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Review article

Selenoprotein S: A versatile disordered protein

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ABSTRACT

Selenoprotein S (selenos) is a small, intrinsically disordered membrane protein that is associated with various cellular functions, such as inflammatory processes, cellular stress response, protein quality control, and signaling pathways. It is primarily known for its contribution to the ER-associated degradation (ERAD) pathway, which governs the extraction of misfolded proteins or misassembled protein complexes from the ER to the cytosol for degradation by the proteasome. However, selenos's other cellular roles in signaling are equally vital, including the control of transcription factors and cytokine levels. Consequently, genetic polymorphisms of selenos are associated with increased risk for diabetes, dyslipidemia, and cardiovascular diseases, while high expression levels correlate with poor prognosis in several cancers. Its inhibitory role in cytokine secretion is also exploited by viruses. Since selenos binds multiple protein complexes, however, its specific contributions to various cellular pathways and diseases have been difficult to establish. Thus, the precise cellular functions of selenos and their interconnectivity have only recently begun to emerge. This review aims to summarize recent insights into the structure, interactome, and cellular roles of selenos.

1. Introduction

Selenoprotein S (selenos) was first discovered in 2001 as a differentially expressed gene in the liver of type-2 diabetic animals, suggesting a potential link between selenos and metabolic disorders [1]. It was originally named Tanis, but as its cellular roles began to emerge it was also called valosin-containing protein (VCP)-interacting membrane protein (VIMP) and then renamed selenoprotein S (SEPS1, SelS). Since 2015, the community-agreed name has been selenoprotein S (gene: SELENOS, protein: selenos, UniProt Q9BQE4) [2]. Selenos was first recognized as a selenoprotein in 2003 [3]. Selenoproteins are enzymes relying on the rare amino acid selenocysteine (Sec) for their catalytic activity [4]. The physiochemical properties of Sec, such as its low pKa, high nucleophilicity, high polarizability and low redox potential, bestow selenoproteins with high catalytic efficiencies [5,6]. Many selenoproteins have cellular roles in redox pathways, particularly those associated with the management of reactive oxygen species (ROS). ROS are both a cause of molecular damage associated with aging and signaling molecules that modulate protective pathways. Although the number of selenoproteins in each organism is low, they are nonetheless cardinal for health [7,8].

1.1. Localization and expression of selenos

Selenos is present in all tissues and cells; however, according to the human protein atlas, its expression is highest in eight tissues: appendix, colon, duodenum, pancreas, placenta, rectum, small intestine, and tonsil. It is a membrane-bound protein and endogenous selenos was reported to reside in the ER membrane, the perinuclear space, and sections of the Golgi [9]. The pool of selenos in the perinuclear region may turnover slower than that at the ER membrane.

A circulating selenos was identified in the serum of human subjects [10]. That form is secreted by hepatoma HepG2 cells but not by other cells examined [10,11]. Western blot assays confirmed that the circulating selenos has the same molecular weight as the full-length membrane-bound form [11]. Selenos was primarily associated with very low-density lipoproteins (VLDL), found at higher levels in the serum of diabetic patients. Additionally, levels of circulating selenos were

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negatively correlated with lower plasma glucose levels due to fasting. (The relation between selenos and diabetes was reviewed in Ref. [12] and is discussed later on). However, selenos was not detected in proteomics-based studies of plasma proteins (secretome) using proximity ligation techniques [13]. Thus, additional experiments are needed to establish the presence and physiological relevance of circulating selenos.

Changes in selenos's expression were observed in a variety of conditions and appear to be regulated by several mechanisms. The promoter region of selenos has an ER stress-response element (ERSE) [14,15] that binds the transcription factors which regulate ER stress [16]. Thus, selenos expression is increased by 2- to 4- fold in response to ER stress. The promoter also contains an NF-κB binding site [17] tying it to the NF-κB signaling pathway. Reports show that selenos is upregulated by tunicamycin, an ER stress inducer that inhibits N-linked glycosylation [18–27]; by thapsigargin, an ER stress inducer that is a non-competitive inhibitor of the sarco/endoplasmic reticulum calcium ATPase (SERCA) [21,24–26]; by β-mercaptoethanol [28]; by hydrogen peroxide [29]; by dexamethasone [27]; by palmitate, which leads to lipid-induced oxidative and ER stress [30]; and by the cytokines TNF-α and IL-1β [14]. In contrast, TGF-β1 and glucose reduce selenos's expression [31]. Selenos is expressed in the liver in inverse proportion to circulating glucose and insulin levels [15,32] and in direct proportion to plasma triglyceride concentrations [1]. In human aortic endothelial cells, however, high glucose, high-oxidized low-density lipoprotein, and high glucose combined with high-oxidized low-density lipoprotein all led to selenos overexpression [33]. Selenos expression is also regulated by the availability of selenium [34], and it was shown that sodium selenite upregulation of selenos took place via the heat shock transcription factor 1 (HSF1) binding to the selenos promoter [35]. Lastly, deficiency of its protein partner, selenoprotein k (selenok, see later) upregulates selenos expression [36]. This extensive list corresponds with the reports that at least some of selenos's cellular roles are tied to protein quality control and lipid storage.

1.2. Structural features of selenos

Selenos is an ER-residing membrane protein [3], considered a type III single-pass transmembrane protein [37]. Initially, selenos was believed to be segmented into a short luminal segment (residues 1–25) with an unknown secondary structure, a hydrophobic α-helix (residues 26–48), and a cytoplasmic segment (residues 49–189) (Fig. 1A) [38]. The cytoplasmic segment was thought to contain a long α-helix between residues 49 and 122 as well as an unstructured region between residues 123 and 189. To avoid the need to provide a mimetic membrane environment, many studies have utilized the segment consisting of residues 49 to 189, which is not hydrophobic. Conversely, AlphaFold2 [39] predicts that selenos has three helices before the intrinsically unstructured segment (Fig. 1B): residues 1–33 (helix 1), residues 34–69 (helix 2), and residues 72–124 (helix 3). Of these helices, helices 1 and 2 have an amphipathic character. Hence, in our opinion, selenos may not be transmembrane after all but potentially a monotopic membrane protein, that is, it strongly interacts with only a single leaflet of the membrane but does not cross the bilayer. Nevertheless, while selenos in experiments strongly associated with membranes, the anchoring of selenos to the lipid bilayer has yet to be investigated.

Residues 125–189 constitute an unstructured region rich in glycine, proline and polar residues. Such composition is the hallmark of intrinsically disordered proteins (IDPs), lacking stable secondary and tertiary structure. The reactive Sec is near the C-terminus at position 188 (Figs. 1–3). This Sec and a neighboring cysteine at position 174 form an intramolecular selenylsulfide (S–Se) bond that creates an internal loop at the C-terminus [40,41]. So far, the only experimental structural information available is for residues 49–123, and for a short peptide at the C-terminus. There is no structural information thus far about the full-length selenos or its oligomeric state. The data availability is

