions with other molecules vary widely [18, 19], looking at the selenoprotein synthesis steps (**Figure 1**).

3. Types of selenoproteins

Selenium can enter the body in various forms, but its absorption is mainly in the form of selenoprotein [3]. As a result of various studies, 25 selenoproteins, 5 of which are glutathione, have been isolated in humans. These selenoproteins are selenium phosphorylate synthetase (SPS), selenoprotein S (SELENOS), selenoprotein H (SELENOH), peroxidases (GPXs), 3 thioredoxin reductases (TrxRs), 3 iodothyronine deiodinases (DIOs), selenoprotein P (SELENOP), selenoprotein W (SELENOW), selenoprotein M (SELENOM), SELENON), selenoprotein I (SELENOI), selenoprotein K (SELENOC), selenoprotein N (selenoprotein O (SELENOO), selenoprotein T (SELENOT), selenoprotein 15 (15 kDa), selenoprotein R (SELENOR), and selenoprotein V (SELENOV) [17, 21]. Selenoproteins are found in various parts of the cell such as mitochondria, endoplasmic reticulum, nucleus, cell membrane, and Golgi membrane. And where they are found, they have various functions such as antioxidant, anti-inflammatory, hormone metabolism, and regulation of ER stress [22, 23]. The types, names, locations, and functions of some human selenoproteins are summarized in **Table 1**.

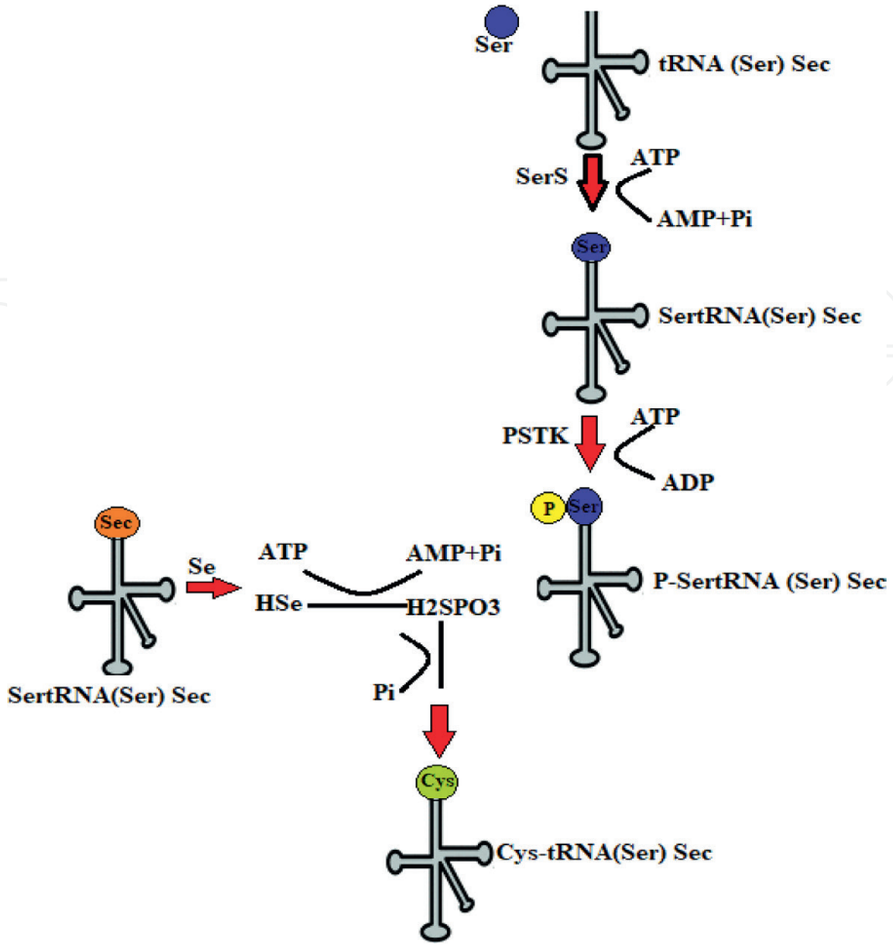

Figure 1.
Synthesis of selenoproteins [20].

