

Selenocysteine

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summary

Selenocysteine, commonly known as the 21st amino acid, is a unique and essential component of proteins that plays a critical role in various biological processes. Distinguished by the incorporation of selenium in place of sulfur found in cysteine, selenocysteine is encoded by the UGA codon, which typically serves as a stop signal in genetic coding. This unconventional incorporation mechanism, facilitated by specific transfer RNA and SECIS (Selenocysteine Insertion Sequence) elements, underscores its distinctiveness and functional importance in the cellular machinery of many organisms, including humans.[\[1\]\[2\]\[3\]\[4\]](#).

The biological significance of selenocysteine is largely attributed to its presence in selenoproteins, which are vital for a range of physiological functions such as antioxidant defense, redox regulation, and thyroid hormone metabolism.[\[5\]\[6\]\[7\]](#) Key enzymes that contain selenocysteine, like glutathione peroxidases and thioredoxin reductases, are pivotal in protecting cells from oxidative stress and modulating inflammatory responses.[\[8\]\[9\]\[10\]](#) The unique properties of selenocysteine, including its higher reactivity and different redox potential compared to cysteine, enhance the catalytic efficiency of these enzymes, thus playing a significant role in maintaining cellular health and homeostasis.[\[11\]\[12\]](#).

Despite its importance, the regulation of selenocysteine and selenoprotein expression can be influenced by dietary selenium levels, highlighting a delicate balance necessary for optimal health. Selenium deficiency can lead to a range of health issues, including immune dysfunction and increased susceptibility to certain diseases, while excessive selenium intake poses risks of toxicity.[\[13\]\[14\]](#) As such, research into selenocysteine and its associated health implications has garnered attention, particularly regarding its therapeutic potential in diseases linked to oxidative stress and inflammation.[\[15\]\[16\]](#).

Understanding the complex interplay between selenocysteine, diet, and health has led to ongoing investigations into its role in various disorders and the potential benefits of selenium supplementation. This continued research is critical for clarifying the optimal levels of selenium necessary for different populations and developing targeted nutritional strategies to enhance health outcomes.[\[17\]\[18\]\[19\]](#).

Chemical Structure

Selenocysteine, often referred to as the 21st amino acid, possesses a unique chemical structure characterized by the replacement of sulfur in cysteine with selenium. The molecular formula of selenocysteine is $C_3H_7NO_2Se$, and it features a selenol group that distinguishes it from its sulfur-containing counterpart, cysteine[1][2]. The IUPAC name for selenocysteine is 2-amino-3-selanylpropanoic acid[3].

Comparison with Cysteine

Structurally, selenocysteine closely resembles cysteine, but the substitution of selenium (Se) for sulfur (S) results in notable differences in chemical properties. The presence of the selenol group in selenocysteine gives it a lower pKa compared to the thiol group of cysteine, enhancing its nucleophilicity and making it more reactive[4][5]. This increased reactivity is believed to play a critical role in the catalytic mechanisms of enzymes that incorporate selenocysteine[6].

Biological Significance

Selenocysteine is incorporated into proteins via a complex mechanism that utilizes a specific transfer RNA (tRNA) and unique elongation factors[7][8]. This process allows selenocysteine to be inserted into the polypeptide chain at specific sites, often in the active sites of selenoenzymes, which are vital for various biological functions, including antioxidant defense and redox reactions[9][10]. The distinct properties of selenocysteine, combined with its unique incorporation process, underscore its significance as an essential amino acid in many organisms.

Biosynthesis

Selenocysteine (Sec), recognized as the 21st amino acid, is synthesized through a unique pathway distinct from that of other amino acids. The biosynthesis of selenocysteine involves a specific incorporation mechanism that utilizes the UGA codon, which typically signals termination in protein synthesis. This dual role of UGA is facilitated by specialized sequences in the mRNA known as SECIS (Selenocysteine Insertion Sequence) elements, which are crucial for the proper recognition and incorporation of selenocysteine during translation[11][12].

Mechanisms of Selenocysteine Incorporation

The process of selenocysteine incorporation requires a specialized elongation factor, eEFSec, which recognizes the SECIS element and promotes the correct interpretation of the UGA codon as a signal for selenocysteine insertion instead of termination[7]. This translation mechanism has been studied extensively, revealing that selenoproteins, which contain selenocysteine, play significant roles in various biological processes, including antioxidant defense and redox regulation[13][14].