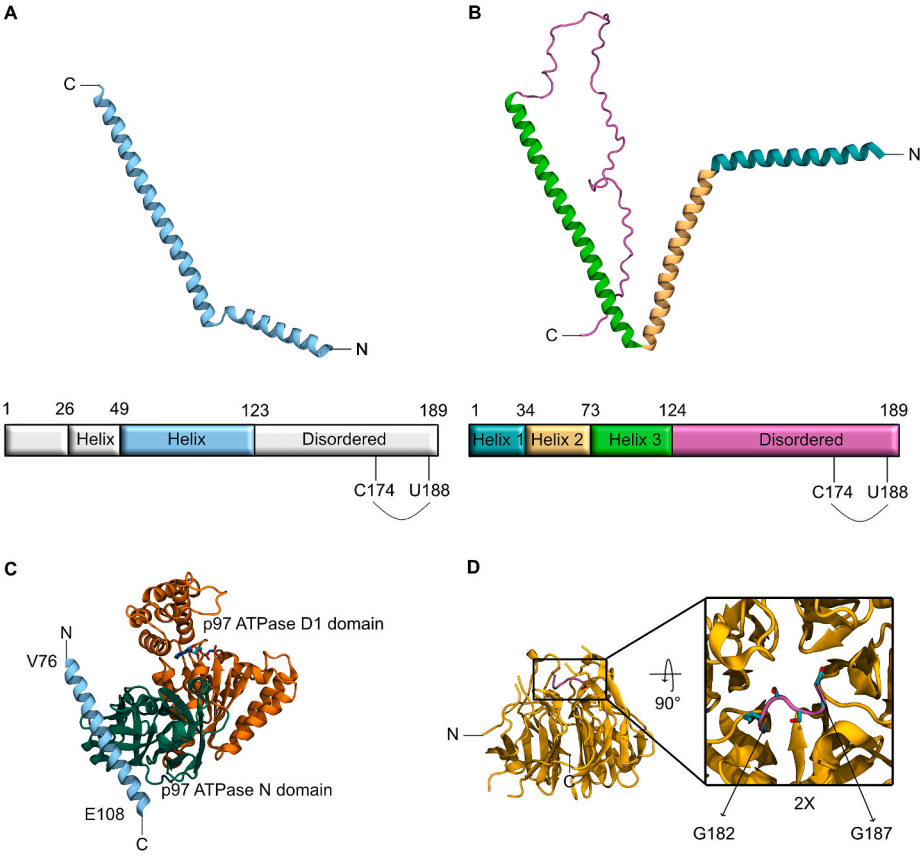

Fig. 1. Structural information about selenos. A) Segmentation of selenos originally predicted a short unstructured N-terminal segment, a single-pass transmembrane helix, followed by a cytosolic soluble helix and an unstructured C-terminus. The crystal structure of selenos residues 49–122 shows a long helix with a kink before Pro71 (PDB ID: 5KIU). B) Segmentation of selenos by AlphaFold2 divides selenos into three helices and an unstructured C-terminus. The structural model of full-length selenos by AlphaFold2 is colored-coded according to the secondary elements identified by the algorithm. C) A crystal structure (PDB ID: 5KIY) showing selenos residues 76–108 (blue) bound to p97 ND1 domain (p97 N-domain in green, and its D1 domain in orange). D) The crystal structure (PDB ID: 6DO4) of selenos residues 182–187 (purple) bound to KLHDC2 (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

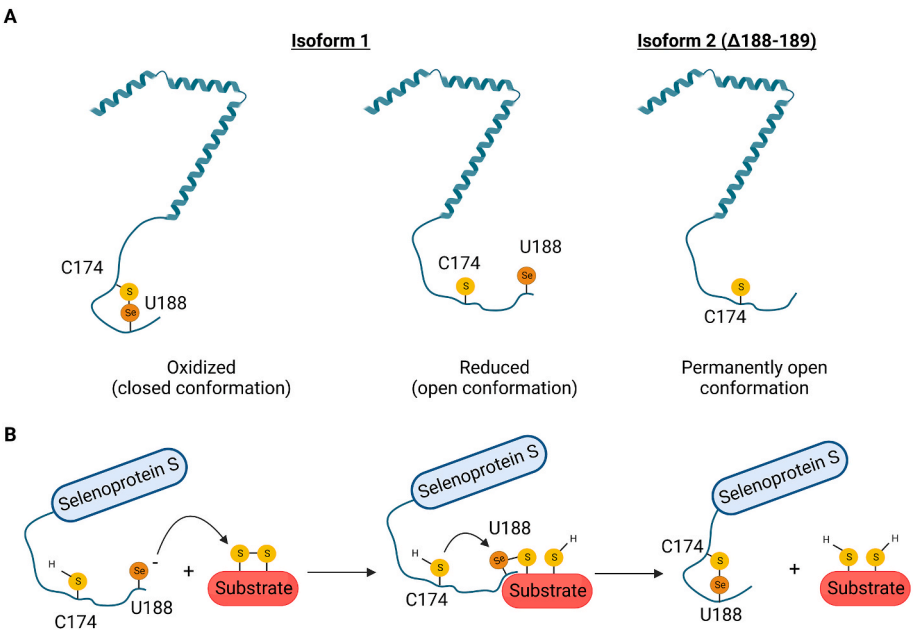

Fig. 2. Selenos's redox-active loop and reductase reaction. A) Selenos has a disordered segment (residues 123-189) housing the catalytic residues Cys174 and Sec188. An intramolecular selenylsulfide bond between these two residues forms a "stapled" loop conformation and controls access to the Sec. Full-length selenos (isoform 1) can be either oxidized, with the loop in a "stapled" "closed" conformation, where the Sec is unavailable to react with substrates, or reduced, with the loop in an "open" conformation, where the Sec is available to react with substrates. By contrast, isoform 2, which is missing the Sec and the last residue, is permanently in the "open" conformation but inactive. B) Selenos's reductase reaction. In the reduced state, Sec188 selenolate attacks the substrate's disulfide bond and forms a transient intermolecular selenylsulfide bond between the selenos and the substrate. The resolving cysteine, Cys174, attacks Sec188 in this intermolecular selenylsulfide with the substrate. Once the intramolecular bond between Cys174 and Sec188 reforms, the substrate can dissociate. Thus, at the end of the reaction, selenos is oxidized and in the "closed" loop conformation while the reduced dithiol substrate is released.

