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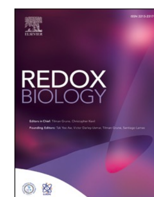

# Emerging roles of ER-resident selenoproteins in brain physiology and physiopathology

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ABSTRACT

The brain has a very high oxygen consumption rate and is particularly sensitive to oxidative stress. It is also the last organ to suffer from a loss of selenium (Se) in case of deficiency. Se is a crucial trace element present in the form of selenocysteine, the 21st proteinogenic amino acid present in selenoproteins, an essential protein family in the brain that participates in redox signaling. Among the most abundant selenoproteins in the brain are glutathione peroxidase 4 (GPX4), which reduces lipid peroxides and prevents ferroptosis, and selenoproteins W, I, F, K, M, O and T. Remarkably, more than half of them are proteins present in the ER and recent studies have shown their involvement in the maintenance of ER homeostasis, glycoprotein folding and quality control, redox balance, ER stress response signaling pathways and $Ca^{2+}$ homeostasis. However, their molecular functions remain mostly undetermined. The ER is a highly specialized organelle in neurons that maintains the physical continuity of axons over long distances through its continuous distribution from the cell body to the nerve terminals. Alteration of this continuity can lead to degeneration of distal axons and subsequent neuronal death. Elucidation of the function of ER-resident selenoproteins in neuronal pathophysiology may therefore become a new perspective for understanding the pathophysiology of neurological diseases. Here we summarize what is currently known about each of their molecular functions and their impact on the nervous system during development and stress.

## 1. Introduction

The endoplasmic reticulum (ER) is an extensive membrane organelle that plays a crucial role in the adaptation of eukaryotic cells to internal and external environmental changes, and in their viability. Remarkably in neurons, the ER forms a continuous structure that follows the shape of the cell, and has been called “a neuron within a neuron [1,2]. Its integrity is essential to maintain the physical continuity of axons over long distances and to prevent degeneration of distal axons. Within the cell body, in connexion with the nuclear envelope, is the rough ER, characterized by its sheet-like morphology and the presence of ribosomes attached to the ER membrane. The dendritic and axonal ER is mainly formed by a network of interconnected tubules, sometimes with sheets or cisternae. The tubules are lipid synthesis regions and the cisternae, with their larger lumen, have a greater capacity to store calcium [3].

The main function of the granular (rough) ER is to participate in the synthesis and maturation of proteins destined to secretion, or exposed at the membrane surface. Most proteins entering the ER are *N*-glycosylated by the oligosaccharyltransferase (OST) at the translocon exit. The resulting *N*-glycan undergoes successive glucose and mannose addition/trimming steps establishing a sugar-based code [4,5]. This code conditions the access of newly synthesized proteins to a complex process that mobilizes dozens of proteins, including chaperones, disulfide isomerases, glucosidases and glucosyl transferases, and contributes to fold them up to the native form while ensuring their quality control [6–8]. Only proteins which are properly folded leave the ER and continue their maturation in the Golgi complex. However, a fraction of them (~10%) is resistant to folding and is degraded through the ER-associated protein degradation (ERAD) pathways. The accumulation of inactive or chemically aggressive proteins in the ER lumen leads to a cellular state

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**Abbreviations**

ACTH Adrenocorticotropic Hormone
AD Alzheimer's disease
AKT RAC-alpha serine/threonine-protein kinase
APP Amyloid precursor protein
ATF6 Activating Transcription Factor 6
Aβ Amyloid-β
BiP, HSP70, GRP78 Immunoglobulin Binding Protein
Cav1.1 Calcium channel, voltage-dependent, L type, alpha 1S subunit
CHOP C/EBP homologous protein
CRAC $Ca^{2+}$ release-activated $Ca^{2+}$ channel
CRF Corticotropin-releasing hormone
Derlin1 Degradation in endoplasmic reticulum protein 1
DHHC6 Palmitoyltransferase
Dio2/D2 Type 2 iodothyronine deiodinase
ER Endoplasmic reticulum
ERAD ER-associated protein degradation
ERK Extracellular signal-regulated kinases
ERO1 Endoplasmic reticulum oxidoreductin 1
ERSE ER stress response element
Gal-1 Galectin-1
GHQ General Health Questionnaire
GPX4 Glutathione peroxidase 4
IP3 Inositol trisphosphate
IP3R Inositol trisphosphate receptor
IRE1 Inositol-requiring enzyme 1
KCP2 Keratinocyte-associated Protein 2
KO Knock-out
MAPK Mitogen-activated protein kinases
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Nes-Cre/SelTfl/fl Brain conditional SELENOT-deficient mice
NFTs Neurofibrillary tangles
OST Oligosaccharyltransferase
OST48 Dolichyl-diphosphooligosaccharide–protein Glycosyltransferase 48 kDa subunit
p97, VCP Valosin containing protein
PACAP Pituitary adenylate cyclase-activating polypeptide
PD Parkinson's disease
PERK Protein kinase R (PKR)-like endoplasmic reticulum kinase
PDI Protein disulphide isomerase
RDH11 Retinol dehydrogenase 11
ROS Reactive oxygen species
RyR1 Ryanodine receptor 1
Se Selenium
SEC, U Selenocysteine
SELENOF, Sep15, 15-kDa selenoprotein Selenoprotein F
SELENOK, SelK Selenoprotein K
SELENOM, SelM Selenoprotein M
SELENOS, SelS, SEPS1 Selenoprotein S
SelT, SELENOT Selenoprotein T
SEPN1, SELENON, SelN Selenoprotein N
SERCA1 ER sarco/endoplasmic reticulum calcium ATPases
SPUR Selenoprotein S positive UGA recoding
STIM Stromal interacting molecule
STT3A Dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit STT3A
T3 3,5,3′-triiodothyronine
T4 3,5,3′,5′-tetraiodothyronine
TXN Thioredoxin
UGGT UDP-glucose: glycoprotein glucosyltransferase
UPR Unfolded protein response
VIMP Valosin interacting protein

referred to as ER stress, which is the signal for activation of the unfolded protein response (UPR) to restore ER homeostasis. However, this cell-rescue pathway can fail and turn into a cell-death pathway (Box 1). Exacerbated ER stress and UPR activation are molecular pathophysiological hallmarks of many neurodegenerative diseases [3,9–11], although ER stress signaling pathways are also important in nervous system physiology, during development and aging [12,13]. Many studies have been conducted to reduce cellular stress and restore proteostasis as a therapeutic strategy for neurodegenerative diseases [14–16].

The brain is particularly dependent on Se because of its high rate of oxygen consumption and increased sensitivity to oxidative stress [17]. This is why it is the last organ to suffer from the loss of Se in case of deficiency [18,19]. In rats, it has been shown that Se levels decrease by 29% in all brain regions analyzed during Se deficiency, compared to more than 98% in the liver and 92% in the kidneys [20], a result partly corroborated in chickens [21]. In the rat brain, the highest Se levels were detected in the anatomical regions containing the most grey matter, with the Se content decreasing in the following order: cerebellum > cortex > medulla oblongata [22]. The hippocampus, certain layers of the cerebellum, brainstem and ventricles were the preferential sites of Se supply in the brain of Se-deficient rats [20]. Se protects against oxidative stress, endoplasmic reticulum stress and inflammation. This trace element has also been shown to promote neurotransmission by maintaining redox balance [23]. After the initial study by Weber et al. demonstrating the alleviation of intractable seizures in children with a low level of

