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Selenoprotein I (selenoi) as a critical enzyme in the central nervous system

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Abstract

Selenoprotein I (selenoi) is a unique selenocysteine (Sec)-containing protein widely expressed throughout the body. Selenoi belongs to two different protein families: the selenoproteins that are characterized by a redox reactive Sec residue and the lipid phosphotransferases that contain the highly conserved cytidine diphosphate (CDP)-alcohol phosphotransferase motif. Selenoi catalyzes the third reaction of the CDP-ethanolamine branch of the Kennedy pathway within the endoplasmic reticulum membrane. This is not a redox reaction and does not directly involve the Sec residue, making selenoi quite distinct among selenoproteins. Selenoi is also unique among lipid phosphotransferases as the only family member containing a Sec residue near its C-terminus that serves an unknown function. The reaction catalyzed by selenoi involves the transfer of the ethanolamine phosphate group from CDP-ethanolamine to one of two lipid donors, 1,2-diacylglycerol (DAG) or 1-alkyl-2-acylglycerol (AAG), to produce PE or plasmanyl PE, respectively. Plasmanyl PE is subsequently converted to plasmenyl PE by plasmanylethanolamine desaturase. Both PE and plasmenyl PE are critical phospholipids in the central nervous system (CNS), as demonstrated through clinical studies involving SELENOI mutations as well as studies in cell lines and mice. Deletion of SELENOI in mice is embryonic lethal, while loss-of-function mutations in the human SELENOI gene have been found in rare cases leading to a form of hereditary spastic paraplegia (HSP). HSP is an upper motor disease characterized by spasticity of the lower limbs, which is often manifested with other symptoms such as impaired vision/hearing, ataxia, cognitive/intellectual impairment, and seizures. This article will summarize the current understanding of selenoi as a metabolic enzyme and discuss its role in the CNS physiology and pathophysiology.

Keywords

Phosphatidylethanolamine; Plasmalogen; Phospholipid; Hereditary spastic paraplegia; Brain

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1. Introduction

Selenium (Se) is an essential micronutrient that plays a particularly important role in the development and function of the central nervous system (CNS). The biological effects of dietary Se are mediated primarily through selenoproteins, a family of proteins that all contain the amino acid, selenocysteine (Sec). Dietary Se is metabolized within cells to Sec via a specialized Sec-tRNA utilized for co-translational incorporation of Sec into nascent polypeptides on the ribosome, which requires unique structures in the selenoprotein mRNAs that recruit dedicated protein factors functioning to facilitate this process [1]. Most members of the selenoprotein family are oxidoreductases involved in redox signaling, protection from oxidant induced damage, endocrine homeostasis, and other cellular and physiological roles [2]. The human genome encodes 25 distinct selenoproteins, 24 of which are Sec-containing proteins in rodents [3]. Most selenoproteins are expressed in all major brain regions, with neurons exhibiting particularly high levels [4]. Mouse studies have shown that multiple selenoproteins are indispensable for neurodevelopment and protection from neuronal damage [5]. Gene disruption studies in mice for all selenoproteins or individual members of this family revealed a particularly important role in GABAergic parvalbumin-expressing interneurons (PVIs) [6–8], a neuronal cell type that synchronizes activity of excitatory neurons and displays elevated metabolic demands. One model that was particularly important for defining a role for Se and selenoprotein expression in the brain was the Selenoprotein P (selenop) knockout mice [9,10]. The neurological phenotype of these mice depended on dietary Se levels and included a variety of symptoms such as epileptic seizures, movement phenotype with ataxia and/or dystonia, overt neurodegeneration with premature death, or death before weaning. Other loss-of-function models have established important roles for different selenoproteins in the brain including glutathione peroxidase 4 (gpx4), thioredoxin reductase 1 (txnrd1), and Selenoprotein T (selenot) [6,11,12].