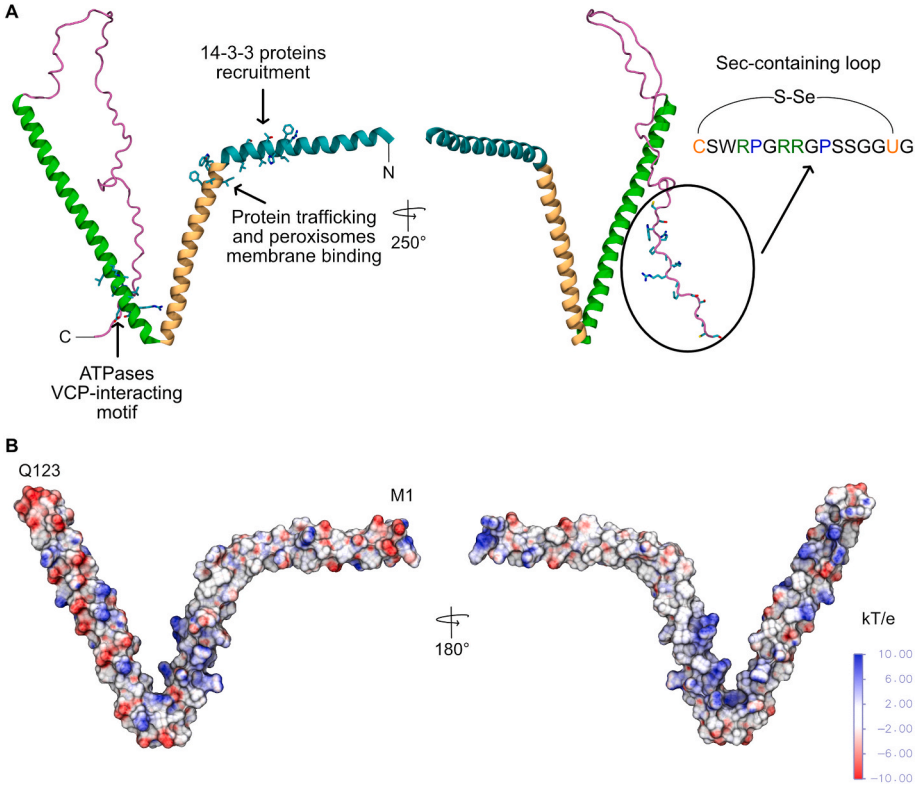

Fig. 3. A) Key predicted protein interaction sites from the Eukaryotic Linear Motif resource for functional sites in proteins (http://elm.eu.org/) mapped on selenos's AlphaFold2 structure. B) Electrostatic surface potential of the helical segment (residues 1–123 of the AlphaFold2 model) generated with APBS electrostatics. A hydrophobic area is present on helices 1 and 2, as well as a positively charged patch. Helix 3 is highly charged, with alternating charges stabilizing the helix.

summarized in Table 1.

Segment 49–122 is helical and binds the ATPase p97, using a recruiting sequence between residues 78 and 88 [42]. The segment is rich in interweaving Lys, Arg and Glu that form strong electrostatic interactions and stabilize the helix (Fig. 3). This segment has four X-ray crystallography derived structures: two structures of the segment itself (PDB entries 2Q2F and 5KIU) and two structures of the segment bound to the ATPase p97 N-terminal and D1 domains (5KIW and 5KIY) [42]. These structures demonstrate considerable flexibility at a hinge region between residues 70 and 73. The segment 49–189 U188C was studied by NMR spectroscopy [43]. (Because sulfur and selenium share many physiochemical properties, the substitution of Sec into Cys is common in studies of selenoproteins). The NMR investigations could not resolve chemical resonances arising from residues 72–123. This might be due to

Table 1
Available information regarding the structure of selenos.

Selenos residues	Selenos alone or with protein partner	Accession number	Reference
52–122	Alone	PDB ID 2Q2F	Uncited PDB release
49–122	Alone	PDB ID 5KIU	[42]
49–122	ND1 domain of p97 variant L198W	PDB ID 5KIW	[42]
49–122	ND1 domain of p97 variant A232E	PDB ID 5KIY	[42]
182–187	Kelch domain-containing protein 2	PDB ID 6DO4	[44]
49–189, U188C Oxidized state	Alone	BMRB 18176	[43]
49–189, U188C Reduced state	Alone	BMRB 18177	[43]

the presence of a coiled-coil region between residues 80 and 120 that might lead to homo- and hetero-oligomerization or associations with protein partners. If so, then this region can engage in a monomer-dimer exchange on the timescale of NMR detection, thus interfering with detection. Redox-dependent conformational changes were observed only in the C-terminal segment, and reduction of the disulfide in selenos 49–189 U188C had little effect on the overall structure. Lastly, there is a crystal structure of selenos's residues 182–187 interacting with the kelch domain-containing protein 2 (KLHDC2), which will be discussed when considering the degradation of truncated selenos [44]. The structure of full-length selenos remains elusive because, as a small unstructured membrane protein, it poses a formidable challenge for existing experimental techniques.

1.3. Selenos isoforms and regulation of selenocysteine's insertion

The incorporation of Sec in selenoproteins is coordinated by a 3′ UTR stem-loop structure, the selenocysteine insertion sequence (SECIS) [45]. In addition, the insertion of Sec in selenoproteins requires a dedicated suite of proteins to reprogram the opal codon UGA to encode for Sec [46]. In the case of selenos, Sec incorporation is regulated by a selenoprotein S positive UGA recoding (SPUR) element at the 3' UTR [47]. The SPUR is required for the proper readthrough of the UGA-Sec codon. This fine level of control over Sec incorporation appears to be required because of the limited bioavailability of selenium in the cell. Sec incorporation in at least four other human selenoproteins, but potentially many more, is similarly regulated [48–51]. In addition to the SPUR element, the presence of Sec is also regulated by splicing. The full-length selenos (isoform 1; residues 1–189) has Sec at position 188, whereas the second isoform deprived of residues 188–189 (isoform 2; selenos Δ188-189) does not [9]. Selenos (Δ188-189) resulted from alternative splicing that led to an mRNA without the SECIS element. The second isoform, selenos (Δ188-189), was present in all cell lines tested, at about 5–16% of the transcript. A separate study confirmed the presence of the SECIS-lacking mRNA and reported that the ratio between the two isoforms was similar in all tissues [52]. A post-transcriptional mechanism that controls selenoprotein expression through the presence of the Sec-encoding codon has been reported so far only for one other selenoprotein–selenoprotein N. There, the mRNA missing the Sec codon was targeted for degradation by the nonsense-mediated mRNA decay [48].

Selenos (Δ188-189) is also generated not only by splicing but also by premature termination of translation at the UGA codon. It is recognized by multiple ubiquitin ligases (see section 1.6) and degraded through the C-end degron pathway [53]. The full-length selenos evades this fate. It may appear as a discrepancy that this second isoform selenos (Δ188-189) is degraded when generated by premature translation termination yet is still produced in the cell by splicing; this may be reconciled by considering selenos's functions related to cellular stress. It is feasible that when multiple stress-related selenoproteins are upregulated, selenium bioavailability for Sec synthesis does not match demand. Selenos, however, most likely has some functions that require the Sec and others that do not. Under such conditions, isoform selenos (Δ188-189) could be used to transiently combat the stress.

1.4. Enzymatic activity and selenos's redox-active loop

All characterized selenoproteins exploit their Sec for an enzymatic function, primarily as oxidoreductases [5]. Because Sec is not easily destroyed by irreversible oxidation, selenoproteins are seen as resilient to damage by ROS [54]. As a selenoprotein, selenos is most likely an enzyme, but unusually, its Sec is positioned in a disordered region (Figs. 1 and 2). This potentially grants selenos membership in a small and distinctive group of proteins–IDPs that are enzymes. Only a handful of IDPs possess enzymatic activity [55].

In vitro selenos is an efficient disulfide reductase [40,41] (Fig. 2). Yet, despite many elegant cellular assays, neither the physiological substrates nor the role of selenos's enzymatic function in the cell has been identified. Furthermore, as mentioned above, in addition to the full-length selenos (isoform 1; residues 1–189) with Sec at position 188, there is a naturally occurring isoform without Sec that is deprived of residues 188–189 (isoform 2; selenos Δ188-189) [9]. This suggests that selenos's Sec is not essential for all cellular roles (Fig. 2).

The aforementioned placement of Sec in a disordered region of selenos is highly unusual because selenoproteins tend to utilize Sec in CXXU/CXU motifs, most notably in a thioredoxin fold [4]. Equally unique is that selenos's Sec is part of a 15-amino-acid-long "stapled" loop formed by a selenylsulfide bond between the Sec and the resolving Cys at position 174 (Fig. 2A). The intramolecular selenylsulfide bond controls the conformation of this "stapled" loop at the C-terminus of selenos (C_{174}SWRPGRRGPSSGGU$_{188}$G), and only reduced selenos will expose the Sec and allow it to react with substrates (Fig. 2). Of note are the two prolines in the middle of the segment, as they were shown to be essential for binding protein partners *in vivo* [26]. Thus, it seems that the "stapled" loop governs access not only to Sec but possibly also access to a linear binding motif made of these prolines and nearby arginines.