Key Components in Selenocysteine Biosynthesis

The key components involved in selenocysteine biosynthesis include specific tRNAs and proteins that interact with SECIS elements. Selenocysteine tRNA (tRNA^{Sec}) is essential for the incorporation of Sec into proteins. The synthesis pathway involves several factors, including the selenocysteine-specific elongation factor SelB and the selenocysteine-binding protein SBP2, which are responsible for delivering the tRNA^{Sec} to the ribosome and ensuring proper translation[15][4].

Regulation of Selenoprotein Expression

Regulation of selenoprotein expression is influenced by several factors, including selenium availability and oxidative stress. Under conditions of low selenium, the expression of selenoproteins can be adjusted to maintain cellular homeostasis[16]. Furthermore, some studies have suggested that the modulation of selenoprotein activity could have therapeutic implications, particularly in diseases associated with oxidative damage[13][17].

Function in Proteins

Selenocysteine, often referred to as the 21st amino acid, plays a critical role in the structure and function of various proteins, particularly in those involved in antioxidant defense and redox reactions. It is incorporated into proteins through a unique mechanism that involves specific elongation factors and a distinct incorporation process at the ribosome, differing from the incorporation of standard amino acids like cysteine[18][13].

Incorporation Mechanism

The incorporation of selenocysteine into proteins is facilitated by the elongation factor eEFSec, which is distinct from the more common elongation factor eEF1A that assists in the addition of most amino acids. The successful incorporation of selenocysteine relies on the presence of a specific RNA structure known as SECIS (selenocysteine insertion sequence) that helps in recognizing the UGA codon, traditionally a stop signal, and promotes its utilization for selenocysteine insertion[18][15]. This process underscores the complexity of selenoprotein biosynthesis and its evolutionary significance, as it expands the functionality of the genetic code and provides unique properties to proteins that contain selenocysteine[7][13].

Biological Functions

Selenocysteine is integral to numerous selenoproteins, which are known to catalyze redox reactions essential for cellular protection against oxidative stress. For example, glutathione peroxidases (GPx), which contain selenocysteine at their active site, are pivotal in neutralizing harmful hydrogen peroxide and lipid peroxides, thereby preventing oxidative damage to cells[4][19]. The presence of selenocysteine in these enzymes enhances their catalytic efficiency compared to their cysteine-containing

counterparts, contributing to greater enzyme activity and stability under oxidative conditions[\[20\]\[21\]\[5\]](#).

Additionally, selenoproteins such as thioredoxin reductase and iodothyronine deiodinases are vital for maintaining cellular redox balance and thyroid hormone metabolism, respectively[\[13\]\[22\]](#). The unique properties of selenocysteine, such as its larger atomic size and different redox potential compared to cysteine, allow for more effective electron transfer and catalytic capabilities in these proteins[\[23\]\[24\]](#). Thus, selenocysteine not only contributes to the functional diversity of proteins but also plays a crucial role in various physiological processes, including immune response and inflammation regulation[\[25\]](#).

Implications in Health and Disease

The modulation of selenoprotein activity has gained significant attention in the context of disease prevention and treatment. Abnormalities in selenoprotein function are linked to various health conditions, including cancer, cardiovascular diseases, and neurodegenerative disorders. Understanding the role of selenocysteine in these proteins may offer promising avenues for therapeutic interventions aimed at enhancing antioxidant defenses and reducing oxidative damage in the body[\[13\]\[25\]](#).

Genetic Code and Codons

Selenocysteine (Sec, U) is often referred to as the twenty-first amino acid, which is unique in its incorporation during protein synthesis. Unlike the canonical amino acids, Sec does not have its own designated codon; instead, it is encoded by the UGA codon, which is typically recognized as a stop codon in the genetic code[\[26\]\[27\]](#). This distinctive feature necessitates a complex mechanism for its incorporation into proteins, involving several specialized components.

The Role of SECIS Elements

The incorporation of selenocysteine is facilitated by a specific mRNA signaling sequence known as the selenocysteine insertion sequence (SECIS) element. This element reprograms the ribosome's interpretation of the UGA codon, allowing it to insert selenocysteine into the growing polypeptide chain instead of terminating translation[\[26\]](#). The presence of the SECIS element, along with the specific transfer RNA species (tRNA^{Sec}) that carries selenocysteine, is crucial for the proper decoding of UGA in selenoprotein transcripts[\[26\]\[27\]](#).

