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Chapter 40

What do we know about selenium contributions to muscle physiology?

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Key Words

Intracellular calcium handling; Muscle; Muscular dystrophies; Oxidative stress; Selenium; Selenoprotein N.

Abstract

Early observations of selenium (Se) deficiencies in human and livestock revealed the importance of this trace element for normal muscle function. However, the molecular and cellular mechanisms impaired consecutive to low Se diet and its connection to the muscular diseases remain elusive. Importantly, mutations in the *SEPN1* gene encoding selenoprotein N (SEPN1) were shown to cause an inherited muscular disease in humans. Therefore, it is expected that understanding the role of SEPN1 and the related pathophysiology will unveil the participation of Se in molecular processes essential for muscle function and pave the way for targeted therapeutics. However, the functional characterization of SEPN1 is still lacking. Analysis of its activity in cellular and animal models pointed to its involvement in oxidative stress defense and in control of calcium (Ca^{2+}) handling. A link between the activities of SEPN1 and of the Ca^{2+} transporters RyR1 and SERCA was shown, but the enzymatic reaction catalyzed by SEPN1 has not been characterized.

40.1 Introduction

Se deficiency is a contributing factor to multiple pathophysiological conditions, including heart and neuromuscular disorders. Its importance for skeletal or cardiac muscular function was revealed by early observations establishing a link between low Se diet and different muscular disorders in farm animals and further reported in several human muscular syndromes. Se supplementation was beneficial against myopathies in livestock in many cases. However, in the human forms of muscular diseases, Se protective role remains more controversial. Altogether, this situation suggests a complex connection

between Se supplementation and other environmental or genetic factors in the development of muscle disorders. Molecular studies, including the identification of the selenoproteome, provide the basis for the understanding of the role of Se in muscular function and it is expected that a more specific mechanistic comprehension will provide the rationale for the design of therapies. Importantly, the identification of mutations in the gene coding for the selenoprotein, SEPN1, as the causative factor for different forms of central muscular diseases, provide the first direct evidence for the importance of Se in muscle function and maintenance. Understanding the molecular and physiological role of SEPN1 is a key step to decipher the link between Se and muscle function.

40.2 Se Sources and Forms in Muscles

Different forms of Se have been characterized in muscle mainly present as selenomethionine and selenocysteine (Sec) inserted into proteins. Other forms of organoselenium compounds have been identified, but their antioxidant activity is poorly characterized. Recently, it has been shown that red muscle of tuna contains large amounts of an organic Se compound that was identified as 2-selenyl-N,N,N-trimethyl-L-histidine, a Se analog of ergothioneine that was called selenoneine [1]. Selenoneine is believed to be a strong radical scavenger that binds to the heme group of hemoglobin and myoglobin and protect them from auto-oxidation under hypoxic conditions [2], but its physiological activity remains largely elusive. The Sec containing enzymes are known to constitute the principal biological active form of Se in muscle as in many organs. Animal studies show that different forms of supplemented Se (selenite, selenate, selenomethionine) can largely influence muscle Se concentration [3-7]. From these studies, it was concluded that for

muscle, organic Se sources are more efficient for Se absorption, and have different outcomes on Sec incorporation into selenoproteins. Selenoprotein gene expression was mapped in skeletal and cardiac muscles from different animals according to Se dietary concentration and forms [8,9]. A transcriptomic experiment was conducted to analyze regulated genes from liver and gastrocnemius muscle in mice fed either Se-deficient diet or diets supplemented with different organic or inorganic forms of Se. Nineteen differentially expressed genes were identified, among them 12 corresponding to selenoproteins [10].

Several studies demonstrated a hierarchy in the distribution of Se between different tissues, making certain tissues more susceptible to Se depletion [11]. Brandt-Kjelsen and collaborators [12] performed a pulse chase experiment in chicken using a ^{75}Se isotope tracer from labeled wheat to measure Se turnover in a whole organism. The uptake of ^{75}Se was assessed in all organs, showing the lowest activity in breast muscle. One week after the diet shift to nonradioactive Se, the excretion of the labeled tracer was followed and Se retention determined in individual organs. The shortest half-lives, four days, were observed in metabolic organs such as the liver, kidney and pancreas, whereas strong retention was measured in muscle (half-life 12 days), brain and lung (13 days) [12]. These results suggest a low metabolic Se turnover in muscle tissue. Dissection of the process at the molecular level provided a more complex interaction: in Se deprived rodent, muscle glutathione peroxidase Gpx1 activity ~~which?~~ decreased to 6% of Se-adequate level, while Gpx4 activity was not significantly decreased. Muscle was more affected by Se depletion in case of dietary Se deficiency compared to other less susceptible organs, such as testis or brain [9].