Selenoprotein I (selenoi; ept1) is a selenoprotein family member that is quite different from other members in terms of its poorly characterized clinical reports, murine models of SELENOI deficiency are shedding some light on impacts of gene mutations and recent progress has been made in better understanding its functional roles in different cell-types and tissues. This review will summarize what is known to date about the importance of selenoi expression in CNS tissues, discussing important concepts regarding how selenoi contributes to neurological development and human health and how further basic research investigations may move the field forward.

2. Selenoi and ethanolamine phospholipid synthesis

The majority of selenoproteins serve as oxidoreductases and contain a catalytic domain with either a Cys-X-X-Sec or Cys-X-Sec motif (where X represents any amino acid) present in a prototypical thioredoxin-like domain [13,14]. Selenoi does not contain this motif nor is there evidence that it functions as an oxidoreductase enzyme. Based on structural data of related phospholipid transferases and amino acid sequence similarities [15,16], the catalytic domain of selenoi has been predicted to reside within the ER/Golgi membrane (Fig. 1). All members of the phosphotransferase family to which selenoi belongs contain the highly conserved catalytic CDP-alcohol phosphotransferase motif, $DG(X_2)AR\ (X_8)G(X_3)D(X_3)D$ [17]. The

corresponding amino acid sequence in selenoi comprising the catalytic domain is located from amino acid residues 107–129 (^{107}DGKQARRTNSSTPLGELFDHGLD^{129}). However, selenoi is the lone phosphotransferase family member that is also part of structure/function and the precise role for the defining Sec residue present in its C-terminal portion. Data have recently emerged to provide important insights into selenoi's biological roles, particularly in the CNS. Selenoi expression has been shown to play an important role in motor neuron function and protective myelination of the CNS, which have been studied mainly in patients with rare biallelic SELENOI mutations that cause a devastating disease pathology. Along with these the selenoprotein family. Moreover, selenoi is the only selenoprotein that catalyzes an enzymatic reaction within a cellular membrane through a process that does not directly involve the Sec residue, which is located near the C-terminus of this unique protein in both mouse and human paralogs. The importance of the Sec residue is highlighted by the inclusion of this unique amino acid across many species as demonstrated by SelenoDB 2.0 [18]. Precisely what role the Sec residue plays in the bioactivity of selenoi is not known. That said, it has been firmly established that selenoi is a bonafide ethanolamine phosphotransferase involved in the synthesis of two different ethanolamine phospholipids that include phosphatidylethanolmine (PE) and plasmenyl PE [19,20]. As shown in Fig. 1, the first committed reaction of this three-step pathway involves the conversion of ethanolamine to phosphoethanolamine by ethanolamine kinase (ETNK). This is followed by the rate-limiting step in this pathway catalyzed by ethanolaminephosphate cytidylyltransferase (ECT) and generates cytidine diphosphate (CDP)-ethanolamine that can be used by selenoi. Selenoi transfers the ethanolamine phospho group from CDP-ethanolamine to one of two lipid donors, 1,2-diacylglycerol (DAG) or 1-alkyl-2-acylglycerol (AAG), to produce PE or plasmanyl PE, respectively [21,22]. This step is catalyzed by selenoi in the membrane of the ER/Golgi continuum [23]. Plasmanyl PE can then be converted to plasmenyl PE, also known as plasmalogen, via desaturation of the 1-alkyl group to a 1-alkenyl group by the enzyme plasmanylethanolamine desaturase [24]. The gene encoding plasmanylethanolamine desaturase was recently identified as *TMEM189* [25,26]. The particular species of PE or plasmenyl PE generated through these pathways depends on the length and degree of saturation in the lipid chains of the DAG or AAG substrates.