**Box 1**
The unfolded protein response

In order to prevent ER stress, eukaryotes have evolved a complex homeostatic mechanism known as the unfolded protein response (UPR), which is divided into adaptive UPR and pro-apoptotic UPR [39–43]. The UPR is a set of tightly interconnected signaling pathways activated by a triad of transmembrane proteins, namely protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6), all of which possess a regulatory domain in the ER lumen. Under normal conditions, this domain is bound to the chaperone protein immunoglobulin binding protein (BiP/GRP78/HSP70). However, the amount of BiP available in the ER lumen is inversely proportional to the protein load. As protein load increases, BiP dissociates from these transmembrane proteins, leading to their dimerization (PERK, IRE1) or cleavage (ATF6), and self-activation. Stimulation of UPR leads to inhibition of global protein translation, increased chaperone activity, enhanced ERAD mediated protein degradation, COPII- mediated secretion and ER-phagy, and activation of antioxidant defence mechanisms, with the primary goal of reducing the accumulation and aggregation of misfolded proteins in the ER lumen. If UPR is not sufficient to restore protein homeostasis, and ER stress worsens, then key regulators of UPR trigger the cascade of apoptotic death signals [39–42,44–46].

glutathione peroxidase (GPX) [24], many studies have suggested a correlation of low selenium (Se) status with seizures, Parkinson's disease (PD), Alzheimer's disease (AD), dementia, cognitive decline [23,25,26] and neurodevelopmental disorders [27]. Se levels in the brain decreased by 40% [28], and a decrease in Se plasma levels was also observed in patients with epilepsy and PD, which was associated with impaired function of GPX [26]. Se has also been used as a therapeutic agent with contrasting results. Hence, Se has been discussed for decades in relation to AD, with absence of conclusive results [29]. It has been used as an adjunct to therapy in a multiple sclerosis mouse model, and has been proposed as preventive and therapeutic measures in distinct clinical forms of this disease [30]. Another strategy was tested successfully to facilitate Se transport by using a cargo peptide to enhance GPX4 synthesis during a ferroptosis neurodegeneration process [31] and stroke [32] in mice. Some benefit of higher selenium status on the risk of prostate, lung, colorectal, and bladder cancer has also been described, but the results of these trials have been contrasting as well.

Although Se supplementation in the brain has shown some therapeutic potential, the exact roles of Se in alleviating neuronal deficits are still unclear. Se is mainly present in cells as the 21st amino acid selenocysteine (Sec, U) in a set of proteins collectively called selenoproteins, which are one of the primary lines of defense against oxidative stress. Sec is a structural homologue of cysteine (Cys) in which the sulphur atom is substituted by a Se atom. Sec is more reactive than Cys to reactive oxygen species (ROS), thanks to its Se atom giving it both a higher nucleophilic power and a lower pKa [33,34]. Se would be more resistant to overoxidation to selenone than S to sulfone, and would have the ability to be reduced to selenide more rapidly than S [34]. These physico-chemical properties give all selenoproteins a more or less established antioxidant role. Some of them, notably thioredoxin reductases, are essential for the regulation of redox homeostasis [35]. It should be noted that Se can also be introduced into proteins in the form of selenomethionine, notably in some plants and bacteria [36]. Remarkably one third of these proteins are located in the ER where they regulate proteostasis, ER and redox stresses and $Ca^{2+}$ flux. In this review, we discuss the current state of knowledge regarding the role of ER resident selenoproteins and their involvement in nervous system physiology and disease [23,37,38]. Given their involvement in regulating oxidative, ER and inflammatory stress, a greater understanding of the role of these ER-resident selenoproteins may offer novel insights into the pathophysiology of neurological diseases.

## 2. Selenoproteins in the brain

During the atypical synthesis of selenoproteins, the Sec residue is synthesized on its own tRNA, the [Ser]Sec tRNA which is encoded by the Trsp gene, and incorporated in an unconventional manner during translation. Briefly, the selenoprotein transcripts contain in their 3′ untranslated region a 60 nucleotide RNA sequence that adopts a stem-loop structure designated as the selenocysteine insertion sequence (SECIS) element. The latter recruits a protein complex including SBP2 (SECIS binding protein 2), eEFSec (eukaryotic elongation factor, selenocysteine-tRNA specific), which together with other factors allows the specific decoding of an UGA stop codon into a Sec codon during the elongation step of protein translation. Twenty-five human selenoproteins, compared to twenty four in mouse, were identified in a bioinformatics screen based on the presence of the SECIS element in the 3′ untranslated region of the mRNAs [47]. All of them have in their sequence a single Sec residue, except SELENOP, which contains up to ten of these residues in humans, and which is produced in the liver and secreted in the plasma to supply the different tissues of the body with Se. Remarkably, a SEC-specific mass spectrometry-based approach has recently identified five putative candidate selenoproteins lacking the SECIS sequence in their mRNAs, suggesting that more such selenoproteins may be discovered in the future [48].

Selenoproteins are mainly present in neurons although Se is mainly distributed in the brain as selenoprotein P (SELENOP, SelP) through glial cells. Circulating SELENOP in blood and cerebrospinal fluid is taken up by LRP8-positive cells [49,50] at the blood-brain barrier and in the choroid plexus, resynthesized in nearby astrocytes, and released to supply Se to LRP8-positive neurons [51]. It is also possible that Se enters the brain as selenosugar [49] or as selenite salt using anion transporters present in the blood-brain barrier [52], in which case it may be neurotoxic [53]. Thus, mice invalidated for SELENOP show severe neurological dysfunctions during weaning which are largely avoided with Se supplementation [54]. SELENOP and selenoproteins are required for the functionality of parvalbumin-expressing interneurons which are highly metabolic active and sensitive to oxidative stress [59–61]. Se can also be sequestered by selenium binding protein 1 in astrocytes, which negatively regulates the production of SELENOP. A significant fraction of Se (20%) supplied by SELENOP is incorporated into the brain as GPX [22], but the majority of the selenoproteins are expressed in this organ in humans and mouse [51,55]. Six members of the selenoprotein family are highly enriched in the mouse brain, in particular SELENOP, GPX4, selenoprotein K (SelK, SELENOK), selenoprotein M (SelM, SELENOM), selenoprotein W (SelW, SELENOW) and selenoprotein F (Sep15/SELENOF) [18]. In humans, the most represented are SELENOF, SELENOW, GPX4, SELENOI, SELENOO and SELENOT. Some of them are essential for the organism such as TRXR1, SELENOI and SELENOT, and GPX4 only in mouse [56]. (Fig. 1) GPX4 has probably been the most studied in the brain. This mitochondrial antioxidant enzyme plays a protective role against oxidative stress, which has the effect of limiting neurodegeneration and ferroptosis [57,58].

Conditional inactivation of GPX4 in forebrain neurons after development leads to cognitive decline and hippocampal neurodegeneration in mice [62]. Human neonates with sedan-type spondylometaphyseal dysplasia with inactivating nonsense mutations in the GPX4 gene have been observed [63]. They show massive brain atrophy and usually die soon after birth, so human foetuses with GPX4 mutations progress further in their development compared to mice with the null mutation. Conditional ablation of TRXR1 in neural precursors leads to cerebellar hypoplasia, ataxia and tremor in mice [64] while its removal in neurons leads to neurodegeneration and aging [56], suggesting a key function in the processes of migration via Bergmann glia or granule cell generation [64]. Ethanolamine phosphotransferase 1 (EPT1/SELENOI), whose gene deletion is also lethal at the embryonic stage, is an enzyme involved in phospholipid biosynthesis that is important for myelination [65,66]. It is probably through SELENOI that the Se deficiency caused by the absence of SELENOP could alter the formation of the myelin sheath in the brainstem [67]. The latest selenoprotein shown to play an essential role in the brain is SELENOT [68,69].