The formation or breakage of the selenylsulfide bond regulates the accessibility of Sec and allows it to react with substrates (Fig. 2A). The reformation of the intramolecular selenylsulfide bond of selenos yields the "closed" stapled loop conformation. Despite the length of the loop, the selenylsulfide bond is rapidly reformed (measured experimentally in our publication [41]). This allows for the rapid restoration of the "closed" conformation even in this surface-exposed loop with a long linker between the redox active residues. Therefore, the presence of Sec not only provides high reactivity but may also enable fast recycling of the "closed" loop conformation. It remains unknown whether the spacing residues (175–187) play a role in coordinating interactions with proteins and which loop conformation(s) is/are responsible for such interactions, especially since selenos's isoform 2, lacking the Sec, is perpetually in the "open" conformation, with exposed residues 175 to 187 (Fig. 2A). Furthermore, an extensive proteomic study failed to identify protein partners that specifically interact with the disordered C-terminal region in which the Sec resides [56]. Hence, the biological role of Sec remains undetermined. The intramolecular selenylsulfide bond of selenos can be reduced by a cellular redox system such as the thioredoxin/thioredoxin reductase system [40].

1.5. Short linear motifs and posttranslational modifications

Selenos is rich in short linear motifs (SLiMs) [57] (Fig. 3), which are protein interaction hubs that frequently appear in IDPs and dictate their interaction with protein partners [58]. SLiMS are short (3–10 residues), and their binding can be governed by posttranslational modifications

(PTMs). These PTMs endow proteins with different functions and can rewire protein interactions according to cellular needs [59]. Like many other ERAD proteins, selenos was reported to be ubiquitinated. Ubiquitination of Lys150 is tied to selenos degradation (see next section) [60]. Ubiquitination of Lys77, Lys134, and Lys150 changes in response to SARS-CoV-2 infection, with the most dramatic change reported for Lys150 [61]. In addition to ubiquitination, there are multiple sites in selenos that are predicted to be phosphorylated; however, at this point only Ser140 has been shown reproducibly in numerous high-throughput studies to be phosphorylated. While the responsible kinase has not yet been identified, bioinformatic-based predictions suggest that a proline-directed kinase (e.g., MAPK) phosphorylates that site on selenos. The predictions of key protein interaction hubs using the eukaryotic linear motif resource for functional sites in proteins [58] are summarized in Fig. 3.

1.6. Degradation

While the average half-life of selenos *in vivo* was determined to be 6 ± 1 h [62], the two isoforms are degraded by two different pathways. Selenos, terminated at position 188 due to failed decoding of the UGA codon (selenos Δ188-189), is degraded by the cullin-RING ubiquitin E3 ligases kelch domain-containing protein 1 (KLHDC1) and kelch domain-containing protein 2 (KLHDC2) [44,53,63]. KLHDC2 recognizes selenos (Δ188-189) C-terminus diglycine at residues 186–187, which act as a C-terminal degron. A crystal structure of selenos's residues G_{182}PSSGG_{187} bound to KLHDC2 was obtained by X-ray crystallography (Table 1 and Fig. 1D) [44]. KLHDC2 has a propeller-like structure and selenos C-end degron peptide binds in the center between the 6 propeller blades. Full-length selenos is spared from degradation [53]. The interested reader can find additional details in the review about selenoprotein degradation [64].

In contrast, full-length selenos is degraded through ubiquitination by the peroxisome proliferator-activated receptor γ (PPARγ), a central regulator of adipogenesis [60]. PPARγ is an E3 ubiquitin ligase. It directly interacts with selenos using its ligand-binding domain and poly-ubiquitinates selenos's Lys150, which is tied to selenos degradation. Using purified PPARγ *in vitro* for ubiquitination assays, it was established that ubiquitination took place *in vitro* even in the absence of selenos's hydrophobic segment (residues 26–48). The binding of selenos to PPARγ required selenos's residues 1–122, suggesting that while residues 24–48 are not critical, other residues in that segment are.

1.7. Consequences of selenos knockout

SELENOS is not an essential gene; in fact, organisms have a high tolerance for its inactivation [65]. Currently, two selenos mouse knockouts have been reported: one was a knockout on an organism-wide level [66], and the other was a knockout limited to the hepatocytes [66,67]. In the first model, only subtle changes in oxidative stress were observed. However, the contractile function of fast-twitch hindlimb muscles was impaired [66]. In the second model, the hepatitis deficiency of SELENOS exacerbated hepatic steatosis (abnormal retention of fat) and insulin resistance [67].

A SELENOS CRISPR knockout was reported in different cell lines. A Caco-2 cell line was used to investigate the contribution of selenos to SARS-CoV-2 infectivity [68]. In this Caco-2 knockout, the lack of endogenous selenos seemed to have no impact on overall cell health, shape, or proliferation. By contrast, cell arrest at G1 cycle and apoptosis were reported for selenos's knockdown in 3T3-L1 [24,25] and MIN6 insulinoma cells [69].

1.8. Non-mammalian selenos

However, there are members of the selenos family that underwent Sec-to-Cys substitution (unpublished observations). There is only one selenos from parasites that has been characterized. Selenos is a highly conserved protein [70]. In vertebrates, selenos's ancestor already contained Sec [71,72]. However, there are members of the selenos family that underwent Sec-to-Cys substitution (unpublished data). There is also one selenos from parasites that has been characterized. This *Plasmodium falciparum* selenos (*Pf*Sel4) was localized to the ER membrane and was found to protect proteins from damage by ROS [73]. However, the relationship between selenos and ROS is complicated. In mammalians, it depends on the cell type because the knockdown of selenos led to decreased cellular ROS levels in differentiating C2C12 myotubes, whereas the levels increased in proliferating myoblast [30].

2. The interactome of selenos

2.1. Overview of selenos's interactome

To identify the cellular roles of proteins, their interaction partners must first be determined. Selenos's extensive interactome has been mapped using both selenos dedicated analysis and high-throughput investigations. An affinity purification and mass spectrometry-based identification was used in two separate publications [56,74]. In the first study, the ERAD networks were mapped, establishing the presence of multiple EARD components (see section 2.2) [74]. The second study focused specifically on selenos using immunoprecipitation to survey selenos variants [56], and included crosslinking of complexes and validation. A study of the changes that take place in the transcriptome when selenos is silenced identified genes that are influenced by selenos's absence and thus possibly linked to it by a common action or pathway [75]. These studies reported that well over 200 proteins interact with selenos. Most of these proteins are members of large protein complexes involved in protein degradation, glycosylation, vesicle trafficking, synthesis and regulation of lipids and fatty acids, and transport to the nucleus [56,75]. High-throughput studies such as a proximity based mapping of the proteome organization in human cells also demonstrated the presence of selenos in these protein assemblies [76]. However, many of these putative protein partners may not be directly bound to selenos, because prevalent methods of establishing these interactomes cannot distinguish between proteins that bind selenos itself from proteins that are only affiliated with the same complex. The task of establishing directly interacting protein partners is further complicated by the fact that interactomes acquired by different methods agree on the same protein complexes but not the specific proteins. Furthermore, the intrinsically disordered segment of selenos (residues 125–189) may–like many other IDPs–bind protein partners only weakly, which adds to the challenge of identifying all proteins that interact directly with selenos. In that respect, selenos resembles other membrane-bound IDPs that contain multiple protein interaction sites. These hydrophobic proteins function as recruiters or adaptors in such diverse processes as modulating the activity of membrane proteins and complexes, linking organelles or protein complexes, and governing membrane shape [77].

