TECHNICAL NOTE

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An Overview on Selenoproteins and Their Functions

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Abstract

Selenium, is a vital trace element required by many living organisms. It is mainly incorporated in selenoproteins functioning in boosting immune system, reducing inflammation, decreasing cardiovascular disease and inhibiting cancer progression. Fifty different selenoprotein families have been identified. They fulfill a broad range of physiological roles, notably functioning as antioxidants and participating in thyroid hormone metabolism. They are key regulators of stress responses, metabolism, and immunity. Selenoproteins will may be utilized in the treatment of various pathologies, including cancer, diabetes mellitus, neurodegenerative disorders, and cardiovascular injuries, in the near future. This technical report will provide a general overview of selenoproteins and their functions.

INTRODUCTION

Selenium (Se), is a vital trace element required by many living organisms. The main sources of Se are bread, cereals, eggs, meat, fish, dairy products, fruits and vegetables. It is an antioxidant and shielding the cells from damage. It is mainly found in selenocysteine (Sec) and incorporated in selenoproteins functioning in boosting immune system, reducing inflammation, decreasing cardiovascular disease and inhibiting cancer progression. Its depletion is accepted as a factor contributing to various pathological conditions, such as cardiovascular disease, neuromuscular disorders, certain cancers, male infertility, and inflammation.[1]

Se, has a very narrow range between beneficial and harmful levels. Deficiency symptoms can appear with daily intake levels below 18 µg, while toxic effects may occur when intake exceeds 400 µg.[2] Concidering cancer, plasma Se concentrations below 140 µg/L are linked to a significantly increased risk. On the other hand, levels above 400 µg/L are associated with selenosis, while concentrations exceeding 1000 µg/L indicate acute Se toxicity. The ideal baseline range for Se in plasma is considered to be between 110-135 µg/L, with the production of plasma selenoproteins reaching a plateau around 130 µg/L.[3]

Our understanding of Se's crucial role has significantly deepened since Rotruck and his team identified the first selenoprotein 50 years ago (Figure 1).[4] Though most selenoproteins serve oxidoreductase functions, its importance for immun regulation, thyroid hormon metabolism and etc, its need for proper brain function is undeniable. Studies have revealed that lacking certain selenoproteins in the brain can harm neuronal health and, may trigger neurodegeneration. Additionally, the redox balance maintained by selenoproteins may play a role in modulating neuronal functions such as neurotransmission.[5,6]

Biosynthesis and Types of Selenoproteins

To date, over 50 different selenoprotein families have been identified. The presence and types of selenoproteins can vary significantly between different species.[5] A majority of Se-containing proteins incorporate the element as the amino acid Sec. Within cells, Sec represents the predominant form of Se and is distinctive because it is encoded by the UGA codon-a codon that normally functions as a stop signal in the standard genetic code (Figure 2).[5] The human selenoproteome is encoded by 25 genes, and it is expected that many more selenoproteins will be found through genome and sequence analysis.

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One key feature common for all selenoproteins is the presence of Sec residues in their sequence. The physiological functions of selenoproteins strictly depend on the presence of Sec, and mutations of Sec to any other amino acid residue leads to enzyme inactivation.[5]

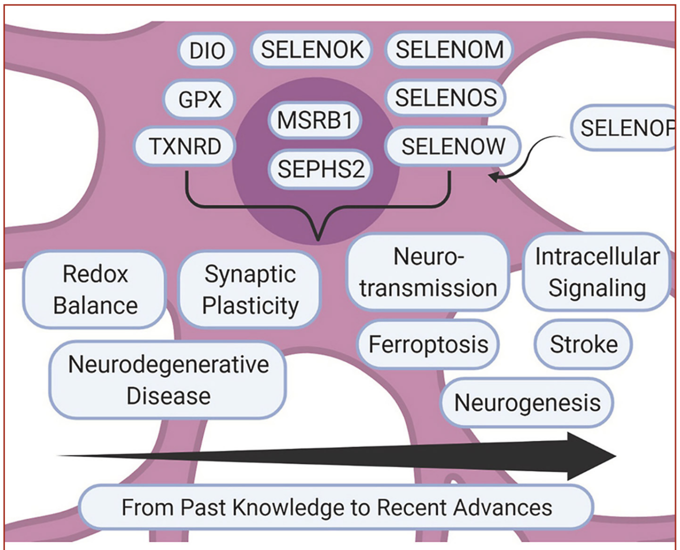

Figure 1. Selenoproteins from past to future[4]

