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Review

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Carmen Beatrice Dogaru [†] , Carmen Duță [†] , Corina Muscurel [*] , Irina Stoian

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Carmen B. Dogaru †, Carmen Duță †, Corina Muscurel * and Irina Stoian

Department of Biochemistry, Carol Davila University of Medicine and Pharmacy, 050474 Bucharest, Romania

* Correspondence: corina.muscurel@umfcd.ro

† These authors contributed equally to this work.

Abstract: Selenoproteins are a group of proteins containing selenium in the form of selenocysteine (Sec, U) as the 21st amino acid coded in the genetic code. Their synthesis is dependent on dietary selenium uptake and a common set of cofactors. Selenoproteins accomplish diverse roles in the body and cell processes by acting, for example, as antioxidants, modulators of the immune function, detoxification agents for heavy metals, and other xenobiotics, key compounds in thyroid hormone metabolism. Although the functions of all this protein family are still unknown, several disorders in their structure, activity or expression have been described by researchers. They concluded that selenium or cofactors deficiency, on one hand, or the polymorphism in selenoproteins genes and synthesis, on the other hand, are involved in a large variety of pathological conditions, including type 2 diabetes, cardiovascular, muscular, oncological, hepatic, endocrine, immuno-inflammatory, neurodegenerative diseases. This review is focused on specific roles in medicine only of selenoproteins that are each named after an alphabet letter, less known than the rest of them, regarding their implications in pathological processes of several prevalent diseases and also in disease prevention.

Keywords: selenium; selenocysteine; selenoproteins; cancer; type 2 diabetes; neurodegeneration; cardiovascular disease; inflammation

1. Introduction

It is now very well known that the history and importance of the implications of selenoproteins in health and diseases began in 1817 when the trace element Selenium (Se) was first discovered by the Swedish chemist Jöns Jacob Berzelius after the Greek goddess of the Moon, Selene, and originally considered a naturally occurring toxicant. In 1957 this point of view changed thanks to Schwartz's and Foltz's unexpected discovery that selenium prevented liver necrosis in rats. This discovery changed since then the perception of selenium as a health threat and as time passed, selenium began to be viewed as an essential and beneficial trace element for health. Based on these discoveries the era of selenoproteins started in 1974 when the American biochemist Thressa Campbell Stadtman added the famous and unique new amino acid selenocysteine (Sec, U) as the 21st „naturally occurring" in the genetic code [1]. Sec is cotranslationally inserted into nascent polypeptide chains in response to the UGA codon, known as the stop codon. For this „magic" to be possible, organisms evolved by using the intensely commented by research papers of the insertion machinery requiring a cis-acting Sec insertion sequence (SECIS) element [2].

Regarding selenoproteins and selenoproteome, 25 selenoprotein genes corresponding to 25 selenoproteins have been identified in humans showing different properties and functions, most of them broadly classified as antioxidant enzymes.

This review focuses on the implications of the selenoproteins that each are named after an alphabet letter, less known than the rest of them. These selenoproteins also play vital roles in the pathogenesis and prevention of many diseases (cardiovascular, gastrointestinal, hepatic, immuno-inflammatory, neurodegenerative, oncological, muscular diseases, type 2 diabetes, etc.) as described

below. The pathological conditions arise, as mentioned above, due to selenium or cofactors deficiency, on the one hand, or the polymorphism in selenoproteins genes and synthesis, on the other hand.

2. Implications of "Alphabet" Selenoproteins in the Pathology of Diseases

An already large number of studies have shown that selenoproteins are involved in so many processes in the organism, such as cellular oxidative stress, ER stress, antioxidant defense, regulating the inflammatory and immune response [3–6], and have essential functions in antioxidant, anti-apoptosis, anti-inflammation, and other various complex mechanisms [7–9]. SELENOK is essentially involved in calcium flux, T-cell proliferation, and neutrophil migration in immune cells, also protecting the cells from ER stress-induced apoptosis [10]. Moreover, SELENOK plays an important role in regulating immunity as a cofactor of enzymes involved in the key post-translational transformations of proteins by enhancing the catalytic efficiency and playing also a biochemical role through antioxidant and protein repair [11].

In the case of selenium deficiency conditions, vascular injury is triggered through multiple pathways mechanisms, such as necrosis, apoptosis, and inflammation [12,13]. Increased selenoproteins expression in vascular endothelial cells may have a protective role by reducing abnormal cell adhesion induced by pro-inflammatory cytokines [14,15]. In addition, the down-regulation of SELENOS under the selenium deficiency conditions can effectively prevent the development of cardiovascular diseases, such as atherosclerosis and hypertension [13]. Generally, selenoproteins protect the heart from the accumulated cholesterol in blood vessel walls by increasing the levels of coenzyme A in myocardial cells and increasing the energy production [16].

Various selenoproteins have an ER response function to ER stress conditions. ER is widely distributed in eukaryotic cells and is an essential organelle involved in protein processing and steroid synthesis [13]. When too many unfolded or misfolded proteins in RE are accumulated for a long period of time, that can lead to an imbalance in calcium homeostasis and consequently to an ER stress response which if it's not well managed activates the corresponding signalling pathway and induces apoptosis [17]. The ER-resident selenoproteins involved in regulating the ER stress include 15 kDa selenoproteins, DIO2 (iodothyronine deiodinase 2), SELENOS, SELENON, SELENOK, SELENOM, SELENOT [18–21]. These ER-resident selenoproteins are implicated in ER stress, inflammation, and/or intracellular calcium homeostasis by regulating the calcium flux [22,23]. SELENON acts as a redox cofactor for ryanodine receptors (RyRs) [20], whereas Sep15, a redox enzyme, is associated with the proteins implicated in protein-folding quality control [24].