4. Roles of selenoproteins in inflammation

Glutathione peroxidase, which protects cells against oxidative damage, is found in the cytoplasm of cells and originates from hydrogen peroxide (H_2O_2). In this way, it prevents the formation of OH from H2O2. Glutathione peroxidase has four protein subunits. Each of the subunits contains a selenium atom. Two main types of glutathione peroxidase enzymes have been identified. The first is selenium-dependent glutathione peroxidase (Se-GPx), which has selenium in its active site. Selenium-dependent glutathione peroxidase has an active role against organic hyper oxides and H_2O_2. Selenium-independent glutathione peroxidase (GST) is known to be more active in the formation of organic hydroperoxides. GPX1 suppresses inflammation in the cell by affecting proinflammatory cytokines and preventing ROS accumulation. Here, the Nrf2/ARE pathway plays an important role [24]. GPX also catalyzes glutathione in various tissues, preventing peroxidation of free radicals and preventing oxidative stress-induced DNA damage in the cell [17, 25–28]. Some studies have shown that Se supplementation increases GPx and SOD activity and decreases MDA levels [29]. In these studies, it inhibits cell inflammation and apoptosis by suppressing ROS-mediated NF-κB production [24, 30]. It has been determined that GPx2 and GPx1 suppress inflammation in intestinal epithelial cells [31–33]. It has been found that vascular inflammation is stimulated in Se deficiency [20]. In another study, it

Selenoproteins	Short name	Main function	Location
Glutathione peroxidase 1	GPx1/cGPx	Antioxidant (detoxification of hydrogen peroxide)	Cytoplasm
Glutathione peroxidase 2	GPx2/GI (gastrointestinal)-GPx2	Antioxidant (detoxification of hydrogen peroxide)	Cytoplasm
Glutathione peroxidase 3	GPx3	Antioxidant (detoxification of hydrogen peroxide)	Secreted
Glutathione peroxidase 4	GPx4/PH (Phospholipid hydroperoxide)-GPx	Antioxidant protects against lipid peroxidation	Cytoplasm, mitochondria, nucleus, and memberanes
Glutathione peroxidase 6	6 GPx6	Antioxidant (detoxification of hydrogen peroxide)	Secreted
Thioredoxin reductase 1	TR1	Reduction of thioredoxins and other substrates	Cytoplasm, nuclear
Thioredoxin reductase 2	TR2	Reduction thioredoxin disulfide bond isomerization, thioredoxin/glutaredoxin/ glutathione reductase	Mitochondria
Thioredoxin reductase 3	TR3		Mitochondrial, nuclear, cytoplasm?
Deiodinase type I	Dio1	Thyroid hormone metabolism	ER membrane
Deiodinase type II	Dio2	Thyroid hormone metabolism	Membrane?
Deiodinase type III	Dio3	Thyroid hormone catabolism	Cell and endosome membrane
Selenophosphate	SPS2	Conversion of selenide to selenophosphate	Unknown
Selenoprotein P	SePP	Se transport and delivery/anti-oxidant	Secreted
Selenoprotein W	SelW antioxidant?	Antioxidant?	Cytoplasm
Selenoprotein K	SelK ER	Antioxidant? regulates Ca2þ flux	ER
15 kDa Selenoprotein	SeP15	Protein folding	ER
Selenoprotein S	SePS/SelS	Inflammatory response, regulation cytokine production, protection against ER-stress-induced apoptosis	ER
Selenoprotein M	SelM	Antioxidant? Or calcium homeostasis?	ER
Selenoprotein N	SelN	Antioxidant? calcium homeostasis? role in muscle function	ER membrane
Selenoprotein T	SelT	Unknown	Golgi/ER
Selenoprotein H	SelH	Nucleolar oxidoreductase, nuclear-localized DNA-binding protein?	Nuclear, nucleolar?
Selenoprotein I	SelI	Unknown	Unknown

Selenoproteins	Short name	Main function	Location
Selenoprotein O	SelO	Unknown	Unknown
Selenoprotein V	SelV	Unknown	Unknown

Table 1.
Types of selenoproteins in humans, their names, location, and functions [23].

was shown that increased selenoprotein activity in vascular endothelial cells suppressed adhesion induced by a proinflammatory cytokine [34, 35]. In addition, it has been determined that selenoproteins protect the structure of the vessel wall by dissolving the cholesterol accumulated in the blood vessel wall [36]. In another study, it was reported that SELENOS has preventive effects on atherosclerosis and hypertension [20].