Mechanism of Incorporation

In bacteria, the incorporation of selenocysteine is characterized by the use of a tRNA molecule that initially carries serine, which is then transformed into selenocysteine through a series of biochemical steps. The seryl-tRNA synthetase (SerRS) first charges the tRNA with serine, resulting in the intermediate Ser-tRNA[Ser]Sec[\[7\]](#). The conversion of serine to selenocysteine involves the action of selenocysteine-specific

enzymes and occurs within the ribosome during translation. The unique structure of tRNA^{Sec}, with its long variable arm and specific cloverleaf conformation, is also critical for its function in this process[7].

In Archaea and Eukarya, the biosynthesis of selenocysteine involves an additional phosphorylation step. The initial serine is phosphorylated to form o-phosphoseryl-tRNA^{[Sep]Sec} before being converted to Sec-tRNA^{Sec} by the enzyme SepSecS[7]. This two-step process highlights the variations in selenocysteine incorporation mechanisms across different domains of life.

The Dynamics of UGA Codon Recognition

The UGA codon serves a dual role in the genetic code, encoding either a stop signal or selenocysteine, depending on the context provided by the SECIS element and the availability of tRNA^{Sec}[26][27]. This flexibility is crucial for the efficient synthesis of selenoproteins, which are essential for various biological functions. The efficiency of selenocysteine incorporation is influenced by multiple factors, including selenium availability and the concentration of uncharged tRNA^{Sec}[27]. As such, the dynamics of UGA codon recognition and the interactions among the translation factors are vital for determining the outcome of protein synthesis involving selenocysteine.

Selenoproteins

Selenoproteins are a distinct group of proteins that contain selenium in the form of selenocysteine, which is recognized as the 21st amino acid[24]. This unique incorporation of selenium allows these proteins to perform a variety of essential functions in biological systems, including antioxidant defense, modulation of inflammation, and regulation of redox homeostasis[13][28].

Types of Selenoproteins

There are several types of selenoproteins, each with specific roles in cellular processes. For instance, glutathione peroxidases (GPx) are well-known selenoproteins that play a crucial role in detoxifying harmful peroxides and protecting cells from oxidative damage[29][30]. Other significant selenoproteins include thioredoxin reductases, which are vital for maintaining cellular redox balance and regulating intracellular signaling pathways[31][28].

Roles of Selenoproteins in Inflammation

Selenoproteins are particularly important in the context of inflammation. They have been shown to modulate inflammatory responses and contribute to the regulation of immune function. This is accomplished through the neutralization of reactive oxygen species (ROS) and the promotion of antioxidant mechanisms, which help reduce oxidative stress associated with chronic inflammation[22][29][32][33]. By mitigating oxidative damage, selenoproteins can potentially lower the risk of developing inflammation-related diseases, including cardiovascular conditions and cancer[29][13][28].

Synthesis of Selenoproteins

The synthesis of selenoproteins involves a unique mechanism that incorporates selenocysteine into polypeptides during translation. This process requires specific sequences in mRNA known as SECIS (selenocysteine insertion sequence) elements, which facilitate the recruitment of specialized translation machinery[22][13]. The regulation of selenoprotein expression is influenced by selenium availability and is critical for maintaining optimal health and metabolic function[28][34].

Function of Selenoproteins in Various Diseases

Research has increasingly highlighted the role of selenoproteins in various diseases. Their ability to protect against oxidative stress and modulate inflammatory processes suggests that they could be targeted for therapeutic interventions in conditions such as cardiovascular disease, cancer, and neurodegenerative disorders[29][13][28][35]. Understanding the precise mechanisms through which selenoproteins exert their protective effects continues to be a significant focus of biomedical research, given their potential implications for human health and disease prevention[33][36].

Selenocysteine and Human Health

Selenocysteine, often referred to as the 21st amino acid, plays a crucial role in human health as it is a key component of selenoproteins, which are essential for various physiological functions. These proteins are integral to antioxidant defense mechanisms and maintaining redox homeostasis in the body[37][17]. Selenoproteins, which include enzymes such as glutathione peroxidases and thioredoxin reductases, are vital in mitigating oxidative stress and inflammation, thereby protecting cells and tissues from damage[19][38].