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2.1. Implications of Selenoproteins in Cardiovascular Diseases

Studies have shown that selenium deficiency could play an essential role in the pathogenesis of Keshan disease (KD) which is an endemic cardiomyopathy that leads to heart failure [25]. The disease was first reported in Keshan County in northeast China in 1935, while similar cases were reported in Nagano Prefecture in Japan, and also in the northern mountains of North Korea in the 1950s. Keshan disease is characterized by cardiac arrhythmia, acute heart failure, and congestive heart failure and can be classified into acute, sub-acute, chronic, and latent KD. Nowadays, acute, and sub-acute cases are almost absent, only chronic and latent are reported but rare and in many geographical areas. Besides KD, selenium deficiency is also correlated with other cardiovascular diseases, such as cardiomyopathies, atherosclerosis, coronary heart disease, myocardial infarction, and heart failure [3].

SELENOT was shown to prevent free-radical injuries and the death of the cell during ischemia/reperfusion as SELENOT-derived peptides protect the heart from these processes by inhibiting apoptosis and oxidative stress [18]. In regulating cardiac apoptosis and survival mechanisms during cell stress conditions, ER stress has an essential role. The ER stress induced by misfolded proteins is regulated by SELENOK in association with SELENOS whereas SELENOM, SELENON, and Sep15 may regulate the cardiac response to ER stress [14–16]. It is well known already that SELENOK is an ER protein with an antioxidant function in cardiomyocytes, having a high mRNA expression in the heart [26]

Plasma SELENOP is supplying cells with selenium so providing the necessary support for an optimal expression of selenoproteins. Moreover, SELENOP reduces peroxynitrite induced by protein oxidation and nitration, as well as lipid, and LDL peroxidation, by oxidizing TRX (thioredoxin reductase) in return [27].

Besides Keshan disease, also Chagas' disease is associated with dietary selenium. KD occurs because of low body selenium levels, a consequence of low-selenium quantities in the soil in Keshan County [28,29], and oral selenium supplementation was found to eliminate Keshan disease a long time ago [30]. Regarding Keshan disease, an infection with Coxsackie virus B3 (CVB3) is a factor that also contributes to this disease [31,32] but the exact mechanism of selenium implication remains unclear [33].

The other disease, Chagas' disease, is caused by low selenium intake and a microbial parasite infection with Trypanosoma cruzi. Some patients infected with this parasite develop cardiomyopathy as a common cause of heart failure in South America [34] Moreover, patients with Chagas' disease tend to develop increased heart dysfunction so that may be suggestive of the protective role of selenoproteins that remains to be fully elucidated [35].

The clinical studies performed to examine the correlation between selenium status and cardiovascular pathology mortality have provided contradictory data, but low selenium levels correlate with the risk of myocardial infarction [36].

Schomburg et al. reported a strong association between low SELENOP levels and the risk of mortality for all causes, including cardiovascular mortality and also a first cardiovascular event. The studies were performed on a large group of Swedish subjects with no history of cardiovascular events [37]. In addition, Schomburg et al. concluded the hypotheses of the mechanisms involved in the SELENOP influence on modifying cardiovascular risk [37,38]. These hypotheses are as follows: SELENOP transports selenium to tissues that have specific uptake receptors ApoER2, or megalin so selenoprotein biosynthesis increases in order to play the roles in antioxidative defense and in regulating the protein quality control systems. SELENOP is capable of catalyzing the degradation of phospholipid hydroperoxides, by exhibiting GPX (glutathione peroxidase) activity, thereby protecting the cell membrane integrity [39] and LDL particles from oxidation [40]. SELENOP reduces peroxynitrite [27], and associates with the extracellular matrix via heparin-binding domain [41]. SELENOP binds heavy metals, such as Cd, As, and Hg so avoiding toxicity in the plasma [42] and also reducing oxidative stress. A recent study has shown that subjects with high selenium intake and levels were less hypertensive and had reduced stroke and myocardial infarction than those with low selenium levels (Table 1)[43].

Table 1. "Alphabet"selenoproteins related diseases.

Related disorders/ diseases	Selenoproteins involved
Cardiovascular	T [18], K in association with S, M, N, F (sep15) [14–16], P [27]
Keshan Disease	P [31–33]
Liver	
NAFLD	P, N, T, W, S [45–48]
Hypercholesterolemia	P, F (sep15) [50]
Intestinal	
Crohn's disease and colorectal cancer (CRC)	P [5]
Inflammation (IBD)	S, K [74–76]
Cancer	P [88,89]
Colorectal cancer (CRC)	F (sep15) [90]
Lung cancer	S [91]
Gastric	K [102]
Tumor suppressor in choriocarcinoma cells	
Melanoma progression	K [103,104]
Neurological	
Alzheimer's Disease (AD)	M [117], P [129]
Parkinson's Disease (PD)	P [137,140], T [140]
Epilepsy	W [152], P [154]
Muscular	W [156–159]
White Muscle Disease (WMD)	
Multiminicore Disease (MmC)	N [160-162}
Immune response	S [176], K [177,178]
Wound healing	S, P [189–191]
Kashin-Beck Disease (KBD)	P [193]
Type 2 Diabetes Mellitus	P [195,196], S [207,208], K [214]
Obesity	P [217,218], S [222], R [223], N, W [224]

2.2. Implications of Selenoproteins in Liver Diseases

Many experiments have demonstrated that selenoproteins are involved in non-alcoholic fatty liver disease (NAFLD), which is, nowadays, considered the most common chronic liver disease and associated with serious complications, such as obesity and/or insulin resistance. The liver secretory selenoprotein SELENOP is related to insulin resistance. By administrating native selenoprotein P, the insulin signals are broken down for managing the insulin function in both hepatocytes and myocytes. In contrast, the knockdown and exclusion of SELENOP enhance common reactivity to insulin and also enhance glucose tolerance in mice. Regarding glucose tolerance, adenosine monophosphate-activated protein kinase (AMPK) is a mediator in the regulatory activity of SELENOP, so this fact is considering SELENOP a future therapeutic target in diabetes mellitus 2 types [44]. Other studies found that the SELENOP levels were positively correlated with insulin resistance and NAFLD, but for serum selenium levels the conclusions were different [45,46]. An. et al. showed that adding 1.0 mg/kg of Se can reduce the liver damage induced by high fat [47]. Moreover, Zhu et al. identified several upregulated selenoproteins, in mild NAFLD liver samples compared to healthy controls, such as SELENON, SELENOP, SELENOT, SELENOW, DIO2, DIO3, GPX4, and GPX5, suggesting that in NAFLD selenium related processes are progressively perturbed [48]. In addition, other experiments