Of the twenty-five selenoproteins present in humans, seven are ER-resident selenoproteins but their molecular functions in the brain are poorly documented. In recent years, numerous studies have been conducted to elucidate the role of these selenoproteins in the regulation of ER homeostasis. There is emerging evidence that implicates them in the regulation of ER stress responses, ER redox status (Box 2), and $Ca^{2+}$ signaling (Box 3). These ER-resident selenoproteins include the 15-kDa selenoprotein F, type 2 iodothyronine deiodinase (Dio2) and selenoproteins S, N, K, M and T [70]. It has recently been shown that selenoprotein I is also localized in the ER among other cellular compartments [71], but we will review here only the literature dedicated to the seven selenoproteins whose localization is restricted to the ER. In this review we discuss the contribution of ER selenoproteins in brain function, in the order of their expression level, from highest to lowest abundance [51, 72].

## 3. SELENOF (15-kDa selenoprotein; Sep15)

The 15-kDa selenoprotein is a soluble enzyme located in the ER lumen, which is involved in posttranslational protein folding. In the mouse fibroblast cell line NIH 3T3, it has been shown that SELENOF

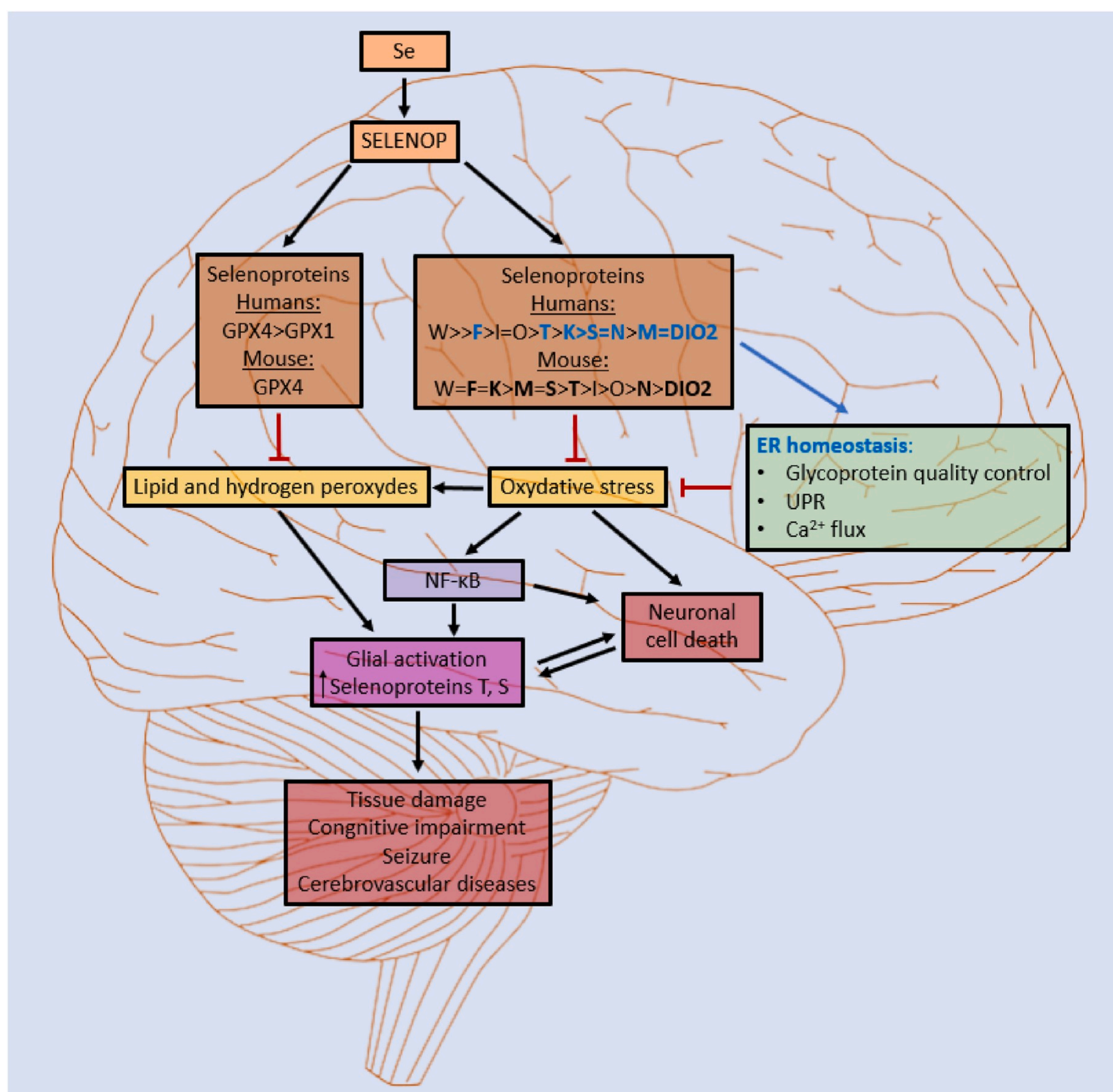


**Fig. 1.** Neuroprotective roles of selenoproteins in the brain
The brain has a high concentration of unsaturated fatty acids and weak antioxidant defense mechanisms, making it susceptible to oxidative stress. Selenoproteins are major components of the antioxidant defense strategy in the brain. Se enters the brain primarily as SELENOP, which enables the expression of other selenoproteins by providing Se as Sec [18,38,184]. The major selenoproteins expressed in the brain are listed according to their expression levels in human and mouse brain [51,72]. GPX1 and 4 reduce lipid and hydrogen peroxides [185]. Most other selenoproteins have antioxidant action as well. Those residing in the ER (bold, blue) participate in the maintenance of ER proteostasis and $Ca^{2+}$ homeostasis. Upon protein overload, the UPR is activated, leading to activation of PDI and increased production of ROS, further exacerbating oxidative stress. When cellular production of ROS overwhelms its antioxidant capacity, it leads to a state of oxidative stress, which in turn contributes to activate the NFκB signaling pathways, neuronal cell death and glial reactivity [186,187]. Whereas selenoprotein expression is prominent in neurons and barely detectable in astrocytes, brain injury results in strong upregulation of SELENOS and SELENOT, specifically in reactive astrocytes in mice [69,129]. Oxidative stress and ER stress contributes to the pathogenesis of several human neurological diseases. In this scenario, Se deficiency further increases sensitivity to oxidative stress, and sensitizes to neurodegeneration [54,188].[54,188]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

interacts with glucose:glycoprotein glucosyltransferase (UGGT), a soluble enzyme which acts as a folding sensor and evaluate the folded status of glycoproteins. UGGT transfers a glucose monomer to the terminal mannose of the A branch of the oligomannose Man3GlcNAc2 chain on misfolded glycoproteins that can in this form enter the quality control process [73]. If at the end of this process, the glycoprotein is not correctly folded, this last glucose is removed by glucosidase II (GII) and reformed by UGGT, then, the folding process starts again until the protein reaches the wright native conformation. Otherwise, misfolded proteins enter a specific degradation process called ERAD (ER-associated protein degradation) [44]. SELENOF interacts with UGGT via a conserved cysteine-rich domain present in its N-terminal moiety, an interaction which is also essential for SELENOF retention in the ER [74]. SELENOF has a thioredoxin (TXN)-like domain containing a redox active C*X*U motif, suggesting a thiol oxidoreductase function for this protein. It has been proposed that the SELENOF uncommon CXU redox motif could be involved in the reduction, isomerization or oxidation of disulfide bonds of glycoprotein substrates of UGGT [75].