Plasma membrane phospholipids are distributed asymmetrically between the outer and inner leaflets of viable mammalian cells. The outer leaflet of the plasma membrane is composed primarily of sphingomyelin and phosphatidylcholine (PC), whereas phosphatidylserine (PS), PE, and phosphatidylinositol (PI) are localized to the inner leaflet through enzymatic action, with cholesterol distributed equally [27,28]. Thus, PE is a major component in mammalian cellular membranes in that it comprises ~15–25% of cellular phospholipids in mammalian cells [29]. Membrane lipid composition defines membrane structure/function and is important for many cell-types, including those of the CNS. PE plays a major role in membrane architecture by regulating features such as membrane curvature and rigidity/fluidity [30–32]. PE is also a precursor of biologically active molecules and influences the activity of membranes. For example, PE serves as a precursor for the synthesis of glycosylphosphatidylinositol (GPI) anchors that tether many crucial proteins to the plasma membrane surface [33,34]. Plasmenyl PE, also referred to as plasmalogen, differs from PE by the presence of a vinyl ether bond in the sn-1 position of the glycerol backbone. While

plasmenyl PE is less abundant compared to PE, this class of ethanolamine phospholipids is important for cell membrane integrity and ubiquitously found within lipid rafts [35]. Plasmenyl PE species are particularly enriched in the CNS, playing a critical role in a variety of biological functions including prevention of neuroinflammation, improvement of cognitive function, and inhibition of neuronal cell death [36]. Plasmenyl PE constitutes 30% of the total phospholipids and 90% of the ethanolamine glycerophospholipids in human neuronal cell membranes [22,37].

While PE and plasmenyl PE species serve important structural functions in cellular membranes, studies in T cells have shown that effective synthesis of these phospholipids by selenoi also contribute to a balanced cellular metabolic state. During an immune response, T cell activation relies on major shifts in metabolism. There is a growing appreciation that these metabolic changes underlie the capacity of T cells to perform particular functions [38,39]. Moreover, the data from activated T cells may provide important insight into the influence of ethanolamine phospholipid synthesis pathways on the highly metabolic neurons. Selenoi deficiency lowered but did not completely diminish de novo synthesis of PE and plasmenyl PE during T cell activation [40]. In fact, membrane organization and biophysical structure may not be significantly altered in SELENOI knockout T cells [16], while the metabolic reprogramming required for optimal T cell activation and proliferation is highly dependent on selenoi expression. A recent study found that cells may compensate for SELENOI knockout by utilizing a different member of the phospholipid transferase family, choline/ethanolamine phospholipid transferase 1 (cept1) [23]. In this sense cept1 is more versatile that selenoi (EPT1) in that CEPT1 can synthesize phosphatidylcholine (PC), plasmenyl PC, PE, and likely for plasmenyl PE [41,42]. However, it is important to note that cept1 is not a selenoprotein and is much less efficient at ethanolamine phospholipid synthesis compared to selenoi. The amino acid sequence alignment of SELENOI and CEPT demonstrates a high degree of homology in the catalytic domains, but not in the C-terminal region predicted to reside in the cytosol that also is the Sec-containing domain in SELENOI (Fig. 2). This suggests that the Sec residue of selenoi may confer some degree of substrate selectivity by interacting with CDP-ethanolamine and not CDP-choline or other substrates, although there is no experimental data that defines the role of the Sec residue in selenoi. While both selenoi and cept1 are widely expressed throughout most tissues, it remains unclear whether the cellular distribution of selenoi and cept1 overlap or whether these enzymes actually compete for the same substrate pool.

3. Tissue distribution of SELENOI

In 2007, identification of SELENOI (a.k.a. EPT1) cDNA from a human EST database was reported and the cDNA was cloned and characterized [19]. This research group used RT-PCR to screen a human tissue cDNA collection and found that the gene was expressed in all tissues. The expression of hEPT1 was particularly abundant in brain, placenta, liver, and pancreas, followed by heart, skeletal muscle, lung, and kidney. Northern blot analysis of human brain revealed that the hEPT1 gene was strongly expressed in cerebellum, followed by the occipital pole and the frontal lobe. Subsequent to this study, multiple single cell-RNA-sequence and tissue atlas databases have been established. Altogether, SELENOI is found in most tissues with low tissue specificity and levels of SELENOI in the brain are

widely abundant with low regional specificity [43–45]. This wide distribution of SELENOI throughout all tissues is found at the level of both mRNA and protein, which corresponds to the ubiquitous distribution of PE and plasmenyl PE throughout the body. It should be noted, however, that the precise roles of selenoi in ethanolamine phospholipid synthesis and cellular metabolism may be tissue- or cell-specific. For example, proliferation and differentiation of T cells are regulated by selenoi [46], and ethanolamine phospholipid synthesis through mechanisms that likely differ from terminally differentiated cells in the CNS. Much more research is needed to compare biological role of selenoi between different tissues or cell-types.