revealed the essential role of selenoproteins in hepatic function after genetically excluding them in mice, which under these conditions developed hepatocellular degeneration and necrosis so leading to early death [49]. At the same time, a selective loss of so-called housekeeping selenoproteins SELENOP, SELENOF, and also DIO1, TXNRD1 determined the upregulation of the genes involved in cholesterol biosynthesis, and the downregulation of the genes that have roles in the cholesterol metabolism and transport, suggesting the effect of these selenoproteins in favoring hypercholesterolemia [50].

In an article, Stergios A. Polyzos et al., concluded that the association between Se or SELENOP and insulin resistance, which represents a principal pathogenic factor in NAFLD, remains inconclusive. Clinical studies results are conflicting, except those performed in advanced liver diseases, such as cirrhosis, or hepatocellular carcinoma, in which lower plasma selenium and SELENOP are constant findings [51].

Other studies regarding SELENOS have shown that its mRNA level in the liver of pigs induced by high fat can be significantly increased, and the expression of SELENOS is negatively correlated with the apoptosis rate and the symptoms of non-alcoholic steatohepatitis suggesting that SELENOS may be essential in the protection of the liver from the high fat-induced damage [47,52].

It is already known that dietary selenium deficiency can reduce liver selenase activity and consequently lead to oxidative stress, and so, afterward, initiates oxidative stress-related signals [53,54]. Selenium deficiency induces redox imbalance by regulating selenoproteins at mRNA and protein levels, by blocking the GSH system while enhancing the GSH synthesis and catabolism [54]. In hepatocellular carcinoma, selenium has an immunomodulatory role by regulating oxidative stress, inflammation, immune response, cell proliferation and growth, angiogenesis, signaling pathways, and apoptosis [53,55]. As shown by Sang et al., Se concentration was usually low in patients with hepatocellular carcinoma, and enhancing the Se concentration by exogenous supplementation was correlated with reducing the number and size of tumors [55].

The mechanism by which NAFLD increases the risk of cardiovascular disease (CVD) is yet to be clarified because is still controversial whether NAFLD is an independent risk factor for CVD or a risk marker that coexists in people having an increased risk of CVD. The plausible mechanism is the development of inflamed visceral adipose tissue [56], which is the main source of a major flux of free fatty acids (FFAs) into the portal vein and their transport to the liver with the subsequent hepatic fat accumulation [57]. That is the reason why NAFLD can be considered a sensitive marker of the dysfunction of visceral adipose tissue, more relevant for the CV prognostic rather than simply adipose tissue mass.

Another mechanism involved in CVD development is that hepatic steatosis itself leads to hepatic inflammation through the activation of NF-κB pathways that enhance insulin resistance both in the liver and generally in the body. In consequence, the liver of patients with NAFLD might release a large variety of proatherogenic, proinflammatory, and diabetogenic mediators with important roles in the development of CVD, such as high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) [58].

Fibrinogen and PAI-1 produced in the liver, are activators of the coagulation pathway thus enhancing atherothrombosis [59], suggesting that the increase in liver-secreted factors in NAFLD leads to systemic inflammation and atherosclerosis. In several studies, hs-CRP, also produced by the liver, a marker for inflammation, was an independent predictor of CVD [60].

Recent experiments have demonstrated that in the liver there is a group of proteins called hepatokines, such as selenoprotein P, fetuin-A, and fibroblast growth factor-21 (FGF-21) that directly affect glucose and lipid metabolisms, similar to adipokines and myokines [61].

Serial analysis of gene expression revealed that SELENOP is a hepatokine associated with insulin resistance in humans [62]. Studies have also shown that patients with type 2 diabetes mellitus and those with NAFLD have higher serum SELENOP than healthy controls [63–65]. Moreover, it was found that salsalate and adiponectin ameliorated palmitate-induced insulin resistance in hepatocytes by inhibiting SELENOP through the AMPK-Forkhead box protein O1α (FOXO1α) pathway,

suggesting that this action might be a novel mechanism in mediating the antidiabetic effects of salsalate and adiponectin [65,66].

2.3. Implications of Selenoproteins in Intestinal Diseases

There is strong evidence that Se levels are linked to the incidence and severity of intestinal diseases that have become very frequent and serious pathology in the world, including inflammatory bowel disease (IBD) and colorectal cancer (CRC) [67,68]. Inflammatory bowel disease is a generalized term that includes Crohn's disease (CD, regional ileitis) and other ulcerative colitis. Selenium reduces intestinal inflammation through the action of selenoproteins which have a protective role. In intestinal infections, their actions involve type-3 innate lymphocytes (ILC3) and T-helper cells 17 (Th17) which protect the intestinal barrier that is essential for maintaining the physiological intestinal function [69,70]. Inflammation leads to barrier damage through an increase in ROS (reactive oxygen species) production while dietary Se supplementation can reduce their levels [71].

SELENOP is significantly reduced in the serum of Crohn's disease (CD) subjects and serum SELENOP concentration is negatively correlated with CRC risk [5].

SELENOP originates from the colonic epithelium, and represents the source of antioxidant-mediated cancer protection associated with colitis, and in contrast, the SELENOP down-regulation promotes oxidative stress in ulcerative colitis [72]. Intestinal epithelial SELENOP knockdown increases tumor load and genomic instability in cancer associated with colitis model, suggesting the important role of SELENOP in colon cancer development [69,72]. Moreover, reduced selenium levels promote helper T-assisted 1 (Th1) cell differentiation in Crohn's disease patients. Selenium supplementation can inhibit Th1 cell differentiation through SELENOW, eliminate cytoplasmic ROS, and so relieving symptoms in patients with Crohn's disease [73]. In addition, experiments performed both in vitro and in vivo on Sep15 knock-out colon cancer cells or mouse models have shown a reversal of colon cancer phenotype and a reduction of the number of chemical-induced tumors [19,24].