SELENOF expression is abundant in secretory tissues such as prostate, liver, kidney, testis, and brain. In particular, SELENOF gene expression is elevated in neurons in olfactory bulb, hippocampus, cerebral cortex, and cerebellar cortex [18]. Only few studies have

**Box 2**
ER redox homeostasis is highly regulated

One characteristic feature of the ER environment is its more oxidative environment compared to the cytosol [81], thus providing the adequate milieu for oxidative folding of secretory and membrane proteins. Glutathione (GSH) is one of the major components that maintain the redox environment in all cellular compartments of both prokaryotic and eukaryotic cells. However, GSH is only synthesized in the cytosol [82]. The ryanodine receptor (RyR) calcium release channel and protein channel Sec61p have been shown *in vitro* to passively transport GSH across the ER [83,84]. In the ER, thiol groups in GSH and nascent secretory or membrane proteins (PSH) react with oxidized protein disulphide isomerase $PDI_{ox}$ to generate PSSP, GSSG, and reduced PDI ($PDI_{red}$). PDI has to be re-oxidized, and this is achieved by the flavoproteins Ero1 (ER oxidoreductin-1α and β) which transfer the two electrons from PDI via FAD to oxygen, thus producing $H_2O_2$. All ER peroxidases Prx4, GPX7/8 couple their $H_2O_2$ scavenging to PDI oxidation, thus promoting oxidative folding. Whether $H_2O_2$ is a toxic byproduct or is physiologically required to contribute to oxidative folding is currently a matter of debate. Meanwhile, $H_2O_2$ levels have to be maintained at acceptable levels since its accumulation can inhibit the proper formation of disulfide bonds, leading to protein misfolding and UPR activation. Abundant PDIs in the ER act as electron acceptors for other oxidoreductases to provide flexibility and robustness in the ER redox environment. In summary, the process of oxidative protein folding is complex and requires multiple co-players [85–88].

**Box 3**
ER serves as an intracellular calcium storage

ER is the major $Ca^{2+}$ storage organelle. $Ca^{2+}$ plays a key function as a cytosolic second messenger that controls muscle contraction, protein secretion, mitochondrial metabolism or cell death (Tannous, Pisoni et al., 2015). Stimulations of G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) result in hydrolytic cleavage of phosphatidylinositol 4,5-bisphosphate by phospholipase C, producing inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). The conjoint binding of IP3 and $Ca^{2+}$ activates the IP3R channel receptor at the ER membrane, opening the pore and initiating the release of $Ca^{2+}$ from ER. Another active mechanism of $Ca^{2+}$ release is based on the gated channel of the RyRs receptor family, which can be inhibited by high concentrations of the ryanodine alkaloid and also opens upon binding of $Ca^{2+}$ ions. ER membrane can also modulate its own luminal $Ca^{2+}$ dynamics and generate appropriate signals to maintain balanced homeostasis through the interaction between the Stromal Interacting Molecule (STIM), an ER resident protein serving as a $Ca^{2+}$ sensor (Stathopulos, Zheng et al., 2009), and ORAI a plasma membrane subunit of the $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channel (Prakriya, Feske et al., 2006). Upon depletion of the ER $Ca^{2+}$, STIM molecules oligomerize to recruit and gate the ORAI channel at the junction of the ER with the plasma membrane leading to the entry of extracellular $Ca^{2+}$ into the cytosol (Stathopulos & Ikura, 2013). Fueled by ATP hydrolysis, sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPases (SERCAs) transport cytosolic $Ca^{2+}$ to the ER (or sarcoplasmic reticulum), thereby restoring calcium homeostasis. The varying redox conditions of the ER govern the flow of $Ca^{2+}$ from the ER. This involves direct disulfide reduction in the ER $Ca^{2+}$ handling proteins such as IP3R and SERCA, but also the regulated interaction of ER chaperones and oxidoreductases with these proteins (Appenzeller-Herzog & Simmen, 2016). Oxidative stress results in $Ca^{2+}$-dependent synaptic dysfunction, impaired plasticity, neuronal demise and neurodegenerative disorders [109].

investigated the role of SELENOF in the brain. SELENOF knock-out (KO) mice carrying a targeted deletion of exon 2 of the *selenoF* gene coding for the cysteine-rich UGGT binding domain showed normal brain morphology, although SELENOF is one of the most abundant ER-resident proteins in the brain in both mice and humans [51]. However, these mice developed an early age cataract without increased oxidative stress or glucose dysregulation [76]. On the basis of their previous studies demonstrating an interaction between SELENOF and UGGT, the authors suggested that the phenotype observed is due to an improper folding of lens proteins caused by SELENOF deficiency. Dai and collaborators (2016) showed the protective effect of selenite supplementation against D-galactose-induced cataract in rats, an effect which was linked to an increase in SELENOF expression [77]. More recently, a yeast two-hybrid system which was used to identify SELENOF partners in a human fetal brain cDNA library revealed an interaction between SELENOF and retinol dehydrogenase 11 (RDH11), an enzyme involved in vitamin A metabolism. This study suggested that both SELENOF and RDH11 might reduce all-trans-retinaldehyde into all-trans-retinol (Vitamin A and its esters), but curiously SELENOF and RDH11 inhibited the enzymatic activity of each other [78]. Although these two independent teams highlighted the potential role of SELENOF in vision, it is yet unclear if cataract development and protein misfolding in lens from SELENOF KO mice results from the lack of interaction with UGGT, or a deficiency in vitamin A and its metabolites due to a lack of interaction with RDH11, or both of these processes. It is likely that due to its high level in the brain, SELENOF interacts with RDH11 which has a similar expression profile, and participates in the development, maintenance and morphogenesis of the central nervous system through the production of retinoids [78,79]. Noteworthy, vitamin A deficiency is positively correlated with cognitive decline in the elderly population [79,80]. Additional studies on SELENOF function in the brain may uncover its contribution to cognition.

## 4. SELENOT

SELENOT is thought to be one of the highest priorities selenoproteins, along with TrxR1, so that its expression cannot fall below a threshold level. For instance, its cellular levels are marginally impacted by Se deficiency [89]. Conversely, the levels of SELENOT mRNA in HEK293 cells are significantly up-regulated compared to that other selenoprotein mRNAs in Se-supplemented conditions [90]. SELENOT is also the most evolutionarily conserved selenoprotein and its gene invalidation in mouse is lethal at early stages of embryogenesis, perhaps at the preimplantation stage [69]. A correspondence in intolerance to SELENOT loss-of-function between human and mouse has been reported, which is only the case also for TRXR1 [91]. However, in *C. elegans* which possesses two *selenot* gene parologs, the double KO is viable [92]. SELENOT mRNA levels are significantly upregulated between control and Se-supplemented conditions in HEK293 cells, whereas the levels of 19 other selenoprotein mRNAs remained unaffected by the change in Se level [121]. SELENOT contains an N-terminal CVSU redox motif within a thioredoxin-fold domain that confers thiol-disulfide oxidoreductase enzymatic activity [69]. A small peptide (PSELT) designed from the redox active site is sufficient to mimic the

antioxidant effect of SELENOT in dopaminergic neurons *in vivo* and *in vitro* [93]. Meanwhile, Sec is substituted by Cys in certain organisms like *C. elegans*, among others [94]. Directed mutagenesis approaches and modeling studies support a topology in which SELENOT is inserted into the ER membrane [95–97].

SELENOT levels are high in all tissues during development, from mouse to nematodes [92,95,98]. However, they decrease drastically after birth, except in the brain, and in tissues with endocrine/secretory activity such as the pituitary, thyroid, thymus or testicle [95,96, 99–102]. In the adult mouse brain, SELENOT mRNA was detected in many areas including the thalamus, the hypothalamus, midbrain, pons and the medulla [101]. SELENOT-like immunoreactivity was found to be intense in some glial cell populations, including astrocytes in the rostral migratory stream and Bergmann glial cells in the cerebellar cortex [98].