4. Murine embryonic development and selenoi

Mouse models have been extensively used to understand how selenoproteins are involved in brain development and function. Whole animal knockout studies have revealed embryonic lethality for 5 of the 24 selenoproteins found in mice: gpx4, txnrd1, txnrd2, selenot, and selenoi [47–52]. Knockouts of all selenoproteins in certain cell-types of the brain as well as the deletion of individual selenoproteins using conditional knockout models have demonstrated profound effects on CNS architecture and behavior [6,53–56]. How results from these mouse models parallel the roles for selenoproteins in human CNS tissues is not entirely known. Limited data in humans with defects in selenoprotein synthesis suggest that multiple tissues are affected, including the CNS, although often the most profound effects described are those that impair thyroid hormone regulation and growth [57,58]. Comparisons between human and mice in terms of the tolerance to loss of selenoprotein expression have revealed some interesting results. In particular, there is a general correspondence in tolerance/intolerance for some selenoprotein deficiences, but there are also some differences between humans and mice [59]. It will be important to continue to compare CNS data from mouse models involving selenoprotein loss-of-function to clinical data available so that similarities or differences between these species can be better ascertained.

Our recent study showed that homozygous deletion of SELENOI in mice led to early embryonic lethality prior to uterine implantation (~E6), with a rare detection of knockout embryos at the E18.5 stage [47]. The detection of perinatal homozygous SELENOI knockout of E18.5 embryos (~1.2% frequency) suggests that, in some cases, murine embryonic development in the absence of selenoi expression may proceed to the perinatal stage development. Bioinformatic approaches used to estimate the impact of individual selenoproteins on human health showed that loss of functional selenoi was strongly selected against, suggesting it may represent one of the most important selenoproteins for human health [59]. These findings combined with the SELENOI knockout mouse data suggest that SELENOI homozygous deletion in humans likely causes embryonic lethality with rare cases in which patients may be born with critical developmental symptoms that require severe therapeutic intervention for survival. This scenario is supported by the limited number of case studies in human selenoi-deficient patients, as is discussed further in the following sections.

5. Ethanolamine phospholipid synthesis and neurological disorders

Hereditary spastic paraplegia (HSP) refers to a group of hereditary, degenerative, neurological disorders that primarily affect the upper motor neurons. A slow degeneration of upper motor neurons leads to a defect in delivery of neuronal messages to the muscles, and this impairment in the modulation of muscular movement that leads to difficulty in walking is the cardinal clinical feature of the HSPs [60]. This disorder is classified as complicated or complex if it involves other neurological or non-neurological features such as impaired vision, ataxia, epilepsy, cognitive/intellectual impairment, peripheral neuropathy, and/or deafness [61]. If only the lower body is affected, HSP is classified as uncomplicated or pure. HSP is considered a rare disease with a prevalence of 0.1–9.6 instances in every 100,000 worldwide [62]. HSP may occur in patients through different inheritance patterns, including autosomal dominant, autosomal recessive, X-linked recessive, and mitochondrial [63,64].