SELENOS and SELENOK have also been implicated in inflammation and IBD [74–76]. It has been reported an increase in the production of cytokines having an inflammatory effect, with a decrease in the expression of SELENOS. Moreover, in the absence of SELENOK the inflammatory cytokines decrease [75]. These findings need to be further investigated.

In IBD, many immune cells, such as macrophages, T cells, and innate lymphoid cells are involved in this pathological condition, and studies have shown the important impact of selenium and selenoproteins in inflammatory signaling pathways implicated in the pathogenesis of this disease. Two transcription factors, nuclear factor-κB (NF-κB) and peroxisome proliferator-activated receptor γ (PPARγ) involved in the activation of immune cells and also implicated in various stages of inflammation, have been shown that are impacted by Se status. In addition, there is a correlation between the levels of NF-κB in the gut and the severity of IBD. Before resection surgery for Crohn's disease, histological colon samples revealed a correlation between NF-κB levels and histological score, that higher levels of NF-κB led to a higher histological score [77]. Because NF-κB is a redox-sensitive transcription factor it is regulated also by selenoproteins, which possibly are acting as antioxidants and can alleviate the symptoms of IBD [78]. Studies regarding SELENOP, which has both reductase and peroxidase activities, have shown that is decreased in IBD. The oxidative stress developed during IBD can lead to the activation of NF-κB, so selenoproteins SELENOP, and GPX2 (glutathione peroxidase 2) have the role and ability to reduce this stress and this could lead to a decrease in the activation of NF-κB [79].

PPARγ is a key receptor that is highly expressed in epithelial cells of the colon, second to adipose tissue, and like NF-κB has been implicated in the inflammation of the colon [80]. In contrast with NF-κB, whose expression is increased in IBD, in the case of PPARγ a greater decrease is observed in patients suffering from ulcerative colitis compared to those suffering from Crohn's disease [81].

Selenium plays an essential role in the activation of PPARγ and its ligands which are derived from the arachidonic acid pathway of cyclooxygenase activity, in macrophages. Selenium can

increase both PPARγ and its ligand, the prostaglandin 15d-PGJ2 [75,82], so, eventually, under selenium supplementation, IBD would be significantly ameliorated.

Colorectal cancer (CRC) could be another complication of IBD and patients suffering from IBD could have a high risk of developing CRC. Clinical trials that administrated Se supplements reported a decrease in the number of colorectal cancer cases compared to those patients that were administered a placebo [83]. Oxidative damage to DNA can lead to tumors development, and in that case, selenoproteins can decrease the risk of CRC [83], so selenium and selenoproteins can be used as chemoprotective agents, knowing the fact that selenium is involved in regulating apoptosis and proliferation of the intestinal epithelium [79].

2.4. Implications of Selenoproteins in Cancer

As a lot of studies have demonstrated, both selenium and selenoproteins play important roles in the occurrence of tumors and the progression of the malignant process [84–87].

Many selenoproteins gene polymorphisms have been linked to the risk of developing cancer. Polymorphisms in SELENOP, besides GPX2, and GPX4 (glutathione peroxidases), have been implicated in colorectal cancer [88,89]. Sep15 polymorphisms have been related to an increase in lung cancer risk [90]. SELENOS promoter polymorphisms have been linked to gastric cancer [91]. Recent experiments have shown that epistasis between polymorphism of SELENOS and mitochondrial superoxide dismutase (SOD) has been linked to prostate cancer risk [92]. Moreover, changes in the expression of SELENOP, Sep15, GPX1, GPX2, and TRXR1 (thioredoxin reductase 1) have been related to different forms of cancer [87,93].

The down-regulation of SELENOP, GPX1, and GPX3 is associated with tumorigenesis in colon cancer [69,72,94,95]. Sep15 it has been found to be down-regulated in liver, prostate, and lung cancers [96–100]. In contrast, the up-regulation of Sep15 and GPX2 occurred in bladder tumors and bladder cancer cells [101].

SELENOK acts as a tumor suppressor in human choriocarcinoma cells because negatively regulates human chorionic gonadotropin β subunit, and β-HCG expression, respectively, which may be used as a novel therapeutic target for human choriocarcinoma in vitro [102]. In addition, regarding SELENOK, it was found that this selenoprotein is critical in promoting calcium fluxes that induce melanoma progression [103,104].

Numerous analyses were performed by NPC (Nutritional Prevention of Cancer) trials in order to determine whether selenium acts as a cancer-preventing agent. One of them has referred to the possibility that selenium supplementation could reduce the risk of skin carcinomas. The trials concluded that although skin cancer incidence did not differ between those groups from the trials, the total incidence of cancer decreases, including prostate, lung, and colorectal cancer [105]. The studies confirmed the protective effect of selenium supplementation in preventing prostate cancer [106]. Another recent study, the SELECT (Selenium and Vitamin E Cancer Prevention) study found no significant decrease in prostate cancer after selenium supplementation. The SELECT study used purified selenomethionine while the NPC study used selenized yeast [107].

2.5. Implications of Selenoproteins in Neurological Diseases

The brain is retaining selenium even under conditions of dietary selenium deficiency. Selenoproteins are most expressed in the brain, especially in the cortex and hippocampus dysfunction [108,109]. Selenoproteins are essential for physiological brain function and a decline in their function can lead to impaired cognitive function and neurological diseases [109–112]. ROS actions and damage are taking place in neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), epilepsy, ischaemic damage, brain tumors, exposure to environmental toxins, and drugs [112].