Stress strongly influences SELENOT expression. SELENOT was induced in various neuronal and neuroendocrine cell lines under exposure to oxidative, neurotoxic and ER stress [96,103]. Stress also triggered the re-expression of SELENOT in tissues where it had been switched off after birth, such as liver after hepatectomy [98] in rat, substantia nigra and striatum in mouse models of PD (in neurons and astrocytes), and striatum of PD patients [69]. Both SELENOT expression and mitochondriogenesis were induced via the AMPK/PGC-1α/NRF-1 cascade during pituitary adenylate cyclase activating polypeptide (PACAP)-induced neuroendocrine differentiation [95,103]. PACAP is thought to reprogram cellular metabolism via an AMPK-dependent pathway, which would allow cells to pass a critical metabolic checkpoint with tolerable ROS levels ensured by antioxidant enzymes such as SELENOT, in spite of increased mitochondriogenesis, and to successfully transition to neuronal-like differentiation [103].

Reduction of SELENOT levels in various endocrine, neuroendocrine and neuronal cell lines, as well as in neuroblasts in primary culture, but not in astrocytes, resulted in increased levels of ROS [68,69,96,103]. SELENOT depleted endocrine cells also developped ER stress characterized by ER enlargement. BiP, CHOP, ATF6, and ATF4 were enhanced as well as other UPR markers. A delay in the elimination of the misfolded null Hong Kong variant of human alpha1-antitrypsin, a truncated variant deriving from the deletion of a dinucleotide which leads to its accumulation in the ER [104], was also observed, indicating ERAD alteration [105]. SELENOT-depletion also abolished the increase in cytosolic [$Ca^{2+}$] induced by PACAP in neuroendocrine cells and the redox center was essential for SELENOT-dependent $Ca^{2+}$ flux regulation [95]. In conditional brain SELENOT deficient mice (Nes-Cre/SelT$^{fl/fl}$), in which SELENOT was depleted in immature neuroblasts, there was a loss of immature neurons by apoptotic cell death, but not of glial cells [68]. Several brain structures, including the hippocampus, cerebral cortex, and cerebellum, showed significant and transient growth retardation during the first postnatal week. Despite an apparent morphological compensation, SELENOT deficiency leads to a hyperactive behaviour in adulthood [68]. Three-dimensional mapping of catecholaminergic neurons in Nes-Cre/SelT$^{fl/fl}$ showed a significant decrease in the number of tyrosine hydroxylase-positive neurons in the area postrema, A11 cell group, and zona incerta of SELENOT-deficient females, as well as in the hypothalamus of SELENOT-deficient females and males [101]. Consistent with these data, the Nes-Cre/SELENOT$^{fl/fl}$ mouse line exhibited greater vulnerability of dopaminergic neurons to neurotoxin action, emphasizing the crucial role of SELENOT in protecting the catecholaminergic neuronal system [69].

A yeast two-hybrid system used to screen for SELENOT partners in a cDNA library prepared from mouse embryos showed its interaction with Keratinocyte-Associated Protein 2 (KCP2/KRTCAP2), a protein that interacts with the oligosaccharyltransferase (OST) type A complex [106, 107]. Immunoprecipitation studies validated the physical interaction with KCP2 and other OST subunits, including the catalytic subunit STT3A, but not the STT3B catalytic subunit of the type B complex [96]. STT3A catalyzes the co-translational N-glycosylation of proteins entering the ER lumen via the translocon [108]. Since SELENOT is not itself *N*-glycosylated [96], it likely acts as a modulator of *N*-glycosylation, similar to KCP2 [106,107]. Knock-out of SELENOT in AtT20 corticotropic cells specifically altered the *N*-glycosylation profile of the main protein produced by these cells, proopiomelanocortin (POMC). POMC is a polypeptide precursor whose cleavage generates adrenocorticotropic hormone (ACTH). ACTH secretion was suppressed in these cells after SELENOT depletion, which may result from altered POMC *N*-glycosylation, a possibility that remains to be confirmed [96]. Work is currently underway to confirm the role of SELENOT in *N*-glycosylation and to identify its target glycoproteins in neurons.

## 5. SELENOK

SELENOK belongs to the same protein family as SELENOS, not that they have similar sequences but because of their very similar organization. Surprisingly, it is one of the most widespread of the eukaryotic selenoproteins but its role is the most poorly understood. SELENOK is a selenoprotein with a single transmembrane domain and a C-terminal end that faces the cytosol. It contains a Sec residue in the third position from the C-terminal end supporting an antioxidant function [110,111]. However, it lacks, like SELENOS, the catalytic CXXU found in the majority of selenoenzymes. SELENOK is present as a homodimer containing an intermolecular diselenide bond. It has a domain which is rich in glycine and proline in the cytosolic tail and is necessary for the interaction with valosine ATPase-containing protein p97(VCP) and Derlin1, proteins that perform retrotranslocation of misfolded proteins into the cytosol [112]. Meanwhile, the interaction between SELENOK and p97 (VCP) is SELENOS-dependent [112]. The degradation of misfolded glycosylated proteins by the resulting ERAD complex (SELENOS-p97 (VCP)-SELENOK), combined with the antioxidant function of SELENOK and SELENOS, contribute to limit ER stress [112–114]. SELENOK deletion results in decreased $Ca^{2+}$ flux into macrophages, T cells and B cells. This effect results from a dysfunction of inositol 1,4,5-triphosphate receptor (IP3R) due to a defect in palmitoylation which is required for its stable expression [115]. In fact, SELENOK also interacts with DHHC6 (the letters represent the amino acids aspartic acid, histidine, histidine, and cysteine in the catalytic domain), a palmitic acid acyltransferase, through SH3/SH3 binding domain interactions. Palmitoylation catalyzed by DHHC6/SELENOK results in the addition of palmitic acid to at least three cysteine residues in the cytosolic portion of each IP3R stabilizing its expression and/or assembly into a functional tetrameric $Ca^{2+}$ channel in the ER membrane [115].

SELENOK expression is ubiquitous in mammalian tissues [110]. In the brain, it is highly expressed, in particular in hippocampus and cerebral cortex [18]. SELENOK gene contains a functional ER stress response element within its promoter region and SELENOK expression can be upregulated by the accumulation of misfolded proteins in the ER [114], suggesting that SELENOK is essential for maintaining ER homeostasis. *Selenok* gene disruption results in increased levels of ER stress markers such as ER BiP, CHOP and ATF6 in N2a cells, and those of CHOP and ATF6 in the cortex and hippocampus of *selenok* KO mice [116]. *Selenok* gene knock-out also increased the cytoplasmic $Ca^{2+}$ level leading to activation of *m*-calpain/caspase-12 cascade and ER stress-induced apoptotic pathway. Neuronal apoptosis might further lead to cognitive impairments and anxiety observed in these mice [116]. In AD mice models, a disequilibrium was found between synaptic and extrasynaptic NMDA receptors, as was also seen in SELENOK knock-out mice. Se-Met treatment upregulated SELENOK levels and restored the balance between synaptic and extrasynaptic NMDA receptors expression in an AD mouse model [117]. Stimulating microglial cells migration and phagocytosis is of importance for reducing the risk of neurodegenerative diseases, such as AD and PD. Se supplementation ($Na_2SeO_3$) significantly increases the expression of SELENOK in microglial cells, leading to increased migration and phagocytosis through up-regulation of IP3 receptors, and an increase in the cytosolic free $Ca^{2+}$ level. The enhanced

migration and phagocytosis of microglial cells by SELENOK expression through increased $Ca^{2+}$ flux could help the microglial cells to perform clearing functions; this is especially true for Aβ deposits [118].