Mutations in a wide variety of genes encoding proteins with diverse functional roles have been implicated in the pathology of HSP, contributing to the heterogeneity of clinical manifestations of this group of diseases [65,66]. In fact, there are more than 80 different genetic types of HSP that share common symptoms as described above. Among the genes found to be linked to HSP are those involved in both branches of the Kennedy pathways that generate CDP-ethanolamine and CDP-choline. Efficient production of PE and PC along with the related plasmalogens, plasmenyl PE and plasmenyl PC, depend on these branches of the Kennedy pathways. Since PE and PC are the most abundant phospholipids in mammalian membranes [67], it may not be surprising that different gene mutations in these two Kennedy pathways can give rise to different diseases ranging from muscular dystrophy to spastic paraplegia to a childhood blinding disorder to bone deformations [68]. One example of the involvement of the CDP-choline pathway in HSP is a recent clinical report describing 6 individuals from 5 families with homozygous and compound-heterozygous pathogenic variants in choline kinase alpha, which catalyzes the first step in the synthesis of CDP-choline used for generating PC and plasmenyl PC [69]. These patients presented with a severe neurodevelopmental disorder characterized by developmental delay/intellectual disability, epilepsy and microcephaly.

Regarding the CDP-ethanolamine pathway, genetic abnormalities in either the *PCYT2* and SELENOI genes may result in autosomal recessive HSP with a broad ataxia-spasticity spectrum. Altogether, there have been 14 reported cases of biallelic variants of *PCYT2* (n = 8) or *SELENOI* (n = 6) that have overlapping clinical features, although the diseases are not manifested in precisely the same manner in all cases. The SELENOI mutations present with clinical manifestation of delayed motor neuron development and spasticity, and neurological disabilities including speech delay and reduced intellect, microcephaly, seizures, and ocular abnormalities [60]. The following section summarizes the clinical reports of patients with loss-of-function mutations in the SELENOI gene and are presented in order of publication.

6. Cases 1–4

Four siblings from a single consanguineous Omani family aged between 19 months and 15 years presented in infancy/early childhood with delayed gross motor development, progressive spastic paraperesis and gradual decline in motor function [70]. All 4 patients demonstrated a mild intellectual impairment and delayed language acquisition. The oldest patient showed evidence of demyelinating peripheral neuropathy, but upper motor neuron signs predominated over any clinical manifestations of this feature. Visual dysfunction and seizures were manifested to varying extents in the 4 patients, who were diagnosed with HSP that included additional clinical features that suggested a broader phenotype. All 4 patients were found to be homozygous for a Arg112Pro mutation in the SELENOI gene, while three siblings that were heterozygous for this mutation did not present with any symptoms. This mutation is within the catalytic domain of selenoi located between amino acid residues 107–129 (^{107}DGKQAR**^{112}R**TNSSTPL-GELFDHGLD^{129}). A yeast enzyme assay utilizing radiolabeled PE synthesis demonstrated that the Arg112Pro mutation exhibited 3% bioactivity compared to wild-type selenoi. Interestingly, no effect was found of the SELENOI mutation on total PE levels in blood as measured by lipidomic analyses.

7. Case 5

A male born to an Israeli Arab couple who are first cousins presented with hypertonia alternating with hypotonia, followed by tonic-clonic seizures that responded to treatment with phenobarbital [71]. MRI revealed progressive white matter abnormalities, and at 3 weeks of age there were signs of hypomyelination but not of atrophy. A year later, a continued delayed myelination pattern was observed along with diffuse atrophy that included the cerebellum. By the age of 4, the patient exhibited recurring clinical seizures, progressive microcephaly, and both visual and sensorineural hearing impairments. There was white matter diminution with hypoplasia of the optic nerves, extremely thin corpus callosum, and continued cerebellar and midbrain atrophy. PE synthesis assays in lysates from patient fibroblasts revealed bioacitivity ~1/3 compared to wild-types, possibly due to cept1 activity. Culturing of skin fibroblasts from the patient and phospholipid profiling revealed a strong decrease in plasmenyl PE synthesis. Sequencing revealed a SELENOI gene c.732–2A > G mutation that produces a mRNA splice variant with skipped exons 6 and 8 leading to a predicted loss of 290 bp associated with a frameshift. Using a radiolabeled lipid assay, this was found to decrease selenoi enzyme activity by ~67%. Interestingly, lipidomic analyses revealed that the total amount of PE was not notably changed in either the patient's fibroblasts or EPT1-knockout HeLa cells generated for this study. This is consistent with data from SELENOI knockout mouse T cells showing a larger decrease on plasmenyl PE levels compared to PE levels [40].