2.5.1. Implications of Selenoproteins in Alzheimer's disease (AD)

Alzheimer's disease, the most common type of progressive dementia, involves parts of the brain that control thought, memory, and language. AD is manifesting in memory loss, impaired cognitive function, and changes in behavior and personality [113]. The brains of AD patients are accumulating abnormal amounts of extracellularly amyloid plaques consisting of the protein amyloid β, and also tau proteins, as well as intracellularly as neurofibrillary tangles, form in the brain, affecting neuronal functioning and connectivity, resulting in progressive loss of brain function. Abnormal interaction of β-amyloid 42 with copper, zinc, and iron, induces peptide aggregation and oxidation in AD. Amyloid β degradation is mediated by extracellular metalloproteinases, neprilysin, insulin-degrading enzyme (IDE), and matrix metalloproteinases. In their autopsy studies, Dorothea Strozyk et al. found a strong inverse correlation between cerebrospinal fluid β-amyloid 42 and cerebrospinal metals, such as copper, zinc, iron, manganese, and chromium with no association with selenium or aluminum. Moreover, it was also found a synergistic interaction of elevated copper and zinc with lower cerebrospinal fluid β-amyloid 42 levels [114].

Most cases of AD are "late-onset" and are progressing with age. [115].

Studies have shown that several autosomal dominant mutations can result in "early-onset" AD. One of these mutations is in presenilin-2, an enzyme that is involved in processing amyloid precursor protein [116].

It is believed that SELENOM might play a suppressive or protective role in AD because, in a mouse model that overexpressed the human mutation in presenilin-2, the levels of brain SELENOM were reduced [117].

Overexpression of SELENOM, as well as selenium supplementation and treatments, activate ERK signaling leading to a decrease in tau phosphorylation, α-secretase and γ-secretase activities, and an increase of β-secretase activity [118]. In mice, SELENOM overexpression due to selenium treatment led to significant ROS inhibition, reduced mitochondrial damage, and decreased γ-secretase activity [119]. The enzyme γ-secretase is a multimeric protease complex, composed of presenilin, and four additional cofactors, nicastrin, Aph-1, Pen-2, and TMP-21) [120,121].

Another selenoprotein, SELENOP, is abundant in the human brain in neurons and ependymal cells [122]. SELENOP expression in the brain enhances while getting older, suggesting a probable role of SELENOP in decreasing oxidative stress [123].   Studies found that genetic deletion of SELENOP results in a decrease in central nervous system-associated selenium levels, suggesting that other selenoproteins compensate for the SELENOP deficiency, and also that probably, the basal brain selenium levels consist a priority for the available selenium in the body [115,124]. Selenoprotein P deficiency determines subtle spatial acquisition learning and memory deficits, and severely disrupts synaptic plasticity in area CA1 of the hippocampus. The researchers concluded that is difficult to discern whether these effects are due to SELENOP itself or the loss of the selenium transport to the brain [125].

Bellinger et al., investigated the expression of SELENOP in the post-mortem human brain and found a unique expression pattern of SELENOP within the center of neuritic (dense-core) plaques, and also found co-localization of SELENOP with plaques and neurofibrillary tangles, which suggests a possible role of SELENOP in reducing the oxidation accompanying plaques [126].

SELENOP is highly influenced by dietary selenium, so selenium supplementation may have a direct neuroprotective role by increasing SELENOP expression [127]. Several studies have even suggested that selenium supplementation can decrease amyloid toxicity in cell cultures and animal models [114,128].

Considering oxidative stress, a hallmark of Alzheimer's Disease, SELENOP, due to its prominent antioxidant role, might act in AD by protecting neurons against oxidative lesions damage or by transporting selenium so also other antioxidant selenoproteins to be synthesized. SELENOP encodes two His-rich regions that are high-affinity binding sites for transition metals, suggesting its possible role in blocking metal-mediated β-amyloid 42 aggregation and subsequent ROS (oxidative reactive species) further generation [129]. In addition, studies found that SELENOP inhibits tau aggregation through its two His-rich domains and disassembles formed aggregates of tau that are induced by the presence of Cu+/Cu2+ [130]. These two His-rich regions of SELENOP associate with the acidic tail of

α-tubulin by an ionic interaction, suggesting that SELENOP may possibly be involved in microtubule events that are associated with the maintenance of cell polarity, intracellular transport, and cell division and migration [108,131].

2.5.2. Implications of Selenoproteins in Parkinson's disease (PD)

Parkinson's disease (PD) is a neurodegenerative disorder characterized by loss of motor control, caused mainly by a dramatic loss of dopaminergic neurons in the midbrain substantia nigra [132,133]. Prior to cell loss, Lewy bodies are formed, which are intracellular bodies of insoluble protein, aggregates of ubiquitinated α-synuclein [134]. Symptoms of PD include rigidity, bradykinesia, resting tremor, flexed posture, "freezing", loss of movement control, and postural reflexes, with mood changes and cognitive impairments occurring in the later stages of the disease. Parkinson's disease is the major cause of Parkinsonism which is a clinical syndrome comprising combinations of motor problems as mentioned above [132].

The substantia nigra and putamen have higher selenium concentrations than other brain regions [135]. Selenium may play an important role in PD by reducing oxidative stress via selenoproteins [135]. In PD was found that plasma selenium decreases [136]. An explanation might be that there is an intense selenium utilization for selenoprotein synthesis in the brain, possibly to prevent further oxidative damage. SELENOP is found together with presynaptic terminals in the striatum. Besides SELENOP, GPX4 is also decreased in substantia nigra in patients with PD [137]. Moreover, glutathione levels in the midbrain are also decreased, which decrease occurs prior to clinical symptoms, so GPX function is impaired, and so promoting oxidation [138,139].