GPX: Glutathione peroxidase, TXNRD: Thioredoxin reductase, SELENOP: Selenoprotein P

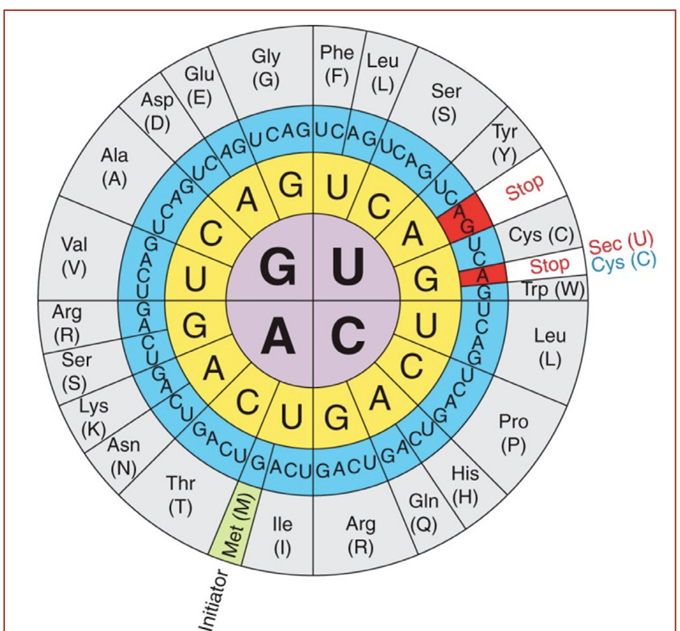

Figure 2. The genetic code illustrating the dual function of the UGA codon and that Sec is the 21st amino acid that is encoded by UGA[7]

Sec: Selenocysteine

All of the selenoproteins contain one Sec residue, only selenoprotein P (SelP) has 10 Sec residues. Selenoproteins are classified into two large groups in accordance with their Sec location. One of these two groups contains Sec in a site adjacent to the COOH terminal region of the protein, such as selenoproteins S, R, O, I, K, and thioredoxin reductases (TRXRs). The other group has Sec in the NH2-terminal region of the protein, such as H, M, N, T, V, W, F (Sep15), selenophosphate synthetase, glutathione peroxidases (GPXs), and deiodinases (DIOs).[7]

The GPXs, TRXRs and DIOs were the first selenoproteins discovered and are the most extensively studied ones. The GPXs are integral to antioxidant glutathione pathways, providing protection from reactive oxygen species (ROS), the TRXRs use NADPH for reduction of thioredoxin in cellular redox pathways and the DIOs ceave iodine-carbon bonds in the metabolism of thyroid hormones.[8]

The synthesis of selenoproteins is variably influenced by the availability of Se. Under Se-deficient conditions, the production of certain selenoproteins-such as GPX1, MsrB1, SelW, and SelH-is markedly reduced. These proteins, which are more sensitive to Se levels, are often categorized as stress-responsive selenoproteins. In contrast, another subset of selenoproteins, including TR1 and TR3, shows relatively stable expression regardless of dietary Se intake. These are typically referred to as housekeeping selenoproteins, reflecting their consistent expression to support essential cellular functions.[5]

Functions of Selenoproteins

Selenoproteins are key regulators of stress responses, metabolism, and immunity. At least 12 of the known selenoproteins are involved in immune functions and cancer mechanisms. Eleven of the selenoproteins primarily have redox-active function. These selenoproteins have emerged as central regulators of cellular antioxidant capacity and maintenance of redox homeostasis. Other 14 selenoproteins such as F, K, M, N, S, and T encoded within the human genome, have been implicated in endoplasmic reticulum (ER) homeostasis and utilize their oxidative capabilities in protein folding.[3]

The primary functions of selenoproteins include:

• Redox-active functions (antioxidant defense)

Protects endothelial cells from peroxynitrite damage.