8. Case 6

A 5-year-old male of Balochi ethnicity from Iran who had been born with a below average birth weight and occipitofrontal circumference (15th percentile) presented with profound growth failure and psychomotor retardation [72]. The patient had impaired vision and failed to develop speech and non-verbal communication skills, and experienced regular

seizures that were treated with phenobarbital. MRI showed several cerebral abnormalities and hypomyelination. The parents were each identified as having SELENOI mutations in one copy of the SELENOI gene (Pro45Leu), and the patient was confirmed as homozygous for this Pro45Leu mutation. Assays using a yeast strain expressing the Pro45Leu mutation showed an increase in radiolabel associated with the selenoi substrate, CDP-ethanolamine, compared with wild-type. The yeast assays also showed a decrease in radiolabel associated with the selenoi product, PE.

For these patients, the phenotypes may be different due to the spectrum of symptoms manifested in HSP, but also because genetic homozygosity may extend further than just the SELENOI gene. In addition to the HSP cases noted above, deficiencies in plasmenyl PE have been reported in neurodegenerative disorders [22], most prominently in Alzheimer's disease [73,74]. Plasmenyl PE is the predominant ethanolamine phospholipid in brain, with highest levels in white matter [75, 76]. Evidence also suggests that plasmenyl PE prevents lipid peroxidation [77], as the vinyl ether bond present in the sn-1 position is preferentially oxidized by reactive oxygen species [78], thereby sparing oxidation of polyunsaturated fatty acids. This oxidative product is subsequently decomposed into chemical species unable to further propagate lipid peroxidation [79]. Interestingly, recent *in vitro* studies in HEK293 cells showed that de novo biosynthesis of plasmenyl PE is critically dependent upon selenoi [23]. This is consistent with findings in selenoi deficient T cells showing a much greater decrease on plasmenyl PE production compared to PE production [40].

9. Conclusions

Selenoi is a unique enzyme that belongs to two different protein families, the phospholipid transferases and the selenoproteins. Clinical studies and basic science research have uncovered important physiological roles of selenoi ranging from embryogenesis to T cell immunity to upper motor neuron functions (Table 1). Selenoi and its participation in the Kennedy pathways leading to ethanolamine phospholipid synthesis are critical for neurological development and CNS homeostasis. Clinically, loss-of-function mutations in the SELENOI gene are rare (Fig. 3), leading to severe disease diagnosed as HSP. HSP is among the most genetically heterogeneous of inherited disorders, providing challenges for developing therapeutics. Murine models involving neuronal knockout of SELENOI may provide the opportunity to better understand how synthesis of PE and plasmenyl PE may be disrupted. These models would also allow investigation into metabolic perturbations that may occur in neurons with a selenoi loss-of-function, as has been observed in the metabolically active SELENOI knockout T cell mouse model. New experimental models are being developed for selenoi based studies, which will provide a more comprehensive picture regarding the role that this unique enzyme plays in cellular metabolism, physiological systems, and ultimately in human health. It remains to be determined if new therapies are possible for the individuals suffering from HSP due to a lack of functional selenoi, but fully characterizing this enzyme and its biological roles through animal and cell models may be a step in the right direction.

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Abbreviations

AAG 1	akyl-2-acylglycerol
DAG 1	2-diacylglycerol
CNS	central nervous system
cept1	choline/ethanolamine phospholipid transferase 1
CDP	cytidine diphosphate
ept1	ethanolamine phosphotransferase
gpx4	glutathione peroxidase 4
GPI	glycosylphosphatidylinositol
HSP	hereditary spastic paraplegia
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PI	phosphatidylinositol
PS	phosphatidylserine
Se	Selenium
Sec	selenocysteine
Selenoi	Selenoprotein I
Selenop	Selenoprotein P
Selenot	Selenoprotein T
txnrd1	thioredoxin reductase 1
txnrd2	thioredoxin reductase 2