Loubna Boukhzar et al. found that SELENOT plays a major role in the protection of dopaminergic neurons against oxidative stress, because in regard to their studies, its loss enhanced neurotoxin-induced degeneration of the nigrostriatal system, decreased dopamine secretion, and impaired motor function. These studies represent the first data that demonstrated that SELENOT is involved in the nigrostriatal pathway and the involvement of a selenoprotein in maintaining the functionality of the dopaminergic system and preserving the motor function under oxidative stress conditions [140]. Previous studies have shown that only several selenoproteins, in particular TrxR (thioredoxin reductase), are able to protect neuronal cells [141,142]. SELENOT exerts an oxidoreductase activity like TxrR, through its thioredoxin-like fold, so it represents a new important component of the thioredoxin system, localized in ER, in addition to the cytosol and mitochondrial TrxR1 and TrxR2 [143]. Experiments performed using quantitative PCR, immunochemical, and Western blot analyses, revealed that SELENOT expression is significantly increased in PD mice models, both in vitro and in vivo. The researchers concluded that SELENOT acts as a gatekeeper of redox homeostasis in the nigrostriatal pathway essential for physiological dopamine secretion and therefore for maintaining motor function under oxidative stress conditions. Moreover, the oxidoreductase activity in the nigrostriatal pathway from the substantia nigra pars compacta to the caudate putamen, prevents rapid-onset motor impairments in the mouse models of PD [140]. Alongside Boukhzar et al. studies, there are Bellinger et al. studies that reported an altered expression of SELENOP and GPX4 in survival nigral cells and in dystrophic putamen dopaminergic fibers in Parkinson's disease patients, so suggesting that different selenoproteins may be useful as complementary biomarkers of PD [140].

2.5.3. Implications of Selenoproteins in Epilepsy

Epilepsy is a chronic neurological disease characterized by periodic episodes of abnormal electrical activity (seizures) that cause temporary interruptions in normal brain function. The types of seizures vary and are clinically classified into partial epilepsy syndromes that have a specific location, and generalized epilepsy syndromes that spread throughout the brain [144]. Generalized epilepsy syndromes seizures typically originate simultaneously in both cerebral hemispheres while in partial epilepsies, seizures originate in one or more foci but can spread throughout the brain. Epilepsies are also classified by etiology as idiopathic and symptomatic. Idiopathic epilepsies develop from reappearing unprovoked seizures, have no apparent neurological problems, have an

unknown cause, and may be influenced by genetic factors. Symptomatic epilepsies are sporadic and characterized by multiple seizures, and have many causes, such as cellular and anatomical inborn brain abnormalities and impaired metabolic brain processes [145].

A considerable number of studies have demonstrated an inverse correlation between serum selenium levels and epileptic seizures [146,147]. In infants, studies have also shown that low levels of selenium serum levels lead to seizures and neurological disturbances [147]. Also, even in the case of febrile seizures, which are not abnormal in childhood, there is an inverse correlation with serum selenium levels, suggesting the preventative role of selenium against certain types of epilepsy [148]. In addition, selenium deficiency promotes the risk of seizures in childhood epilepsy [146,149,150]. A recent study demonstrated though, that there is a decreased serum selenium and zinc in patients with idiopathic intractable epilepsy that were independent of the nutrition intake [151]. It is to be mentioned that epilepsy may increase the utilization of selenium even if the intake is adequate, probably supporting the activity of GPX antioxidant activity and of other selenoproteins to prevent the cytotoxicity of seizures. This hypothesis is confirmed by the increased expression of SELENOW, GPX1, and TrxR1 observed in the excised brain tissue of patients with severe epilepsy requiring surgery [152]

Epilepsy, ischemia, and brain trauma may trigger the initiation of a cascade of free radicals and the activation of pro-apoptotic transcription factors with consequently neuronal loss [153].

Knockout of SELENOP increases seizures in selenium deficiency, while brain-specific knockout of all selenoproteins leads to severe seizures [154].

2.6. Implications of Selenoproteins in Muscle Diseases

Selenium deficiency causes muscle disorders observed both in humans and animals, especially in regions having low selenium soil quantities. Selenium deficiency is causing myotonic dystrophy with weakness and muscle pain. White Muscle Disease (WMD) is a muscle disorder developed in farmed regions, with livestock raised on land with low selenium levels [155] The muscles of affected animals appear paler than normal and may show distinct longitudinal striations or a distinct chalky appearance due to abnormal calcium storage. This disease can affect both skeletal and cardiac muscles where SELENOW is highly expressed. SELENOW was the first selenoprotein described to be linked to a muscular disorder [156]. SELENOW is less abundant in the muscles of WMD animals. The sarcoplasmic reticulum of the muscles in WMD has calcium sequestration impairment so resulting in the calcification of both skeletal and cardiac muscle tissue. Studies also revealed that SELENOW is complexed with glutathione in the cytosol by a covalent linkage to one of the cysteine residues. SELENOW is named after white muscle disease, and its levels are up-regulated in response to exogenous oxidants in muscle cells [157,158].

The term "muscular dystrophy" includes a number of muscular disorders characterized by slow degeneration of muscle tissue [159]

Several of these muscular disorders have genetic causes. One of these muscular dystrophies that is termed "Multi-minicore Disease", is a recessively inherited form characterized by multiple small lesions, cores, scattered throughout the muscle fiber on muscle biopsy and clinical features of a congenital myopathy [160]. Although there is genetic heterogeneity with clinical variability, the classic phenotype is easily recognizable by spinal rigidity, early scoliosis, and respiratory impairment. The Multi-minicore Disease is due to recessive mutations in the selenoprotein N gene (SEPN 1) whereas recessive mutations in the skeletal muscle ryanodine receptor gene (RYR 1) have been associated with wider clinical features, such as ophthalmoplegia, distal weakness, and wasting or predominant hip girdle involvement, resembling central core disease (CCD). In CCD there may be a histopathologic continuum at biopsy, with multiple larger lesions ("multicores") due to dominant RYR 1 mutations [160,161]. The role of SELENON in these diseases is yet elusive because its exact function is still incompletely known. One mutation that is causing Multi-minicore Disease involves the loss of a selenium-response element (SRE) that is a cis-element found in some selenoproteins in addition to SECIS element. The SRE is localized within the RNA-coding region following the UGA

codon. A SRE mutation prevents read-through so this is leading to an early termination of translation [162].