Role in Antioxidant Defense

Selenoproteins contribute significantly to the body's antioxidant defense system. They help to break down peroxides, which can lead to cellular damage if not adequately managed[17][39]. By participating in the detoxification of reactive oxygen species, selenoproteins support cellular health, thereby playing a preventive role against various diseases, including chronic inflammatory conditions and certain types of cancer[38][39].

Impact on Thyroid Function

Selenocysteine also plays an essential role in thyroid health. Selenoproteins are involved in the synthesis and metabolism of thyroid hormones, and adequate selenium status is critical for proper thyroid function[38]. Studies have indicated that selenium supplementation may benefit individuals with chronic autoimmune thyroiditis (Hashimoto's thyroiditis) by reducing thyroid antibody levels and improving overall thyroid function[39].

Selenium Deficiency and Supplementation Risks

Although selenium deficiency is rare in developed countries, it can occur in populations living in low-selenium regions. Deficiency can lead to serious health issues, including impaired immune function, thyroid dysfunction, and increased risk of certain diseases[\[17\]\[40\]](#). Conversely, excessive selenium intake can result in toxicity, leading to symptoms such as nausea, vomiting, and neurological disturbances[\[17\]\[40\]](#). Therefore, it is recommended that individuals consult healthcare providers before beginning selenium supplementation, especially since the tolerable upper intake level for selenium is set at 400 micrograms per day for adults[\[17\]\[41\]](#).

Dietary Sources of Selenocysteine

Selenocysteine is obtained through the consumption of selenium-rich foods. Major dietary sources include Brazil nuts, seafood, meat, poultry, and eggs, which are typically high in protein and consequently rich in selenocysteine[\[42\]\[39\]](#). The selenium content in plant-based foods can vary significantly depending on the selenium levels in the soil where they are grown, affecting the overall dietary intake of this important amino acid[\[42\]\[41\]](#).

Research and Applications

Overview of Selenocysteine

Selenocysteine, known as the 21st amino acid, is crucial for various biological functions and is synthesized in organisms through a unique mechanism involving the incorporation of selenium into proteins[\[36\]](#). It plays a pivotal role in the catalytic activity of several selenoproteins, which are essential for maintaining cellular redox balance and combating oxidative stress[\[43\]](#).

Health Implications

Research indicates that selenium, particularly in the form of selenocysteine, has significant health benefits. It exhibits antioxidant, anti-cancer, immunomodulatory, and hypoglycemic properties[\[36\]\[9\]](#). Selenocysteine-containing enzymes, such as methionine sulfoxide reductases, are vital for the reduction of oxidized proteins, thereby protecting cells from damage caused by reactive oxygen species (ROS)[\[43\]](#). Selenium deficiency can lead to numerous health issues, including increased susceptibility to viral infections, cardiovascular diseases, and various forms of cancer[\[36\]\[9\]](#).

Selenium Supplementation

Selenium supplementation has been shown to be beneficial in various populations, particularly those with low selenium status. However, the relationship between selenium intake and health outcomes is complex, exhibiting a U-shaped dose-response

curve[36]. Individuals with low baseline selenium levels may gain health benefits from supplementation, while those with adequate or high levels could experience adverse effects from excessive selenium intake. This highlights the necessity of personalized approaches to selenium supplementation[36].

Research Funding and Collaborations

The ongoing research into selenocysteine and its effects has been supported by various grants from institutions, including the National Nature Science Foundation and multiple provincial programs in China. Collaborations between universities and research institutes have enabled comprehensive studies on selenium's role in nutrition and health[36].

Ethical Considerations and Conflicts of Interest

Research in this area is conducted under strict ethical guidelines to ensure the integrity and safety of the studies. Authors in recent studies have declared no conflicts of interest, ensuring that the findings are objective and reliable[36][9].

Future Directions

Continued exploration of selenocysteine's mechanisms and its implications in human health is essential. Research efforts aim to clarify the optimal selenium levels for different populations and to investigate the potential therapeutic applications of selenoproteins in combating diseases related to oxidative stress and inflammation[36][9]. As our understanding of selenocysteine expands, it may lead to novel interventions for improving health outcomes across diverse demographics.

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