Yet, selenos's role as a protein recruiter in different cellular pathways is most likely not its only function, because as a member of the rare group of selenoproteins, it contains the highly reactive Sec and thus should be an enzyme (see section 1.4). Although we do not yet understand the details of selenos's associations with all of these diverse complexes, a growing number of proteins have been shown to interact directly with selenos using immunoprecipitation, biochemical assays, and structural biology. These better-characterized proteins partners and their associations with selenos are discussed in the following.

2.2. Selenos's partners in the ER-associated degradation pathway

The ER is responsible for folding and posttranslational modification of about one-third of the total proteome in eukaryotic cells. The accumulation of misfolded proteins in the ER leads to ER-stress, and triggers the unfolded protein response (UPR), which tightly controls protein

fidelity [78]. Because misfolding, aggregation, misassembly, and improper degradation of proteins have been recognized as fundamental aspects of aging and neurodegenerative diseases, the UPR plays a central role in combating both. Arguably a key UPR process is the ERAD [79], which governs the extraction of misfolded proteins or misassembled protein complexes from the ER membrane and lumen, their transport to the cytoplasm, polyubiquitylation, and finally degradation by the proteasome (Fig. 4) [80,81]. As an important part of the cellular 'waste management,' the ERAD contributes significantly to proper cellular homeostasis [82,83].

In humans, selenos is relevant for routine ERAD functions as well as the rapid response to stress [38,84]. As detailed above, ER stress leads to an increase in the cellular levels of selenos. Inversely, it was found that, upon the silencing of selenos, ERAD substrates accumulated [20,26]. Likewise, the ER is stressed if selenos is downregulated or sequestered by protein partners [36,85]. However, ER stress is not a universal consequence because it is not induced by selenos knockdown in some of the examined cell lines [22,75]. In the ERAD (Fig. 4), selenos was shown to interact with derlin-1 and -2 and the AAA ATPase valosin-containing protein (p97, VCP) that provides the energy for extracting and unfolding ERAD substrates [38,84,86]. Selenos is particularly important for p97 recruitment because when selenos was silenced p97 was unable to join the ERAD complex and process substrates [20,26].

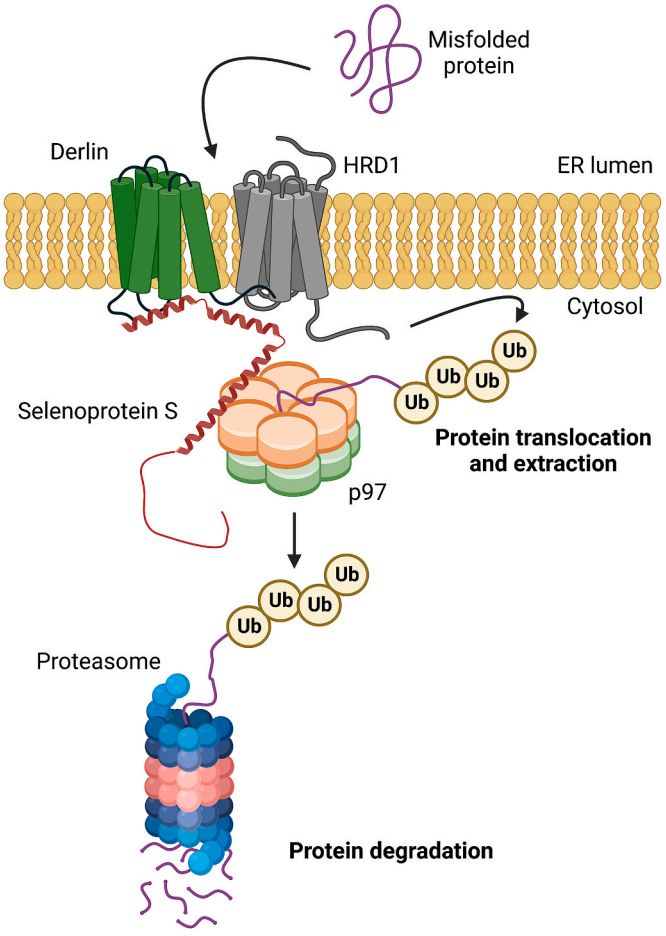

Fig. 4. The role of selenos in the ERAD pathway. Misfolded proteins are translocated through a channel composed of several transmembrane proteins (here, only derlin and HRD1 are shown) using the ATPase p97, which provides the energy to translocate proteins through the channel. Substrates are subsequently degraded by the proteasome. Selenos associates with derlin-1 and -2, and recruits p97 to the complex.

2.2.1. Derlins

Derlins are inactive members of the rhomboid intramembrane-cleaving serine protease family [87]. Most rhomboids have lost the ability to cleave substrates (rendering them pseudoproteases) but have preserved their basic capability of recognizing transmembrane helices. There are multiple examples where rhomboids' interactions with target proteins in the membrane contribute to the stabilization of proteins or the regulation of signaling pathways [88]. Derlins contribute to multiple degradation pathways and are not exclusive to those specialized in membrane protein degradation [89,90]. A cryo-electron microscopy structure of the yeast core ERAD complex [91] has led to the hypothesis that ERAD rhomboids similar to derlin may distort the lipid membrane and thus reduce the energy barrier and facilitate extraction of ERAD substrates passing through the ER membrane [92]. Unfortunately, because yeast has no selenoproteins and no homolog of selenos, these findings shed little light on the role of selenos and its binding to derlins in the human ERAD pathway.

Multiple studies have shown that in mammalian ERAD complexes, selenos binds derlin-1 and -2 [18,38,56,74,84] to form a complex of derlin, p97, and selenos [93]. Many rhomboid proteins have partners that regulate their function [94]. Thus, it is not surprising that derlin-1 and -2 have accessory proteins such as selenos; however, neither the mode of the selenos-derlin interaction nor the mechanistic significance of this binding are currently known. For example, selenos binding to derlin's transmembrane helices could regulate the entrance of client proteins, or the ability of derlin to act as an unfoldase to distort helical segments. By contrast, if selenos binds to the cytoplasmic tail of derlins (where there is a known docking site for p97 [95]), it could assist the recruitment of additional accessory proteins. What is clear, though, is that selenos is frequently reported to associate with derlins, and consequently recruits p97 to the ERAD complex (Fig. 4), and specifically to the contact point with derlins.

2.2.2. The AAA ATPase valosin-containing protein (p97)

p97 is an AAA+ protein [96] that provides the energy for segregating and extracting misfolded or misassembled proteins through the protein-conducting membrane channel (often termed the 'dislocon'). Thus, p97 serves as the bridge between the dislocon and the proteasome (Fig. 4). Since p97 takes part in multiple cellular processes, the timing and specific localization to different complexes is tightly governed. While selenos is one of several adaptor proteins responsible for spatio-temporal recruitment of p97 to the ERAD, it is an important recruiter because, when selenos is depleted, binding of p97 to the ERAD is significantly reduced [42]. Selenos is required for bringing p97 to the ER membrane regardless of ER stress [26].

Structurally, p97 is composed of three domains: the N-terminal domain (NTD) and the D1 and D2 ATPase domains [97]. These domains, as well as the notches, nooks and crannies that are formed between them and across the homohexamer ring interface provide binding locations for more than 40 protein partners. These adaptors are rapidly exchanging [98], and profoundly modulate p97 ATPase activity and conformation [99–101]. Most adaptors bind the NTD and NTD-D1 interface, while substrate processing factors with enzymatic activity, such as deubiquitylation and sugar removal, typically bind the C-terminus of p97. For in-depth reviews on how p97 aids unfolding of proteins, see Refs. [102,103].