Ryanodine receptors are channels in the sarcoplasmic reticulum that are responsible for the redox-sensitive calcium-stimulated release of calcium from intracellular stores [163]. These receptors potentiate calcium signals that may be initiated from the membrane calcium channels and receptors, or by other calcium store channels, for example, InsP3-sensitive channels [164].

All the early onset muscular disorders caused by mutations in SEPN 1 gene include, besides multi-minicore myopathy (MmD) [165,166], congenital muscular dystrophy with spinal rigidity (RSMD1) [167–170], rare cases of desmin-related myopathy with Mallory body-like inclusions (MB-DRM) [171], and congenital fiber-type disproportion myopathy (CFTD) [172].

2.7. Implications of Selenoproteins in Inflammation and Immune Response

Selenoprotein S is one of the selenoproteins involved in the immune response. SELENOS is an ER membrane protein that interacts with the ER membrane protein Derlin and the VCP (p97, valosin-containing protein), which is a cytosolic ATPase [173–175]. VCP is translocated to the ER membrane by binding to SELENOS during endoplasmic reticulum-associated degradation (ERAD), and is responsible for the retro-translocation of misfolded proteins from the ER, where they are tagged with ubiquitin and then transported to the cell proteasome [115,173]. Because of its action, SELENOS is also named VIMP for VCP (valosin-containing protein)-interacting membrane protein [176].

Selenoprotein K is another known p97(VCP)-binding-selenoprotein, and the expression of both SELENOK and SELENOS is increased under ER stress. The translocation of p97 (VCP) to the ER membrane is regulated by SELENOS, not by SELENOK but p97(VCP) is required for the association of SELENOK with SELENOS. In addition, the interaction between p97(VCP) with SELENOK is regulated by SELENOS. The degradation of ERAD substrates requires p97 (VCP), and its translocation from the cytosol to the ER membrane is essential, in order to shuttle ERAD substrates to the proteasome. Both SELENOK and SELENOS are essential to forming the ERAD complex, alongside p97(VCP), in their response to ER stress [177,178].

The polymorphisms of SELENOS promoter can lead to down-regulate expression of SELENOS and cause the accumulation of a large number of misfolded proteins in ER. Subsequently, ER stress can induce NF-κB which can up-regulate inflammatory cytokines and can also lead to apoptosis [115].

The expression of SELENOS in liver cells is regulated by inflammatory cytokines and also by extracellular glucose [179,180]. Studies reveal that polymorphisms significantly impair the expression of selenoprotein S, for example, a change from G to A at the position -105 in the SELENOS promoter [181]. Moreover, subjects having this polymorphism had increased plasma levels of inflammatory cytokines TNFα and IL-1β and also this polymorphism correlated with increased incidence of stroke in women [182], pre-eclampsia [183], coronary heart disease [184], and gastric cancer [91]. The -105 polymorphism exhibits epistasis with -511 polymorphism of IL-1β and both increase the risk of rheumatoid arthritis, although there was no correlation of polymorphisms with rheumatoid arthritis alone [185]. On the other hand, other studies didn't find correlations with stroke [186], autoimmune disorders [187], or inflammatory bowel disease [188].

Selenoproteins are also implicated during wound healing. SELENOS, SELENOP, GPX-1, and GPX-4, perform together various actions in the inflammatory phase, such as antioxidant actions, inhibition of inflammatory cytokines, and elimination of peroxynitrite radical ion [189–191]. Wound healing is a complex process following many cascades of events that have different stages, such as hemostasis (1), inflammation (2), proliferation (3), and remodeling or maturation (4) [192].

In the inflammatory phase of wound healing, soluble factors are released, such as chemokines and cytokines in order to phagocyte the debris, bacteria, and damaged tissues. Recent studies revealed that SELENOS has an essential role in this inflammatory phase. As mentioned in this review, SELENOS is a transmembrane protein found in ER whose function includes removing the misfolded proteins from ER lumen, protecting the cells from oxidative damage, and contributing to ER stress-induced apoptosis. The depletion of SELENOS by siRNA increases the release of inflammatory

cytokines IL-6 and TNF-α, so SELENOS may regulate the cytokine production in macrophages, and subsequently participate in controlling the inflammatory responses [192].

Other research has shown that the results of real-time PCR study revealed a lower expression of SELENOP mRNA in whole blood in Kashin-Beck Disease (KBD) patients compared to healthy controls, having a higher expression in the articular cartilage tissue. Those findings suggested that the decreased SELENOP mRNA expression in KBD reflected the selenium deficiency condition in KBD patients. Under the selenium deficiency condition, the glutathione (GSH) metabolism is impaired and glutathione peroxidase activity decreases leading to an increase in bone and articular cells oxidative damage [193]. KBD is a particular type of chronic osteoarthritis, an endemic disease in the northern part of China, Russia, and a few northern areas of North Korea. KBD affects mainly the knee, ankle, and hand joints causing articular cartilage damage and chondrocytes apoptosis. KBD has traditionally been classified as a non-inflammatory osteoarthritis but recent studies demonstrate that inflammation plays an important role in its development and evolution. Also recently, it was found that KBD is not anymore only an endemic disease because of non-endemic factors such as age, altered biomechanics, joint trauma, and secondary osteoarthritis that also can cause this disease. It was concluded that advanced stages of KBD joint complications and failure are tightly linked with the immune response, and the subsequent stage of chronic inflammation leads to the progression of the disease [194].

2.8. Implications of Selenoproteins in Type 2 Diabetes Mellitus

SELENOP which originates from the liver is essential for supplying extrahepatic tissues with selenium that is required for the biosynthesis of selenoproteins. It has been shown that increased plasma SELENOP levels are associated with hyperglycemia in patients with type 2 diabetes mellitus (T2DM) [195,196]. Moreover, recently, it was found that high SELENOP plasma levels are also associated with hepatic steatosis and fibrosis in NAFLD patients [45]. Insulin sensitivity in the liver and skeletal muscle was improved in SELENOP-deficient mice, while intraperitoneal injection with SELENOP impaired insulin signaling, suggesting that SELENOP is a hepatokine capable to induce insulin resistance [197,198].