40.3 Muscular Dysfunction Associated with Se Deficiencies in Livestock

Nutritional muscular dystrophy (also called nutritional myopathy, rigid syndrome or white muscle disease) is an acute, degenerative disease of cardiac and skeletal muscles caused by a dietary deficiency of Se, sometimes combined with lack of vitamin E. Such disorders have been described in different animal species with different presentations. In lamb, when cardiac muscle is affected, animals display respiratory distress, cardiac arrhythmias and sudden death, as primary skeletal muscle affection leads to signs of muscle weakness, back stiffness, postural instability and disabled walking. Skeletal muscle degeneration is characterized by a pale discoloration of affected muscles and intramuscular edema. The white streaks seen in cardiac and skeletal muscle bundles correspond to bands of coagulation necrosis, fibrosis and calcification [13].

Se deficiency was classified as a prevalent determinant, as it was observed that animals raised in regions with low Se content in the soil, or born from mothers with low Se status during gestation, are the usual pre-conditions for the disease in lambs [14]. In addition Se supplementation appeared to be more efficient than vitamin E in preventing nutritional muscular dystrophies [15-17]. The Se deficiency was correlated with a reduced expression of a subset of selenoproteins in liver and muscles [18]. In pigs, a higher frequency of Mulberry heart disease, another muscle pathology related to vitamin E/Se deficiency was described in animals fed torula yeast diets containing low levels of Se. Mulberry heart disease has been experimentally reproduced in animals with diets deficient in vitamin E and Se [19,20]. The common manifestation is sporadic and sudden death of young rapidly growing pigs, often accelerated by exercise. This condition is characterized by deposition of fibrin strands in the myocardium, leading to necrosis and

hemorrhages. Supplementation with vitamin E and Se resulted in a reduced incidence of the lesions including decreased myocardial degeneration and skeletal muscle wasting [21].

Inadequate vitamin E level combined with sulfur amino acid deficiency also results in severe muscular dystrophy and exudative diathesis in young chicks [22]. This disease is characterized by degeneration of breast and leg muscle fibers, pancreatic atrophy, liver necrosis and severe edema of the subcutaneous tissues. Initial studies involving the effects of diet on muscular dystrophy showed that Se and vitamin E supplementation in the diet reduced the incidence of muscular dystrophy in chicks, [23]. In addition, exudative diathesis was replicated in broiler chicks fed a corn-soy diet produced in a Se-deficient area of China. In these conditions, several selenoprotein genes were down-regulated in muscle and liver tissues [8,24], inducing increased oxidative stress that consequently triggered the activation of p53-dependent and p38 MAPK/JNK/ERK signaling pathways [8,25].

From the analysis of these animal disorders, it is not clear yet whether the pathogenic mechanism results from a general increase in an oxidative stress linked to a general decreased expression of selenoproteins or in the dysfunction of a specific pathway, due to lower activity of a selective subset of selenoenzymes. Interestingly, it was reported that most of the affected animals present a high metabolism level and a rapid growth rate, suggesting a link between the Se-related activity and the energetic or metabolic status of the affected animals. Many studies conducted in animals arrived at a conclusion of a cooperative effect of Se and vitamin E supplementations to alleviate muscles disorders, suggesting the convergence to a common antioxidant process. In a recent study, Fujihara

and Orden [26] showed that in rats, higher vitamin E consumption resulted in a decreased Se concentration in various organs of the body, indicative of a compensatory interrelationship between the two compounds.

40.4 Muscular Dysfunction Associated with Selenium Deficiencies in Humans

Keshan disease is a cardiomyopathy characterized by multiple necrotic lesions, inflammatory areas and calcification throughout the myocardium [27,28]. This disorder has been described in individuals with low Se status in different areas of eastern China, due to low Se concentrations in the soil (for reviews see, [29-31]). Experimental approaches conducted in mice concluded a dual etiology for the disease: i) a lack in Se; and ii) an infection by an otherwise non-virulent strain of the enterovirus *Coxsackie*. Increased oxidative stress in the Se-deficient host induces mutations in the genome of the benign or mildly pathogenic viral strain, turning it into a cardiovirulent one [32].