5. The function of selenoproteins in inhibiting ER stress

The endoplasmic reticulum is an organelle in the eukaryotic cell that spreads throughout the cell, especially involved in protein synthesis. When the ER is opened too much, the ER stress response occurs due to misfolded proteins and imbalances in calcium homeostasis. This causes cell apoptosis [34]. Some selenoproteins, SELENON, SELENOK, SELENOM, specifically the 15 kDa selenoproteins DIO2, SELENOS, and SELENOT, regulate ER stress [35–38]. Selenoproteins located in the ER is involved in regulating oxidative stress, inflammation, and intracellular Ca homeostasis. SELENON acts as a cofactor for the ryanodine receptor on the ER membrane and thus regulates the intracellular Ca level [20], while Sep15 is also involved in protein folding [39]. Aforesaid, GPx1 can reduce the accumulation of proinflammatory factors and increase the body's antioxidant capacity and expression [40]. It is affected by the Nrf2/ARE pathway [41]. When the body is exposed to oxidative stress, Nrf2 dissociates from the Keap1 protein, enters the nucleus, and binds to ARE, activating the Nrf2/ARE pathway, enhancing downstream GPx1 gene expression, and attenuating oxidative stress [42, 43]. Selenoprotein expression can reduce the expression of inflammatory factors and attenuate the NO-induced proinflammatory response [38]. NADPH oxidase (NOX) can mediate excessive ROS production [44, 45], thereby suppressing ER stress that oxidative stress induces. In addition, selenoproteins increase the enzyme level of DNA methyltransferase 1 (DNMT1) and protect the cell against oxidative stress and ER stress [46] (**Figure 2**).

6. Function of selenoproteins in various diseases

In various studies, it has been reported that there are some differences in selenoprotein types and levels in some diseases. Selenium deficiency causes muscle disorders in humans and animals. White muscle disease is a disease in animals characterized by a selenium deficiency. In this disease, skeletal and cardiac muscles show

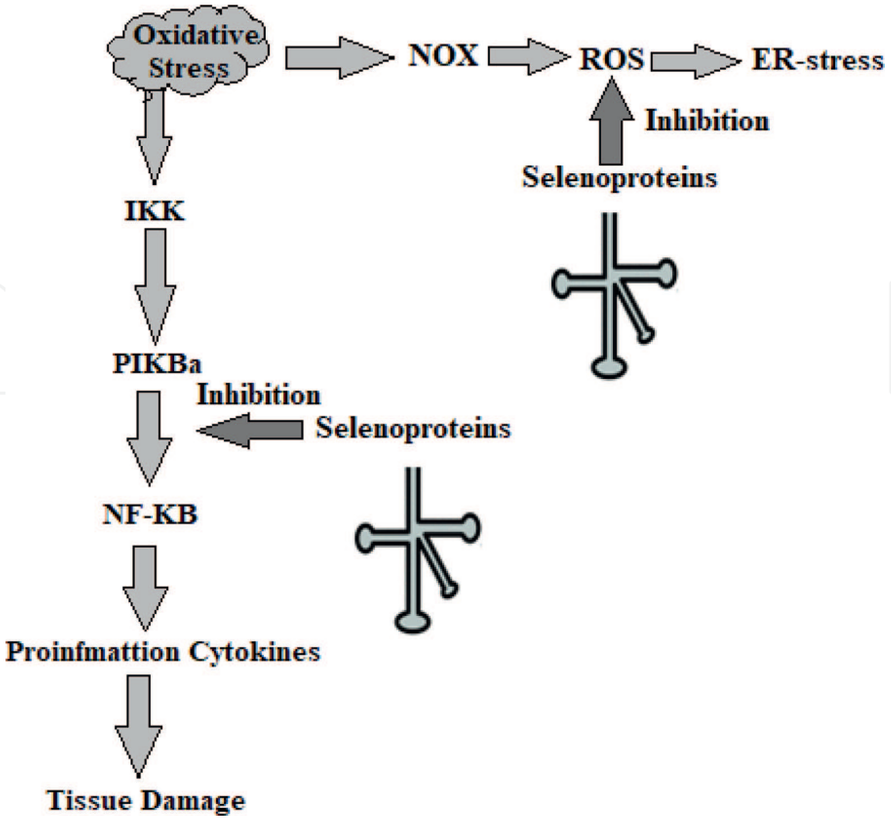

Figure 2.
The effects of selenoproteins in ER stress and inflammation [40].