Several studies revealed that in humans, plasma SELENOP levels were saturated at a daily intake of approx. 50-100 µg Se and didn't further increase by ingesting selenium supplements in larger doses [197–199]. Increased plasma SELENOP levels may be an accompanying effect of insulin resistance and hyperglycemia because research has shown that hepatic SELENOP biosynthesis is suppressed by insulin and increased by high glucose concentrations [197,200,201]. So it may be concluded that hepatic SELENOP transcription is regulated like that of a gluconeogenic enzyme through transcription factors FoxO1 and HNF-4α together with the co-activator PGC-1α and may also become dysregulated in hyperglycemia and insulin resistance states [197,201,202].

A large number of researchers suggest that the suppression of SELENOP may provide therapeutic ways to treat T2DM and its vascular complications [203]. Metformin (an antidiabetic drug), phosphorylates and inactivates FoxO3a via activation of AMPK (AMP-activated protein kinase) and suppresses SELENOP expression in hepatocytes [204]. Eicosapentaenoic acid (an ω-3 polyunsaturated fatty acid) downregulates SELENOP by inactivating sterol regulatory element-binding protein-1c, independently of the AMPK (AMP-activated protein kinase) pathway[205]. Moreover, the novel molecular strategy for neutralizing SELENOP monoclonal antibody AE2 was reported to improve glucose tolerance, insulin secretion, and insulin resistance both in vivo and in vitro [206].

Serum SELENOS which is mostly secreted by the hepatocytes was associated with T2DM and its macrovascular complications (macroangiopathy) [207,208]. SELENOS has antioxidant and anti-inflammatory functions, so it contributes to the maintenance of the morphology of ER and regulation of ER stress, suggesting that it may be involved in the occurrence and development of T2DM [209,210]. Moreover, several genetic polymorphisms in the SELENOS gene it was demonstrated to be related to T2DM, serum insulin levels, blood glucose levels, and homeostasis model assessment of insulin resistance [208,211].

SELENOK protects cells from the apoptosis induced by ER stress, and is essential for promoting Ca2+ flux during immune cell activation [212,213]. Experiments performed in vitro have shown that the expression of SELENOK, as well as DIO2 (deiodinase2), was down-regulated by about 10% due to high glucose levels [214]

Recent studies have discovered the role of SELENOV in protection against the oxidative damage of oxygen and nitrogen reactive species (ROS/RNS) mediated by ER stress [215,216].

2.9. Implications of Selenoproteins in Obesity

Adipocyte SELENOP is significantly influenced by proinflammatory stimuli involved in the pathogenesis of obesity and its associated metabolic disorders. Studies have shown that differentiated adipocytes responded to omentin exposure in vivo with a significant decrease in SELENOP expression as well as the pro-inflammatory response [217]. Omentin is a novel adipokine, having insulin-sensitizing effects, and is especially produced by visceral adipose tissue, where circulating levels are decreased in insulin-resistant conditions, such as obesity and diabetes. Other studies concluded that SELENOP gene expression in 3T3-L1 adipocytes was reduced in response to TNF-α or H2O2 treatment, so indicating the link between adipose tissue inflammation and oxidative stress in obesity and also in altered selenoprotein metabolism [218]. Moreover, also negative regulation of SELENOP levels occurs in increased pro-inflammatory cytokine IL-6 and MCP1 induced by hypoxia [218].

Researchers demonstrated a significant decrease in SELENOP gene expression in the adipose tissue of obese (ob/ob), HFD-fed, and Zucker rats, and also in insulin-resistant patients [219]. When leptin treatment was administrated in ob/ob mice, there was a shift to lipid catabolism genes that involved inhibition of SREBP1 downstream signaling, as well as up-regulation of SELENOP and SREBP1 expression in the liver [220]. In contrast, SELENOP expression was found to be two-fold higher in obese adipose tissue of OLETF rats [221].

Regarding the SELENOS expression in adipose tissue, it is increased in obese patients, and is significantly correlated with anthropometric measures of obesity and insulin resistance. Studies performed in vitro using isolated human adipocytes have demonstrated that insulin up-regulates SELENOS expression suggesting a link between insulin resistance and SELENOS expression in obesity [222].

In the development of obesity and/or its associated metabolic impairments methionine sulfoxide reductases (MSRs) may also be involved. Experiments studying diet-induced obesity in HFD-fed, with 45% calories from fat, reduced both MSRA and MSRB (predominantly MSRB1, also known as SELENOR) activities and also their protein abundance in VAT (visceral adipose tissue), but not in SAT (subcutaneous adipose tissue) [223].

It has also been demonstrated that obesity up-regulates hepatic expressions of MSRB1, SELENON, SELENOP, and SELENOW, as well as GPX4 in diabetic patients by 33-35% compared to non-obese subjects [224].

3. Conclusions

Members of the selenoproteins family which are named after alphabet letters, also require, like the other selenoproteins, a common set of cofactors for their synthesis, being dependent upon dietary selenium intake, and the energy consumed for their synthesis suggests their great importance for cell physiological function, a consequence of their quite varied roles. „Alphabet" selenoproteins are also involved in numerous diseases and pathological conditions, including type 2 diabetes, cardiovascular, muscular, brain, liver, neurodegenerative, immuno-inflammatory, and gastrointestinal diseases as described above in this article. Consequently, it is also of great importance to expose the medical correlations and implications of these "alphabet" selenoproteins less known than the rest of the selenoproteins which otherwise could risk remaining overlooked, especially in regards to establishing quicker both the prevention, on one hand, and the diagnostic and therapeutical management of the diseases, on the other hand. Given the numerous and varied roles of these selenoproteins, strategies to target the expression of specific selenoproteins could and should

be considered in the future for therapeutic and prevention management. Although the functions of several selenoproteins remain unknown, further research and understanding of each member of this whole selenoproteins family, including the „alphabet" selenoproteins, will be essential in establishing the health benefits of selenium.

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