Prolonged parenteral nutrition is another cause for severe Se deficiency linked to skeletal muscle disorders [33-35]. The myocardic morphological features reported in such conditions at autopsy are similar to those described in Keshan disease. Low plasma Se concentrations and lower erythrocyte Gpx activities were associated with muscle pain and weakness. Accordingly, affected patients responded positively to Se administration [36]. The benefits of Se administration were also tested in patients with myotonic dystrophies, since it was observed that their Se levels in blood decreased with the evolution of the disease [37]. However, no conclusive evidence of beneficial effects of Se treatment were obtained [38,39]. Similarly, no improvement on muscle function was reported for Se or vitamin E supplementation to patients with Duchene muscular

dystrophies [40-42]. From these analyses Se does not appear as a contributing factor for the two human muscular dystrophies, but one should mention that in all these studies, Se was provided as sodium selenite, a non-organic form, and increased Se concentration in the plasma was not addressed systematically. Several studies reported a significant lower serum Se level in elderly persons ~~was~~ associated with sarcopenia, a muscle disorder with symptoms such as poor muscle strength or low skeletal muscle mass [43-45]. However, no supplementation trials have been conducted to validate the importance of Se as a contributing or aggravating factor in this pathology.

In conclusion, other than Keshan disease and the deficiency during parenteral nutrition, Se did not constitute a contributing, nor an aggravating factor for muscular dystrophies, despite the previously reported link between Se concentration and the severity of the symptoms in most cases.

40.5 Selenoproteins and Congenital Muscle Disorders

Mutations in *SEPN1*, the gene coding for SEPNI, were initially associated with an inherited muscular disease in humans, which is the rigid spine form of congenital muscular dystrophy [46]. Subsequently, the same and additional SEPNI mutations were found in other pediatric muscular disorders, e.g., the classical form of multi-minicore disease [47], desmin-related myopathy with Mallory body-like inclusions [48], and the congenital myopathy with congenital fiber type disproportion [49]. These disorders share common symptoms characterized by an early onset phenotype including muscle weakness from infancy, predominantly affecting neck and trunk muscles and generalized muscle atrophy, leading to spine rigidity, severe scoliosis and potentially lethal

respiratory insufficiency [50,51]. Insulin resistance was also described in a few patients [49]. This clinical pattern, supported by muscle magnetic resonance imaging, is an essential basis for the diagnosis of SEPN1-related myopathies. In contrast, the spectrum of histopathological abnormalities associated with the disease is unusually large. It includes an increase in the endomysial extracellular matrix, changes in the number and size of type 1 fiber, and/or the presence of intracellular lesions such as areas of sarcomere disorganization termed minicores or protein aggregates. Hence, four neuromuscular disorders historically distinguished as independent clinical entities based on the histological defects described in muscle biopsies from patients are now recognized as one pathological entity, the SEPN1-related muscular dystrophy or SEPN1-RM. All *SEPN1* mutations identified to date are autosomal recessive (for a list see [52]), including nonsense or missense, consistent with a loss of SEPN1 function. In particular, several of the identified mutations affect the Sec insertion machinery, such as mutations affecting the UGA codon that codes Sec or the Sec Insertion Sequence (SECIS) element and selenocysteine redefinition element, *cis* sequences required for efficient Sec insertion and protein expression [53,54]. No clear-cut genotype-phenotype correlations have been established.

Some mutations in the gene coding for the Sec-specific translation cofactor SECISBP2 have also been associated with muscle weakness. Nonsense mutations were identified in three patients with multisystemic disease characterized by abnormal thyroid hormone metabolism, delayed bone maturation, delayed motor development, muscle weakness, scoliosis and mildly reduced lung vital capacity [55,56]. The radiological distribution of muscle involvement was similar to that in SEPN1-RM, and in two cases

reduced levels of SEPNI were detected in cultured fibroblasts from patients. However, reports of other mutations in the *SECISBP2* gene were reported in patients with growth retardation and thyroid defects, but lacking muscular symptoms ([57-59] and Chapter 44). Loss of function of *SECISBP2* affects the translation of several selenoproteins and it has been shown that *SECISBP2* can discriminate the different SECIS elements, resulting in the hierarchical binding to SECIS elements from different selenoprotein mRNAs and selective outcomes for different selenoproteins expression [60,61]. This observation implies that the nature of the amino acid mutated in *SECISBP2* might differentially affect the set of depleted selenoproteins, including or not SEPNI, in connection with the severity of the muscular symptoms.