Reduces the effect of many reactive oxygen species such as hydrogen peroxide and lipid hydroperoxide.

Protects immune cells from oxidative stress.

Reduces cytokine release.

Regulates many antioxidants.

• Thyroid hormone metabolism

• Immune regulation

• **Protein folding and quality control:** Selenoproteins localized in the ER contribute to proper protein folding and the regulation of cellular stress responses. They also help in the removal of misolded proteins.

• **Anti-inflammatory and anti-apoptotic functions:** These proteins participate in the suppression of inflammatory pathways and the inhibition of programmed cell death.

• **Regulation of energy metabolism:** Mitochondrial selenoproteins support cellular energy production and metabolic homeostasis through their roles in oxidative phosphorylation and redox regulation.

Other than, SelP and selenoprotein W (SelW), majority of selenoproteins have no known functions. SelW is a small intracellular protein, binds glutathione and function in oxidant defense. SelP is an extracellular glycoprotein and is the most common selenoprotein found in the plasma. It was shown that, patients with high SelP levels (>5.9 mg/L) had significantly lower risk for all-cause mortality and cardiovascular mortality.[9] Plasma concentration of SelP also correlates with protection against diquat liver injury, suggesting that the protein protects against oxidant injury. The disturbance in SelP cellular concentration results in pathophysiological conditions such as insulin resistance, diabetes mellitus type 2, hyperglycemia and pulmonary arterial hypertension.[10]

Selenoprotein N, is expressed in skeletal muscle, heart, lung, and placenta and it controls redox state of the intracellular calcium-release channel [ryanodine receptor (RyR)], and affects Ca^{2+} homeostasis. Its encoded by the *SEPN1* gene. Mutations in the *SEPN1* gene, causing the knockdown of selenoprotein N accompanied by recessive gene RYR1 that encodes RyR1, which are both proteins implicated in calcium homeostasis, cause severe congenital myopathies. In addition to myopathies, these mutations also lead to impaired insulin action in skeletal muscle by decreasing Akt (protein kinase B) phosphorylation and high ER stress. All these facts indicate a correlation between the decrease in glucose tolerance, insulin activity, and increased ER stress in muscles.[5]

Selenoproteins also possess a strong correlation with human cancer. Selenoproteins, enzymes that selectively include the amino acid Sec, make up major classes of antioxidant proteins critical for the protection of cancer cells to elevated ROS. Nearly all GPX and TRXR enzymes fall into this category as a catalytic Sec is essential for their activities. Selenoprotein gene polymorphisms have been linked to risk of cancer, such as; SelP is associated with the tumogenesis of colon cancer, whereas Sep15 polymorphisms may increase lung cancer risk. SelK can inhibit cell adhesion and the migration of human gastric cancer cells, besides it is critical in promoting calcium fluxes that induce melanoma progression.[11] Due to the limited research on selenoproteins, the relationship between selenoproteins and cancer has not yet been revealed. Se supplementation do not change all selenoproteins equally, the direct roles of selenoproteins need to be examined to assess whether supplementation is advisable for treatment or prevention of a specific cancers.

CONCLUSION

In conclusion, selenoproteins, including those containing the amino acid Sec, are intrinsic components of living organisms. They fulfill a broad range of physiological roles, notably functioning as antioxidants and participating in thyroid hormone metabolism. In mammals, the diverse functions of selenoproteins involved in the regulation of energy metabolism, as well as in anti-inflammatory, anti-apoptotic, and anti-ferroptotic responses, require precise spatial and temporal regulation. Innovative research on the medical applications and therapeutic potential of selenoproteins is expected to continue. In the near future, it is anticipated that selenoproteins will undoubtedly be utilized in the treatment of various pathologies, including cancer, diabetes mellitus, neurodegenerative disorders, and cardiovascular injuries.

Footnotes

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