white streaks due to calcium deposition. White muscle disease can affect both the skeletal and cardiac muscles in which SelW is highly expressed [21]. SelW derives its name from white muscle disease, and SelW levels are upregulated in muscle cells in response to exogenous oxidants [47, 48]. In the case of oxidative stress, damage to vascular endothelial cells occurs, in which case atherosclerosis, hypertension, and congestive heart failure are exacerbated [49]. Selenoproteins prevent the progression of damage due to their antioxidant properties in cardiovascular system diseases [50]. As a result of various studies, selenium supplementation increases the expression and the activity of GPX1, GPX4, and TRXR1, thus protecting the cardiovascular system against oxidative damage [51, 52]. Various studies have shown that selenoproteins have important roles in cancer [53]. Many selenoproteins have been reported to be associated with various types of cancer. For example, polymorphisms of GPX1 have been associated with various types of cancer, including breast, prostate, lung, head, and neck cancer [54, 55]. Polymorphisms in GPX2, GPX4, and SelP have been associated with colorectal cancer, Sep15 polymorphisms with lung, SelS promoter polymorphisms with stomach, and SelP polymorphisms with prostate cancer [56–59]. Studies have shown that selenoproteins play an important role in preventing neurological disorders. Some of the dietary selenium is stored in the brain tissue and it has been determined that it has a protective effect on the brain tissue in nervous system diseases such as ROS-induced Alzheimer's, Parkinson's, and ischemic brain damage [60–62]. In some studies, it has been determined that selenoproteins are protective against hyperglycemia-induced increased ROS production and resulting tissue damage in diabetes mellitus [63, 64].

7. Hazards of selenium supplementation

Apart from these mentioned issues, excessive intake of selenium causes harmful effects on the organism. If selenium absorption is excessive, selenium excess, in other words, selenium poisoning, selenium toxicity, or selenosis occur [65]. In the case of selenosis, mood changes are seen due to fatigue, vomiting, diarrhea, changes in nail structure, hair loss, or nerve damage [66]. In addition, excess selenium can cause such severe damage to the liver or heart tissue that they cannot adequately perform their liver and heart functions [67]. In case of damage to the liver tissue to this extent, cirrhosis, heart failure, which leads to damage to the heart and deterioration of heart functions, occurs [68]. When selenium comes into contact with the skin and mucous membranes, it also damages these organs [69]. Damage to the skin and mucous membranes is manifested, among other signs, by skin blistering. Excess selenium in the organism may lead to the development of malignant tumors other than those listed above [70]. For this reason, selenium in the composition of cigarettes is thought to cause cancer.

8. Conclusion

Selenium shows its effect on living things through selenoproteins. Its main biological form is selenocysteine, and its synthesis begins with the binding of the serine amino acid to tRNA. Selenocysteine is similar to cysteine, but it has a selenium atom instead of sulfur and is ionized at physiological pH. In the study, replacing selenocysteine with cysteine significantly reduces enzyme activity. This supports the critical role of the ionized selenium atom. Selenoproteins contain one or more selenocysteine residues in their primary structure. Selenium can enter the body in various ways, but its absorption is mainly in the form of selenoprotein. As a result of various studies, 25 selenoproteins, 5 of which are glutathione, have been isolated in humans. These selenoproteins are GPXs, TrxRs, DIOs, SPS, SELENOS, SELENOO, SELENOT, SELENOH, SELENOP, SELENOW, SELENOM, SELENON, SELENOI, SELENOC, 15 kDa, SELENOR, and SELENOV. Selenoproteins are found in various parts of the cell such as mitochondria, endoplasmic reticulum, nucleus, cell membrane, and Golgi membrane. And where they are found, they have various functions such as antioxidant, anti-inflammatory, hormone metabolism, and regulation of ER stress. In this study, the synthesis, types, locations, and roles of cell proteins in inflammation and ER stress are explained.

Author details

Volkan Gelen[1*], Adem Kara[2] and Abdulsamed Kükürt[3]

1 Faculty of Veterinary Medicine, Department of Physiology, Kafkas University, Kars, Turkey

2 Faculty of Science, Department of Genetics, Erzurum Technical University, Erzurum, Turkey

3 Faculty of Veterinary Medicine, Department of Biochemistry, Kafkas University, Kars, Turkey

*Address all correspondence to: gelen_volkan@hotmail.com

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