Selenos employs residues 69–108, which are part of the highly charged helix 3 in the AlphaFold2 model, to interact with the p97 NTD [42]. This segment includes a p97/valosin-containing protein (VCP)-interacting motif (VIM, residues 77–88), a linear motif present in multiple p97 adaptor proteins [104]. This stretch was shown to interface with the p97 NTD in an X-ray crystallography structure of selenos residues 49–122 bound to active variants of the p97 ND1 domain (Table 1 and Fig. 1C). By recruiting p97 through the ND1 domain, selenos not only locates p97 to the membrane but also prevents the binding of competing effectors. Furthermore, p97 conformation depends on the

bound nucleotide, with the ATP-bound p97 interacting the strongest with selenos [42].

Intriguingly, selenos may interact with p97 using not only its third helix but also the disordered C-terminal region [26]. In studies of the recruitment of p97 to ER membranes, selenos's residues 168 and higher were shown to be essential. Even when the VIM motif was deleted, selenos was capable of recruiting p97 to the membrane. The C-terminal residues 177–185 were essential for the interactions. Similarly, when the prolines in the C-terminal segment (Pro178 and Pro183) were deleted, p97 was no longer recruited to the membrane. This can be attributed to the internal structure of the C-terminal loop, and suggests that the prolines are part of the p97 recruitment motif. It was not possible to distinguish between the actions of selenos, selenos U188C, and selenos (Δ188-189) in the degradation of substrates, possibly due to the redundancy of the ERAD pathway [26]. The study also demonstrated that the hydrophobic segment (residues 26–48) was not needed for p97 recruitment. When it was deleted, the selenos variant was still able to interact with p97 but lost its membrane association and was instead found in the cytoplasm [26]. Overall, all current data support the view that helix 3 of selenos and parts of the C-terminal loop (residues 177–185) play important roles in p97 recruitment.

2.2.3. Selenoprotein K (selenok)

Another repeatedly identified protein partner of selenos, selenoprotein K (selenok, previously called SelK), binds the same dislocon partners as selenos [21,26,29]. However, selenok's specific role in this pathway is unknown. Like selenos, selenok contains a Sec and thus should be an enzyme. It can form a diselenide (Se–Se) bond *in vitro*, and has weak lipid peroxidase activity [105]. Yet, this does not appear to be its primary enzymatic activity, which remains to be established. Selenok binds the ER palmitoyl transferase DHHC6 and partake in palmitoylation [106,107].

Ample evidence suggests that the functions of selenok and selenos are linked: each can be extracted from the cell using the other as bait [18]; their expression and degradation are similarly regulated [60,108]; deficiency of selenok upregulates selenos [36]; and they share SLiMs and the same ERAD protein partners [21,26]. Yet, they do not interact directly, and require p97 to form a complex [21]. Recruitment of p97 by selenos to the ERAD was a prerequisite for selenok binding to p97, but the selenos/p97 complex forms in the absence of selenok. It was also shown that binding of selenok to selenos is not controlled by selenos's redox state and does not involve selenos's residues Cys173 and Sec188 [56]. Because both selenos and selenok bind derlins, it could be that both are accessory proteins involved in regulating substrate recognition or release; however, this remains to be tested.

2.3. Other protein partners of selenos

2.3.1. Importin β

Multiple importins and exportins proteins are present in selenos's interactome [56], although their expression levels are not altered by selenos silencing [75]. While selenos itself has no classical nuclear localization signal, when its hydrophobic residues 24–28 were deleted, the variant selenos was primarily localized in the nucleus [56], possibly suggesting a motif targeting selenos to the nucleus if it is not anchored to the ER membrane.

Importin β was shown to directly bind selenos [109] using a fusion of selenos (glutathione S transferase-selenos) for pulldowns from HEK293 cell lysates. It was also found that the first 297 amino acids of importin were sufficient for the successfully capturing selenos. This suggests that selenos does not interfere with the binding of import cargo. It is possible that selenos binding may be relevant for localizing importin β (and its cargo) to the ERAD complex.

2.3.2. Serum amyloid A-1 protein (SAA1)

The SAA1 protein is involved in signaling within the innate and adaptive immune system to control inflammation [110,111]. Among its many cellular roles are the routing and repair of high-density lipoprotein, cholesterol transport, and the removal of cell membrane debris from sites of injury. It has both secreted (primarily LDL-bound) and cytoplasmic localizations, and is expressed in response to proinflammatory cytokines such as IL-1, IL-6, and TNF-α. It can activate toll-like receptors, RAGE and additional receptors relevant for the response to trauma, infection and other stimuli. When aggregated, SAA1 causes amyloid A amyloidosis, a protein misfolding disease.

When selenos was first identified, it was found through yeast two-hybrid screening to bind SAA1β [1]. This association was also detected in a study of SAA1's role in causing renal interstitial fibrosis by inducing ER stress [85]. That study also reported that SAA1 is transcriptionally activated by the signal mediator STAT3 (signal transducer and activator of transcription 3). In addition, it linked the interactions between the SAA1 and selenos to the ERAD pathway because SAA1 bound selenos competitively, thus preventing the formation of the derlin-1/selenos/p97 complex. Therefore, SAA1 binding to selenos inhibited the ERAD, preventing protein degradation and leading to ER stress.

2.3.3. Proteins that bind the cytoskeleton

Selenos associates with a cytoskeleton-linking membrane protein called cytoskeleton-associated protein 4 (climp-63; p63), which mediates ER interactions with microtubules [112]. Overexpression of selenos led to rearrangement of the ER, while the knockdown of selenos caused ER spreading. The interactions between climp-63 and selenos were mapped by immunoprecipitation and were shown not to require selenos residues 1–73. A segment of selenos, residues 48–189 U188C, was sufficient to sediment with polymerized microtubules. A different study has shown that knocking down selenos led to abnormal expression of adhesion molecules and matrix homeostasis disorder in hypertrophic chondrocytes [22]. The chemotherapy drug paclitaxel, which targets tubulin, reduced selenos promoter activity. In addition, tunicamycin-induced upregulation of selenos was lowered by paclitaxel treatment at both the mRNA and protein levels [113].

3. Selenos in signaling pathways

Selenos has been linked to signaling pathways in multiple studies (see previous reviews about selenos [12,37,114,115] and subsequent publications [22,24,25,69,116–118]). Yet, pinpointing its precise role in these pathways has been challenging due to its interactions with multiple protein partners and complexes and because silencing leads to ER stress. Hence, while the literature points to its involvement in various signaling pathways, the underlying molecular mechanism by which selenos influences these paths was unknown. Recently, however, a study analyzing the transcriptome following selenos silencing illuminated selenos's role in the calcium–calcineurin–NFAT (nuclear factor of activated T cells) signaling pathway (Fig. 5). The study established that selenos was temporarily upregulated following T cell receptor activation in $CD4^+$ effector T cells (Teffs), and that selenos inhibited the production of several inflammatory cytokines [75]. The correlation between selenos expression and cytokine expression is well documented but the underlying molecular connection was mostly unknown [119]. This study demonstrated that selenos in Teffs inhibited the production of inflammatory cytokines by controlling the Ca^{2+}/NFATC2 signaling pathway and regulating the expression of the transcription factor E2F5.