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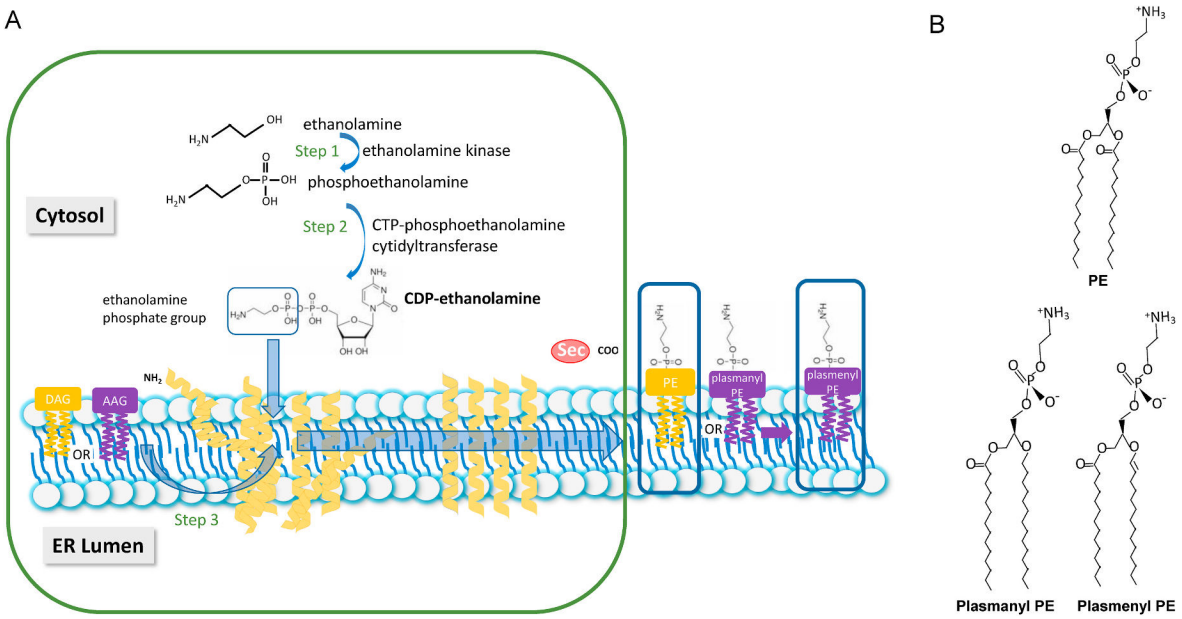

Fig. 1.

Selenoi is involved in synthesis pathways for both PE and plasmenyl PE. **A)** The ethanolamine branch of the Kennedy pathway is outlined in green and final phospholipid products are outlined in blue. Selenoi catalyzes the third step of this branch of the Kennedy pathway that transfers the ethanolamine phosphate group from CDP-ethanolamine to either DAG or AAG. The former generates PE and the latter generates plasmanyl PE that is converted to plasmenyl PE by plasmanylethanolamine desaturase. PE and plasmenyl PE are important phospholipids for CNS development and function. In the absence of selenoi, cept1 enzyme may compensate to some extent for maintaining phospholipid products of this branch of the Kennedy pathway. Phyre Alarm program was used to predict the structure of selenoi, with catalytic amino acid residues shown in red. Alternate structural features may be obtained with other prediction programs such as AlphaFold2. **B)** Structures of PE, plasmanyl PE, and plasmenyl PE are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