40.6 SEPNI-Related Myopathy Pathophysiology: Translational Research and Therapeutic Implications

SEPNI-RM is the first inherited disease identified that is due to mutations in a selenoprotein gene. Thus, understanding the physiological role of SEPNI and the pathophysiology of SEPNI-RM emerged as a model paradigm to appreciate and therapeutically target other selenoproteins involved in human health and disease. Yet, the pathogenesis of SEPNI-RM remained undetermined for long time and no specific treatment was available for this potentially lethal disorder.

Studies of an ex vivo model of SEPNI deficiency provided the first indication that SEPNI plays an important role in cell defense against oxidative stress and redox homeostasis in human skeletal muscle cells [62]. Primary cultured myotubes from patients with *SEPNI* null mutations showed a significant increase in basal intracellular

oxidant activity and global oxidized protein content compared to controls, including excessive oxidation of the contractile proteins actin and myosin heavy chain II which potentially contributes to mechanical dysfunction. Accordingly, the amount of oxidized proteins was globally increased in fibroblasts from patients. Increased protein oxidation was also described in mice deleted of the *Sepn1* gene, an animal model for SEPNI-RM. Adult *Sepn1*^{-/-} mice display no phenotype under standard laboratory conditions, but only develop skeletal muscle alterations after inducing oxidative stress [63,64], e.g., when submitted to a forced swim test (FST). This test generates physical activity in a general stress context, with unusual stimulation of back and neck muscles to maintain the head above water. After 3 months of FST, mutant mice developed a strong kyphosis and were less mobile than their wild-type littermates. At the tissue levels, a switch toward smaller and slower fibers was observed in paravertebral muscles, and tubular aggregates were detected in muscle fibers from older mutant mice [63]. In addition, analysis of the *Sepn1* mouse knockout model showed that SEPNI deficiency leads to abnormal lung development, raising the possibility that the respiratory syndrome observed in patients with *SEPNI* mutations may have a primary pulmonary component in addition to the weakness of respiratory muscles [64].

On the other hand, SEPNI-deficient human myotubes showed increased resting cytosolic Ca²⁺ concentration, reduced sarcoplasmic reticulum Ca²⁺ load and caffeine-induced Ca²⁺ release, suggesting that in the absence of SEPNI, the reactive oxygen and nitrogen species generated by muscle cells regulate intracellular Ca²⁺ concentration via modulation of redox-sensitive Ca²⁺ channels (the ryanodine receptor RyR1 and/or the Ca²⁺ ATPase SERCA and/or the IP3 receptors), favoring Ca²⁺ release or leaking from the

endoplasmic reticulum [62]. Accordingly, in myofibers from *Sepn1*^{-/-} mice, the Ca²⁺ release channels RyR showed lower sensitivity to caffeine [64]. Furthermore, zebrafish studies support the role of SEPNI as a RyR modifier [65], and it has been recently confirmed that SEPNI contributes to maintaining the reduced state of SERCA [66]. In this later publication, the authors reported that SEPNI activity enhanced SERCA2 activity and protected SERCA2 luminal cysteines (Cys) against the hyper-oxidizing conditions elicited by the endoplasmic reticulum oxidoreductin 1, ERO1.

Finally, there is evidence to suggest that SEPNI is also involved in modulation of cell survival pathways. Patient-derived primary fibroblasts and muscle cells devoid of SEPNI show a higher susceptibility to H₂O₂ induced oxidative stress, manifested by a severely increased cell death rate [62]. In addition, adult skeletal muscles from the *Sepn1* knockout mouse showed a reduced pool of muscle progenitor cells (satellite cells), associated with defective muscle regeneration [67].