## 6. SELENOS, SELS, SEPS1, VIMP, TANIS

SELENOS was first identified as Tanis by differential display PCR from mRNA obtained from livers of fed and fasted rats [119]. It was also identified and later named SELENOS, SELS, SEPS1 following bioinformatics screening of mRNAs with the SECIS sequence [120]. The name of p97(VCP)-interacting protein (VIMP) was also given to this selenoprotein as will be discussed later [121]. SELENOS is predicted to cross the membrane only once with a short luminal segment and a longer (~141 amino acids) disordered cytosolic domain. The latter contains the p97/VCP interaction motif (RX5AAX2R where X denotes positions without significant conservation), a coiled-coil domain, and a region rich in glycine, proline, and positively charged amino acids (G-rich) [114,121,122]. The Sec residue is located at the second or third position from the C-terminus and confers a reductase function to SELENOS *in vitro* [123,124]. A SPUR element in the 3′ UTR of SELENOS mRNA would bring SECIS into position to interact with the ribosome at the UGA-Sec codon and facilitate Sec insertion [125].

During ERAD, recruitment of p97(VCP) to the ER membrane is important for ERAD substrate degradation, and binding of SELENOS to p97(VCP) is required for this process. SELENOS also interacts with Derlins, with SELENOS serving as a link between Derlins and p97(VCP) during ERAD [121]. As mentioned before, SELENOS is required for the interaction of p97(VCP) with SELENOK, an interaction required for ERAD and cellular restoration after ER stress [112]. The *selenos* gene promoter contains an ER stress response element (ERSE), and overexpression of SELENOS limits ROS, ER stress and apoptosis in various cell lines [126–132]. Cross-linking experiments have shown that SELENOS interacts not only with p97(VCP) and Derlins but also, through its coiled-coil domains, with proteins enriched in various multiprotein complexes, suggesting that it participates in intracellular membrane transport and maintenance of protein complexes by anchoring them to the ER membrane [133]. Depletion of SELENOS caused the ER membrane to spread and disrupted the link between the ER and microtubules, indicating that SELENOS is an ER-shaping protein [134].

SELENOS is expressed ubiquitously. It is detected in the serum of some human subjects, with hepatocytes probably being the source of circulating SELENOS [135]. High expression is found in metabolically active tissues (kidney, liver, adipose tissue, blood vessels, pancreatic islets and skeletal muscle) [132,136]. Moreover, SELENOS expression is deregulated in metabolic disorders. It is overexpressed following glucose deprivation and lipopolysaccharide-induced inflammation [119,132, 137]. Expression of SELENOS mRNA is positively correlated with serum amyloid A in type 2 diabetic and control subjects, supporting the hypothesis that SELENOS may be the cell-surface receptor for serum amyloid A [128,138]. Its upregulation can also lead to insulin resistance [139]. SELENOS is also a regulator of contractile function in skeletal muscle [126,140].

SELENOS is expressed throughout the brain, at higher levels in the cortex, hippocampus and cerebellum [18,129]. SELENOS immunoreactivity is primarily localized to neurons in the healthy mouse brain. However, brain injury, inflammatory stimuli and ER stressors upregulate SELENOS expression in activated astrocytes [129]. SELENOS expression in stimulated astrocytes leads to a reduction in ER stress markers such as CHOP and spliced XBP-1, as well as the inflammatory cytokine IL-1β [129]. It has been proposed that it may be relevant to astrocyte function in the context of inflammatory neuropathologies [141].

SELENOS expression is regulated by ER stress in neurons as well. AD is pathologically characterized by the deposition of β-amyloid (Aβ) plaques and the accumulation of neurofibrillary tangles (NFTs). Furthermore, the formation of NFTs in AD is increased by ER stress [142]. Inhibition of SELENOS expression under ER stress increases Tau phosphorylation and phosphorylated Tau aggregation [142]. Se in the form of sodium selenate reduces NFTs formation and aggregates of hyperphosphorylated tau protein in Alzheimer's disease models and in the brain of AD patients, and selenate (selenite) significantly increases SELENOS expression in neurons [143–145]. Thus, selenate may decrease Tau hyperphosphorylation by increasing SELENOS expression in AD. Ubiquitination-dependent degradation of the AD-associated C99 fragment of APP was inhibited in a SELENOS-knockdown cell model of AD, and the β-amyloid (Aβ) level was significantly increased, indicating that SELENOS participates in the C99 degradation process through ERAD [146]. In the postmortem brain from AD patients, SELENOS expression correlates with NFTs, but not with Aβ plaques supporting a role in the phosphorylation of tau [142].

## 7. SELENOM

SELENOM is another luminal ER-resident oxidoreductase that is structurally homologous to SELENOF but is still to be fully characterized. SELENOM is shorter than SELENOF because it lacks the N-terminal cysteine-rich domain responsible for the binding to UGGT [75]. It includes a TNX fold in its tertiary structure, i.e. a single domain with a central five-stranded mixed β-sheet flanked by two α-helices on each side common to thioredoxin and enzymes that catalyze disulfide bond formation [147] and isomerization, and a CXXU redox motif. These features, in addition to the measured redox potential, and the localized conformational changes observed upon thiol-disulfide exchange, rapidly indicated a disulfide exchange activity [148]. Indeed, a TXN intrinsic activity was recently demonstrated for SELENOM immunoprecipitated from mouse hypothalamic extracts [149].

The expression pattern of SELENOM in rodents is characterized by higher expression levels in brain than in other organs [18]. SELENOM is highly expressed around birth in hippocampal CA3 region and later in all the principal divisions of the hippocampus. High levels were measured in adult cerebellum, main olfactory bulb, cerebellar cortex and isocortex [150]. Overexpression of the protein in murine hippocampal HT22 cells, cerebellar astrocyte C8-D1A cells, and primary neuronal cultures resulted in a reduction in ROS levels and oxidative stress-induced apoptotic cell death, suggesting a neuroprotective function for SELENOM [151]. Several studies have been conducted to investigate the neuroprotective role of SELENOM in the physiopathology of AD. SELENOM was identified among the genes whose expression was differentially modulated due to the over-expression of human mutant presenilin-2 in transgenic mice [152]. SELENOM levels were reduced in these mice indicating that SELENOM may play a suppressive or protective role in the pathophysiology of AD, a hypothesis confirmed by several works performed in different cellular and animal models. Thus, in the transgenic rat overexpressing human SELENOM, Se treatment and SELENOM attenuated alpha/gamma-secretase-mediated proteolysis and Tau phosphorylation to protect brain function through activation of the ERK pathway [153]. In an Aβ-expressing cell model SELENOM attenuated oxidative stress-induced mitochondrial damage through inhibition of Aβ oligomer formation [154]. Aggregation and cytotoxicity of Aβ with transition metal ions in neuronal cells has been implicated in the progression of AD. SELENOM chelates $Zn^{2+}$, probably via its redox motif CXXC, and due to its metal binding capacities, SELENOM suppressed $Zn^{2+}$-induced Aβ aggregation and thus exhibited antioxidant and neuroprotective functionality in the neuroblastoma N2A cell line [155]. Cytosolic calcium is very important in the pathogenesis of neurodegenerative diseases. In several cellular models (hippocampal HT22 cells, cerebellar astrocyte C8-D1A cells, and primary neuronal cultures) SELENOM decreased calcium release from ER in response to oxidative stress and reduces apoptotic cell death [151]. The *anti*-Aβ aggregation function of SELENOM still needs to be confirmed *in vivo*, and the mechanism involved should be investigated, in particular its link to $Ca^{2+}$ homeostasis and energy metabolism in the brain.