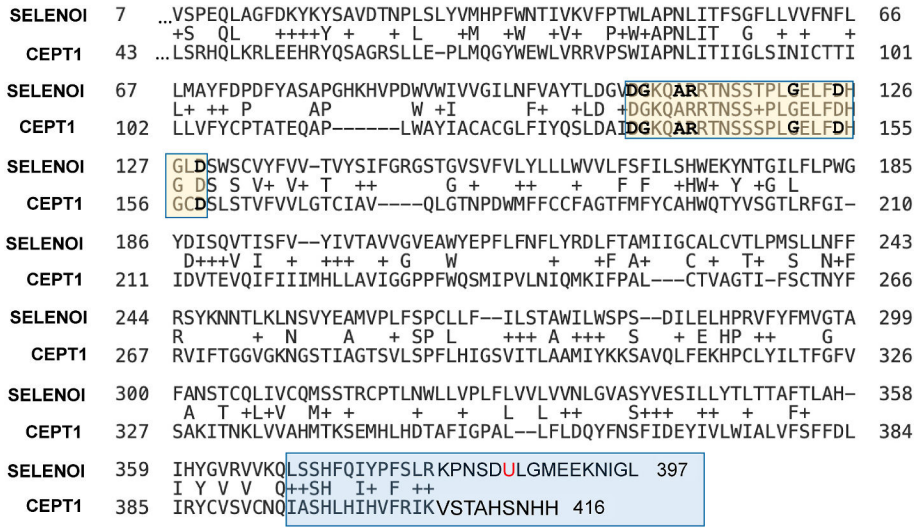

Fig. 2.

A) Amino acid sequence alignment for human selenoi and cept1. As members of the phosphotransferase family, Selenoi (NCBI NP_277040.1) and cept1 (NCBI NP_006081.1) exhibit low overall amino acid identity (102/383 = 27%). The catalytic domains (highlighted in orange with key amino acid residues bolded) are highly conserved while the C-terminal tail regions exhibit little similarity. Identical and similar amino acids are shown in the center sequence by the amino acid or + symbol, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

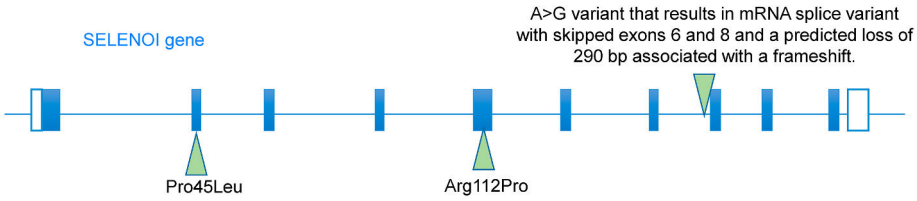

Fig. 3.

Human SELENOI gene structure located on chromosome 2 showing locations and effects of the three homozygous mutations found in clinical cases.

Table 1

Evidence for functional roles of selenoprotein I.

Biological Role	Findings from Study	Reference (s)
Embryonic development	SELENOI is essential for murine embryogenesis. SELENOI$^{-/-}$ mice fail to develop past the E6 stage of uterine implantation.	[47]
Phospholipid synthesis	SELENOI catalyzes ethanolamine phosphotransferase reaction required to maintain levels of certain PE and plasmenyl PE species. A lack of SELENOI (EPT1) expression in HEK293 cells leads to decreased plasmenyl PE, but CEPT1 can partially compensate with	[23,40]
T cell differentiation	SELENOI and other enzymes in the PE synthesis pathway are crucial for T follicular helper cell differentiation.	[37,46]
T cell proliferation	SELENOI is important for de novo PE and plasmenyl PE synthesis during T cell proliferation as well as metabolic reprogramming. SELENOI$^{-/-}$ T cells exhibit reduced proliferatve capacity, an accumulation of [ATP] and disrupted metabolic pathways.	[40]
T cell plasma membrane organization	SELENOI deficiency does not perturb lipid raft organization or membrane fluidity in mouse T cells. However, levels of some GPI-anchored are decreased.	[16,40]
Neurodevelopment and myelination	SELENOI mutation in one patient caused severe complicated hereditary spastic paraplegia, sensorineural-deafness, blindness, and seizures. Neuroimaging of one individual with SELENOI mutation revealed hypomyelination.	[71]
Neurodegenerative motor neuron disorders	Patients with SELENOI mutations develop a neurodegenerative condition best categorized clinically as a complex form of Hereditary spastic paraplegia (HSP) with brain white matter involvement. PE levels were broadly unaffected in blood.	[70,72]