NFAT are a group of transcription factors that regulates genes related to cell cycle, apoptosis, angiogenesis, and metastasis [120]. Normally, NFAT regulatory domains are phosphorylated and inactive, retaining NFAT proteins in the cytosol. Repetitive or prolonged calcium signals lead to dephosphorylation and the translocation of NFAT to the nucleus [121]. The calcium influx that is responsible for NFAT dephosphorization was higher when selenos was silenced. It was found that in that case the phosphorylation of NFATC2 (nuclear factor of activated T cells 2)

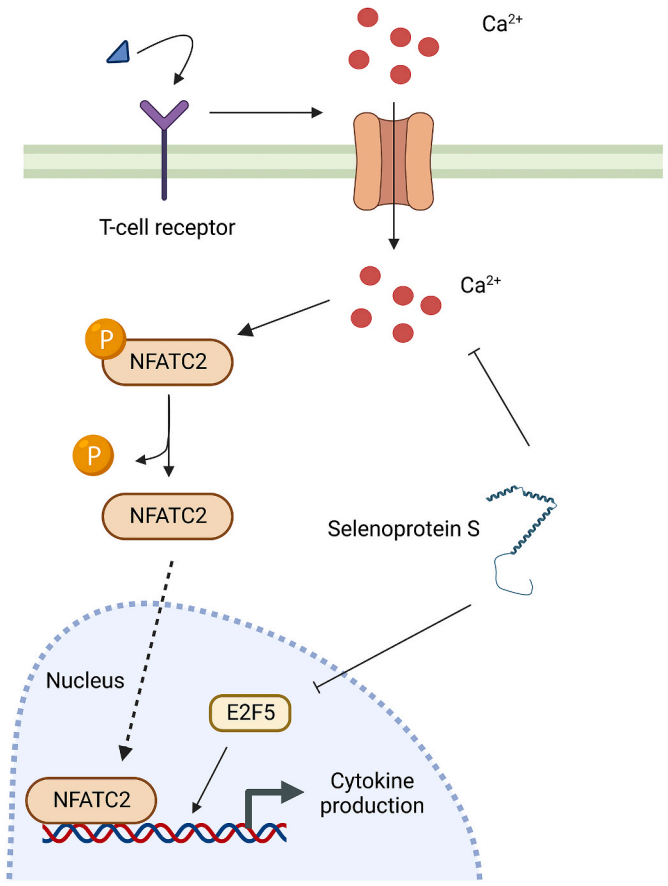

Fig. 5. Selenos as a gene-inhibiting cytokines secretion, adapted from Ref. [75]. Selenos silencing leads to dephosphorylation of NFATC2 and its relocation to the nucleus where it induces the production of cytokines. In addition, silencing upregulates the transcription factor E2F5.

was significantly reduced. The authors suggested that this decrease in NFATC2 phosphorylation was at least in part responsible for the upregulation of cytokine expression.

In addition to altering NFATC2 phosphorylation, the expression level of the transcription factor E2F5 was also modified. E2F5 binds promoters with E2F-binding elements, which are involved in cell proliferation [122,123]. In addition, the expression of genes for NF-κB, NFAT, and MAPK signaling pathways was influenced by selenos silencing. Overall, this study revealed the cellular pathways influenced by selenos silencing as well as a connection to the NFAT signaling pathway. However, to identify exactly how selenos influences NFATC2 phosphorylation or E2F5 expression, further identification of direct interactors is needed.

Another link between selenos and cytokines is its partner SAA1, which has been shown to act in the STAT3 pathway [85]. STAT3 is a major signaling pathway in which the dimerization of the transmembrane protein Janus kinase (JAK), leads to phosphorylation of different members of the STAT protein family, and their subsequent translocation to the nucleus to regulate transcription [124]. STAT3 itself is involved in multiple processes involving cytokines and growth factors, e.g., cell proliferation, differentiation, apoptosis, and immune function [125].

There is no evidence, though, that selenos's signaling activity regulates the ERAD or UPR, and there is growing consensus that selenos might be only a marker of ER stress [23,30]. Specifically, transcriptome data of Teffs with selenos knockdown showed no significant change in key genes that respond to ER stress [75]. Only the expression of the X-box-binding protein 1 (XBP1), a transcription factor regulated by the UPR, was moderately decreased. Ramifications of the latter for regulation of lipid storage are elaborated below.

4. Selenos in lipid storage

Selenos was initially discovered through its contribution to type-2 diabetes, where its expression in the liver was shown to be inversely proportional to circulating glucose and insulin levels and in direct proportion to plasma triglyceride concentrations [1,126]. We now know that selenos influences lipid storage and adipogenesis—the process whereby fibroblast-like progenitor cells become adipocytes. Adipocytes then store triglycerides in lipid droplets. Clearly, adipogenesis has profound implications for health [127].

Adipogenesis is controlled by PPARγ (peroxisome proliferator-activated receptor γ, which was introduced during discussion of selenos degradation) and associated with elevated ER stress and activation of the UPR. Selenos's expression levels are tightly regulated through the process: selenos levels initially decrease during the early phase of adipogenesis and then increase later on as adipogenesis progresses [27]. Indeed, overexpression of selenos during the early phase of cell differentiation impaired adipogenesis; by contrast, its knockdown promoted adipogenesis. Downregulation of selenos and its protein partner selenok in early phase adipogenesis, was demonstrated to take place through PPARγ-mediated ubiquitination and proteasomal degradation [60]. The levels of selenos were inversely related to PPARγ, and when PPARγ was silenced, the levels of selenos and selenok were higher, and intracellular lipid accumulation was low.

Several follow-up studies demonstrated a connection between selenos and the inositol-requiring enzyme 1α (IRE1α)/X-box binding protein 1 (XBP1) branch of the UPR [25,35], shedding light on why selenos levels are governed during adipogenesis and what role selenos may play in the UPR. Selenos's knockdown and overexpression led to changed expression levels of genes associated with UPR response during adipogenesis: CHOP (DNA damage-inducible transcript 3 protein), GRP78 (ER chaperone BiP), XBP1 (the ER stress-induced transcription factor X-box binding protein 1), and XBP1s (XBP1 spliced gene) [27]. XBP1s mRNA level was lower in selenos's knockdown, and adipogenesis was inhibited by increasing cell death. However, this could be reversed through overexpression of XBP1s [24]. (The ability of selenos suppression to induce apoptosis was demonstrated in other cell lines as well [67,69], and selenos overexpression in response to injury was found to protect human aortic endothelial cells from autophagy by activating Akt/mTOR signaling [33]). Therefore, based on the accumulated data, selenos's upregulation increases the levels of spliced XBP1, IRE1α and phosphorylated JNK. This activates the XBP1s/PPARγ pathway and promotes lipogenesis and lipid accumulation. However, the preponderance of data does not offer insight into the mechanism by which selenos communicates with the UPR pathway.

These observations on the molecular level are supported by findings on the organism level. In hepatocyte-specific selenos knockout mice, selenos deficiency caused hepatic steatosis via increased fatty acid uptake and reduced fatty acid oxidation [67]. This knockout also led to impaired insulin signaling due to decreased phosphorylation of the insulin receptor substrate 1 (IRS1) and protein kinase B (PKB/Akt). The regulatory influence of selenos on lipid storage and UPR is also echoed in studies of selenos's relation to type-2 diabetes. In MIN6 cells, selenos knockdown suppresses UPR activation through the IRE1α and PERK pathways, and decreases proinsulin levels while increasing insulin levels and secretion [69]. Due to selenos's contribution to lipid storage and adipogenesis, it is associated with type-2 diabetes mellitus [67,126,128–131], obesity [132], and insulin resistance. Selenos expression in adipose tissue is elevated in obese subjects [24] and high-fat diet-fed mice [24,129]. Genetic variations in selenos are associated with an elevated risk for diabetes and macroangiopathy (see Table 1 in Ref. [12]). Polymorphisms also elevated plasma triglyceride levels in subjects without diabetes [133]. In fact, polymorphisms increase the risk

for multiple other diseases (section 5).