SELENOM was used to screen a human fetal brain cDNA library by the yeast two-hybrid system for potential partners. Galectin-1 (Gal-1), a lectin that binds β-galactoside and a wide array of complex carbohydrates, which is essential for the production of new neurons and the recovery from brain damage, was identified as an interacting protein [156]. The interaction between SELENOM and Gal-1 hence indicated important roles in preventing neurodegeneration. Moreover, SELENOM was found expressed in hypothalamic regions involved in leptin signaling [149], and was previously linked to energy metabolism [151]. Leptin promoted hypothalamic expression of SELENOM, and leptin-induced STAT3 phosphorylation was hampered by SELENOM deficiency. SELENOM knock-out mice had no deficits in motor coordination and cognitive function but exhibited increased weight gain, increased white adipose tissue deposition, and attenuated hypothalamic leptin sensitivity, indicating that SELENOM plays an important role in maintaining redox balance in key brain regions involved in energy metabolism [150]. NF-κB and ER stress pathways largely crosstalk and converge to stimulate transcriptional programs that promote antioxidant defense, cell survival and the inflammatory response in the hypothalamus [149]. Microarray studies in hypothalamic tissue and mHypoE-44 cells indicated that SELENOM promotes both TXN and NF-κB activity, a finding that was not surprising since TXN facilitates NF-κB signaling through the reduction of redox-sensitive cysteine residues in the p50/p65 heterodimer [149]. At the opposite, SELENOM deficiency in mHypoE-44 cells provoked a decrease in the leptin-activated NF-κB signaling pathway and enhanced vulnerability to ER stress-mediated cell death. $Ca^{2+}$ imaging data revealed that SELENOM-deficient cells showed no visible response to leptin. It has been suggested that this may be caused by a disrupted communication between the leptin receptor and ER proteins involved in $Ca^{2+}$ signaling, such as Inositol trisphosphate receptor (IP3R) or sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) pump [149,157]. The possible redox regulation of thiol groups by SELENOM on these ER $Ca^{2+}$ channels and/or pumps needs to be further explored.

## 8. Dio2 (D2)

Thyroid hormones have multiple functions during growth and development, and in metabolism regulation in adult. The type 1, 2 and 3 iodothyronine deiodinases (DIO1, DIO2, and DIO3) are transmembrane selenoproteins which remove a iodine residue from the outer or inner ring of thyroid hormones. DIO2 and DIO3 finely regulate thyroid hormone signaling during development through local activation (DIO2) or inactivation (DIO3) of thyroid hormones, and distinct expression patterns. Dio3 to Dio2 expression switches are found in many organs, including the brain, leading to amplification of the T3 signal during developmental transitions [158]. This review will focus on DIO2 which resides in the ER and more specifically catalyzes the deiodination of T4 (3,5,3′,5′-tetraiodothyronine) into T3 (3,5,3′-triiodothyronine).

*dio2* mRNA expression was detected in the neonatal rat brain, in the cerebral cortex, olfactory bulb, hippocampus, caudate, thalamus, hypothalamus and cerebellum, and it was observed more particularly in certain population of glial cells (astrocytes and tanycytes lining the third ventricle) [159]. In contrast, dio2 mRNA expression is absent in most regions of the adult mouse brain [18], with a few exceptions, since DIO2-producing glial cells were observed in the arcuate nucleus of the hypothalamus, in direct apposition with neurons co-expressing neuropeptide Y and agouti-related protein [160]. Altogether, these observations support a model whereby separation of T3-producing glial cells and T3-responding neurons provides a paracrine-like form of control [159]. Fasting increased DIO2 activity and local thyroid hormone production in the arcuate nucleus supporting a function in the central regulation of food intake [160]. In addition, DIO2 expression peaks in the retina at juvenile stages, suggesting that it may be important in amplifying T3 content during retinal maturation, but this has not been confirmed in DIO2 KO mice, which exhibited a very mild neurological phenotype [161].

Today, research on DIO2 mainly focuses on psychiatric and depressive disorders. Yet, the relationship between hypo/hyperthyroidism and depression is not clearly established despite the large number of studies [162,163]. Hence, *dio2* gene is linked with bipolar disorder in Asian population [164] and activity of DIO2 in the brain may be a determinant of well-being and neurocognitive function according to the answers given to the General Health Questionnaire (GHQ) score [165]. Thr92Ala is a well-studied polymorphism present in 12–36% of the population that leads to ER stress and hypothyroidism [166]. It has been postulated that the Thr92Ala substitution may result in the instability of a loop into the DIO2 protein that affects the process of ubiquitination, slowing down DIO2 turnover and targeting to the proteasome, and leading to its detrimental accumulation in the ER. The contribution of DIO2 polymorphisms to the ethiology of recurrent depressive disorders could be related to the DIO2 increased activity and subsequently to thyroid hormone levels in the brain [167].

This polymorphism has also been investigated in AD. Thr92AlaD2 DIO2 accumulates in neurons and escapes from the ER to the Golgi apparatus, which exhibits a perturbed morphology. Human temporal lobe samples from subjects carrying the Thr92AlaD2 DIO2 mutation exhibit transcriptional alterations in processes associated with neurodegenerative diseases, such as Aβ processing [168]. The altered Golgi trafficking of APP processing has been implicated in development of AD, because Aβ peptide accumulation causes Golgi structural defects that further affects APP trafficking and processing [169]. Finally, population study has shown that the Thr92AlaD2 polymorphism is associated with development of AD in African American but not European American populations, supporting the hypothesis that Thr92AlaD2 might represent one factor contributing to ethnic discrepancies in incident AD [170].

## 9. SELENON (SEPN1; SelN)

SELENON is a 62 kDa type II transmembrane glycoprotein which senses ER calcium fluctuations by binding this ion through a luminal EF-hand domain. It responds to diminished luminal calcium levels by changing its oligomeric state, turning on its redox activity towards its partner, the SERCA pump, and many other interactors. Its interaction with SERCA leads to a reduction of the luminal cysteines of this $Ca^{2+}$ pump, which are hyperoxidized by ERO1-generated peroxides (Boxes 2 and 3). SELENON function becomes essential in the case of a hyperoxidized ER elicited by over-expressing ERO1, as indicated by the failure of myoblasts to grow under these conditions in the absence of SELENON [171]. SELENON-depleted cells are also clearly defective in ER calcium re-uptake [172]. Single amino acid substitutions in the EF-hand domain of SELENON impaired its calcium-binding properties and calcium-dependent structural changes, which suggests a key role of the EF-hand domain in SELENON function.

SELENON loss of function leads to a congenital myopathy associated with insulin resistance (SEPN1-related myopathy). Identification of 65 SELENON mutations, including a pathogenic copy number variation, unveiled exon 1 as the main mutational hotspot [173]. Muscles of patients with SELENON variants contain lower amounts of key proteins involved in calcium regulation and skeletal muscle excitation-contraction coupling like RyR1, Cav1.1 and SERCA1 [174]. Absence of SELENON in myoblast primary cultures from patients with null SELENON mutations is associated with abnormal susceptibility to $H_2O_2$-induced oxidative stress, causing cell death [175]. Unlike in humans, limb muscles are protected from disease when at rest in SELENON deficient mice, but an inappropriate response to ER stress triggers dysfunction in highly active muscles of these mice [176]. *chop* gene ablation in SELENON KO mice precludes diaphragm dysfunction, the prolonged limb muscle relaxation after fatigue, and restores $Ca^{2+}$ uptake by attenuating the induction of ERO1. Altogether, these observations indicate that SELENON would be a part of an ER stress-activated

antioxidant response that, upon failure, results in a CHOP- and ERO1-dependent maladaptive response leading to oxidation and inhibition of SERCA2 in highly active muscles [176]. SELENON also protects skeletal muscle from saturated fatty acid-induced ER stress and insulin resistance, indicating that all environmental factors causing ER stress in skeletal muscle (such as a high-fat diet) could affect the pathological phenotype of SEPN1-related myopathy [177].