Altogether, the pathophysiological data mentioned above point to redox homeostasis as a primary pathogenic defect that could potentially be targeted to develop therapies for this so-far incurable infantile disease. Indeed, primary cultured cells from patients with *SEPNI* mutations have been used to evaluate the ex vivo effect of antioxidants drugs. Interestingly, pre-treatment with N-acetyl cysteine (NAC) rescued the cell phenotype, improving significantly myoblast survival upon H₂O₂ exposure and rendering the cell death rate of *SEPNI*-mutant fibroblasts identical to that of control, unchallenged cells. In addition, NAC normalized the levels of oxidized proteins in *SEPNI*-mutant myotubes [62]. Pre-treatment of the *SEPNI*-deficient cells with the flavonoid fisetin or the carotenoid astaxanthin prior to H₂O₂ exposure had a partial or null protective effect.

These findings demonstrate that NAC is an effective *ex vivo* treatment of SEPNI deficiency. Remarkably, they also establish that not all types of antioxidant drugs have the potential for therapeutic replacement of a particular selenoprotein function. The specificity of NAC consists in its Cys-donor activity, which could partially replace the hypothetical thiol exchanger activity of Sec in SEPNI. However, this molecule also has other numerous biological roles [68]. NAC is one of the rare antioxidant drugs approved for human use, has been shown to inhibit muscle fatigue in healthy adults and has no serious side effects when administered at the established dosage. This, together with its *ex vivo* efficiency on *SEPNI*-defective cells and recent data showing an *in vivo* effectiveness in the *Sepn1* KO mouse model [69], paves the way to a first therapeutic trial of SEPNI-RM in human patients, which is currently under preparation.

In summary, our current knowledge shows SEPNI as a key protein at the crossroads of cell stress, redox signaling, Ca^{2+} homeostasis and cell survival pathways. More importantly, it identifies SEPNI-RM as one of the rare monogenic human condition primarily due to antioxidant defense failure, and the only structural myopathy primarily due to oxidative stress and antioxidant protection failure. As such, it represents an useful model paradigm for more complex, multifactorial disorders (such as cancer, cardiovascular disorders, diabetes or aging) in which selenoproteins have been implicated. Therefore, finding a specific pharmacological treatment for this rare disease could also open interesting perspectives to human health at large.

40.7 Selenoprotein N Expression, Phylogeny and Predicted Functions

The *SEPNI* gene is located on chromosome 1p35-36 and is composed of 13 exons, the UGA selenocystein codon resides within exon 10. This gene codes for two alternative transcripts and the shorter isoform, in which exon 3 is spliced-out, is predominantly expressed. This third exon consists of an Alu sequence that contains an additional in frame UGA codon, and accordingly is found only in primates. It was reported that only the shorter isoform is translated into protein. Therefore, it was assumed that the UGA codon located within exon 3 of the larger isoform is not reprogrammed by the SECIS element into a Sec codon, but rather recognized as a premature stop codon [70]. Inclusion of the Alu-derived exon may be important for regulating *SEPNI* activity in muscle, since qPCR analysis revealed a tissue-specific increase in its inclusion level between humans and chimpanzees [71]. In agreement with the non-coding nature of the longer transcript, the *SEPNI* transcript was not found on the list of the protein-coding Alu exons established on the basis of high-throughput proteomic and ribosome profiling data [72].

The major transcript of *SEPNI* codes for a 556 amino acids protein with a predicted mass of 62 kDa, but migrating at a higher apparent molecular weight due to protein modifications. Glycosylation of the protein was experimentally validated using deglycosylation assays [70]. SEPNI is an endoplasmic reticulum (ER) resident protein. The ER targeting sequence located between residues 30-49 consists of a di-arginine motif and a stretch of hydrophobic amino acids located at the N-terminus of the protein [70]. Protease protection experiments allowed the characterization of SEPNI topology: it contains a single transmembrane domain located at the N-terminus, and SEPNI corresponds to a type II transmembrane protein with a single membrane-spanning domain

at the N-terminus and most of the protein, including the predicted active site, being localized within the lumen of the ER (unpublished data). This topology is in agreement with the amino acid charge distribution flanking the hydrophobic membrane signal, the so-called “positive inside rule”.

In several instances, prediction of selenoproteins redox activity has been derived from protein sequence analysis and alignment. Bioinformatics searches using SEPN1 protein sequence revealed no significant homology to any other known protein. In SEPN1, aside from the N-terminal transmembrane domain, motif prediction searches identified a typical EF-hand motif, corresponding to a Ca^{2+} binding domain. Selenoprotein activity may also be deduced from the sequence context of the Sec residue, which constitutes a landmark of the catalytic center. SEPN1 harbors a SCUG predicted catalytic site, reminiscent of the thioredoxin reductase GCUG motif. This similarity suggests a reductase activity. However, the classical animal thioredoxin reductases contain two additional important domains: the FAD and the NADPH binding domains. These two domains, essential for reduction of the N-terminal thiol active site and electron transfer to the C-terminal selenenylsulfide bond [73], are absent in SEPN1. Lack of this second redox active center might be compensated by interactions with partners that remain to be identified. In addition, the highly accessible selenolate active site at the C-terminus of thioredoxin reductase is supposed to confer a broad substrate specificity to these enzymes, from small molecules such as selenite, lipid hydroperoxides, and dehydroascorbate, to proteins such as thioredoxin, protein disulfide isomerases or glutathione peroxidases. In contrast, the localization of the active site in the central part of SEPN1, therefore possibly less accessible, might reflect a higher selectivity of SEPN1

for its substrate(s). Moreover, SEPN1 and the thioredoxin reductases are located within different cellular compartments, the endoplasmic reticulum and cytoplasm, respectively, whose display are significantly different Redox potentials [74]. The endoplasmic reticulum contains the most oxidative systems to introduce disulfide bounds into secreted proteins [74]. The Redox level of the compartment directs the oxidative status of the enzyme reactive center, and therefore the nature of the catalytic reaction, oxidation versus reduction. In addition, the SCUG catalytic motif of thioredoxin reductase was shown to be involved in two consecutive reactions; on one hand the reduction of thioredoxin, and on the other hand, the oxidation of a N-terminal two Cys redox motif (Cys59-Cys64 of thioredoxin reductase), which can accept electrons from the protein-bound FAD [73]. Whether SEPN1 is also involved in a similar electron transfer or catalyzing one reaction and being regenerated by one cellular Redox system, is currently not known. Interestingly, two publications reported that the SEPN1 C-terminal domain between positions 389-566, which contains the Sec residue, shares similarity with the UAS domain, a structural motif of the thioredoxin-like superfamily [75,76]. This domain is present in proteins such as the FAS-associated factor 1 (FAF1) or the UBX domain-containing proteins, UBDX7 and UBDX8. In FAF1 and UBDX8, the UAS domain was shown to bind long-chain unsaturated fatty acids and to mediate polymerization of the proteins [77]. Moreover, the thioredoxin-like fold of SEPN1 was modeled based on its homology with other oxidoreductases and it revealed that the SCUG redox motif is correctly positioned for catalysis [75, 76].

Orthologs of SEPN1 were identified in many animal species, both vertebrate and invertebrate, including sponges, annelids, echinoderms or some arthropods. However,

based on the available sequenced genomes, no SEPNI coding gene was detected in the protists, the nematodes, nor the crustacean and hexapode lineages. Protein sequence comparison revealed strong conservation among animal species, notably two blocks of amino acids, the second one flanking the Sec residue is likely to form the active catalytic pocket [52,78].

The *SEPNI* gene had already evolved in ancestral metazoans, which are organisms lacking organized muscle structures. This phenomenon suggested that SEPNI possesses an original function unrelated to muscle differentiation and maintenance. Moreover, analysis of *SEPNI* expression pattern in human or mouse tissues demonstrated that SEPNI expression is not specific to the muscle tissues, but present ubiquitously in all tissues examined [79]. Together, the expression pattern and phylogenic distribution of SEPNI suggested that this selenoprotein may have additional functions that remain to be characterized. Another interesting feature revealed by the sequence comparison of SEPNI homologs from different animal species, is that there exists no SEPNI with a Cys instead of the Sec residue. Most selenoproteins present Cys orthologs or paralogs, and Sec forms a selenenylsulfide bond resulting in a redox motif equivalent to the Cys containing ones in non-selenoproteins oxidoreductases [80]. Hence, this observation suggests that presence of the Sec residue is strictly required for SEPNI catalytic activity, a situation that may be important to address the unique role of this unique amino acid in selenoenzymes, once this activity is characterized.

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