The *selenon* gene is expressed in the mouse brain, with a higher rate in olfactory areas, hippocampus and both the cerebral and cerebellar cortexes [18]. Meanwhile, the role of SELENON in the central nervous system is largely unexplored. No patient with SELENON-related myopathy showed intellectual disability or CNS involvement [173], which may discourage further research into possible central functions of SELENON.

## 10. Conclusion

It is clear today that selenoproteins not only protect cells and organisms against oxidative stress, but that each of them has specific molecular functions and partners, in connection with their structure and localization, and in relation with a role in redox and $Ca^{2+}$ homeostasis and protein folding/degradation (Fig. 2). Up to now, their molecular functions are particularly difficult to study for many reasons: acting as oxidoreductases, they establish transient redox boundaries that are difficult to capture, and conversely their overexpression can lead to nonspecific redox interactions. Furthermore, it is obvious that their molecular partners may be different depending on the cell type, developmental stage, or stress versus resting conditions. Furthermore, the recombinant proteins produced are most often Cys variants, as Sec isoforms are difficult to express in mammalian cells. High oxidative stress has been identified as a key factor in the onset and development of several neuropsychiatric disorders. To date, apart from Se supplementation, few studies have investigated selenoprotein-based treatments for neurological disorders. Several recent ones have recently reported the use of selenoprotein-derived peptides with promising results in brain disorders. The selenopeptide, PSELT, composed of 10 amino acids with a Sec redox center, is protective in a rat model of peripheral nerve neurodegeneration and a MPTP mouse model of PD, but also in a rat model of cardiac ischemia-reperfusion [93,178–180]. Transcriptomic analysis revealed that gene regulation by PSELT after MPP + treatment of

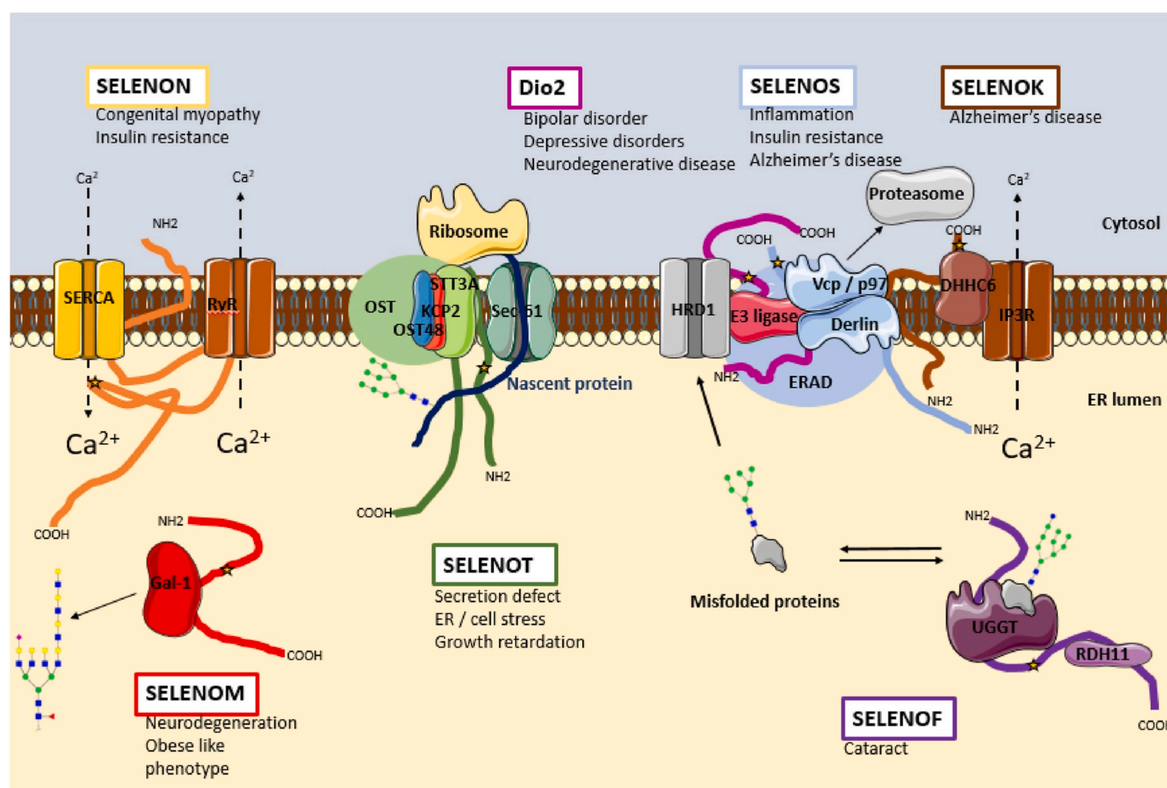


**Fig. 2.** Schematic summary of the different functions performed by the seven ER-resident selenoproteins.
Pathologies and cellular dysfunctions associated with each of them are indicated**. SELENON** is activated by low ER calcium level. This leads to its interaction with SERCA pump and its activation. Its loss of function leads to hypersensibility to ERO1, defect in $Ca^{2+}$ reuptake, and to a disease called SEPN1-related myopathy associated with insulin resistance. **SELENOM** reduces ROS level in cell culture and is able to interact with Gal1, a lectin with higher affinity for galactose, preventing neurodegeneration and promoting neuroprotection in the brain. Deletion of SELENOM leads to obesity without cognitive impairment. **SELENOT** deletion from neuronal precursor leads to brain growth retardation associated to high ROS levels, and increased vulnerability to neurodegeneration. It interacts with the OST complex and modulates *N*-glycosylation. Its inhibition leads to secretion defects and ER stress in endocrine cells. **Dio2** catalyzes the deiodination of T4 (3,5,3′,5′-tetraiodothyronine) into T3 (3,5,3′-triiodothyronine). DIO2 in the brain may be a determinant of well-being and neurocognitive function. The Thr92Ala mutation, a well-studied polymorphism present in 12–36% of the population, leads to ER stress and hypothyroidism. This mutation is presumably responsible of a decrease of DIO2 through ubiquitination by E3 ubiquitin ligase and degradation by the proteasome. **SELENOS** inhibition increase Tau aggregation. It is involved in C99 degradation through its interaction with ERAD complex involved in clearing of misfolded glycoproteins, and its expression correlates with NFTs from post-mortem human brain. SELENOS upregulation can also lead to insulin resistance. **SELENOK** interacts with SELENOS and ERAD, limiting ER stress. It also interacts with DHHC6, a protein responsible for IP3R palmitoylation, a necessary step for its stabilization. It is believed that this link with $Ca^{2+}$ regulation supports microglial migration and Aβ deposit clearance in AD. **SELENOF** is a partner of UGGT, a folding sensor of the ER transferring a glucose residue to the A branch of oligomannoses from misfolded glycoproteins to make it join the quality control process. If the protein isn't correctly folded after a few cycles, it will join the ERAD pathway. SELENOF deletion in animal leads to an early age cataract. This could be due to an increase of misfolded protein or to the lack of interaction with RDH11, a protein involved in vitamin A metabolism.

neuroblastoma cells is positively correlated with that after resveratrol treatment. A second selenopeptide, Tat SelPep, has been derived from SELENOP. Tat SelPep contains two Sec residues, crosses the mouse blood-brain barrier, and protects against ferroptosis and cell death by stimulating GPX4 expression after stroke [32]. These peptides may be more specific than selenium supplementation [181] or intravenous hydroselenide injection [182], with fewer side effects. A better understanding of their mechanism could lead to the development of useful therapeutic tools specifically targeting $Ca^{2+}$ handling proteins and protein quality control or degradation, similar to chaperone therapies [183].

### Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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