5. Significance for human health

As selenos's role as a regulator in several signaling pathways emerges, it is becoming clear why genetic variations are associated with risk factors for diabetes mellitus and inflammatory processes, vascular and cardiovascular disorders, and cancer. The link to metabolic disorders was discussed at length above and may also partly explain the tight association of selenos with coronary heart disease and ischemic stroke [134,135]. A single nucleotide polymorphism (SNP) located in the ER stress-response element was associated with impaired expression of selenos, and led to increased circulating levels of the pro-inflammatory cytokines IL-6, IL-1β, and TNF-α [119]. Selenos is highly expressed in vascular muscle cells, and is proposed to be relevant for atherosclerosis and vascular inflammatory diseases [136,137].

Polymorphisms also elevate the risk for Kashin-Beck disease (a chronic and degenerative osteoarthropathy) [138], Hashimoto's thyroiditis [139], colorectal cancer [140–142], and gastric cancer [143]. Lower expression of selenos was associated with a poor prognosis of gastric cancer patients [60], and a recent preprint before peer review reported that selenos downregulation is associated with poor prognosis in thyroid cancer [144]. Selenos has been proposed to be a prognostic biomarker in triple-negative breast cancer [145]. Additionally, selenos is upregulated in Crohn's disease [23], and following focal cerebral ischemia [146], it accelerates renal interstitial fibrosis [85] and is also involved in inflammation [147,148]. Increased expression of selenos led to decreased tau phosphorylation in Alzheimer's disease and potentially other neurodegenerative disorders [149]. Reduced expression was shown to exacerbate the inflammatory profile of fast-twitch muscle fibers in a dystrophic mice model [150] (for the role of selenos in muscle cells, see Refs. [30,66,151]). Selenos was identified as one of six hub genes in serous ovarian cystadenocarcinoma and potentially linked to ferroptosis [152]. It was also recognized as a significant differentially expressed gene in an analysis of lupus nephritis IFN-K-immunosuppressive therapy [153]. Moreover, exosomes from patients with septic shock contained levels of selenos [154]. Lastly, selenos is frequently modified by drugs and pollutants due to its highly reactive Sec [155,156].

In summary, this extensive list shows that selenos's genetic polymorphisms and expression level influences the risk for the development of diabetes, dyslipidemia, and cardiovascular diseases. High expression levels correlate with poor prognosis for several types of cancer. These observations can be explained by selenos's role as an inhibitor of cytokine production and a regulator of signaling pathways.

6. Selenos and viruses

In addition to its involvement in human diseases, selenos is implicated in the life cycles of various viruses [157]. Selenos plays a role in HIV reactivation [158], porcine circovirus type 2 replication [159], jamming of the ERAD during enterovirus 71 infection [160], and the coronaviruses SARS-CoV-1 and -2 [61,68,161–164]. The cellular expression of selenos is downregulated by viruses [160,165]. Until recently, it was assumed that selenos is relevant for virus infections because it recruits p97 to the ERAD pathway and thus could assist viral proteins in evading degradation [166]. The interactome of SARS-CoV-2 with human proteins, however, reveals that selenos itself is an interaction partner of several viral proteins [61,68,161–163,167–169] (Fig. 6). Intriguingly, among these is the coronavirus nonstructural protein 7 (nsp7), a small adapter protein that, along with nonstructural protein 8 (nsp8), activates the RNA-dependent RNA polymerase (RdRP; nsp12) of the virus [170]. Indeed, interactions between selenos and the coronavirus's replication-translation complex were reported in cells infected with SARS-CoV-1 [162]. nsp7 is part of the viral replication-translation complex but also acts as a transcription factor [171]. This raises the intriguing possibility that selenos assists the replication-translation complex via its oxidoreductase activity or by recruiting additional human protein partners. Other SARS-CoV-2 viral partners of selenos are the open reading frame proteins orf7a, and orf7b, which disrupt STAT1

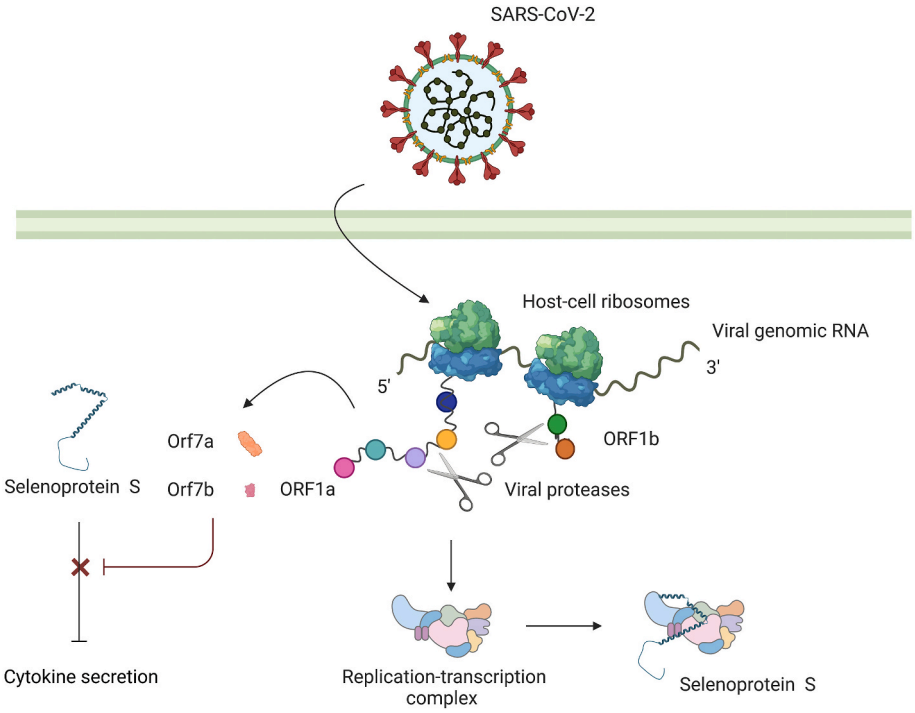

Fig. 6. Selenos putative roles in SARS-CoV-2. Scheme demonstrating invasion of SARS-CoV-2 into the cell, transcription of its genetic material, and assembly of the coronavirus replication and transcription complex. Selenos binds the nonstructural protein 7, which aids the core of the replication, the RNA-dependent RNA polymerase. Selenos also interfaces with orf7a and orf7b, which disrupt signaling pathways and control cytokine secretion.

and STAT2 signaling pathways [172]. Here, it seems that the virus is sequestering selenos and preventing its inhibitory effect on cytokine secretion.

7. Concluding thoughts and open questions

At this point, selenos was unambiguously shown to coordinate the recruitment of p97 from the cytosol and its anchoring to derlins in the ERAD pathway. Nevertheless, because selenos binds multiple protein complexes, it is likely to have other cellular functions waiting to be revealed. Selenos's interactome and its SLiMs suggest that these roles may be connected to vesicle trafficking, glycosylation, and functions of peroxisomes. In addition, selenos participates in NF-κB signaling and the regulation of cytokines. It also contributes to the invasion of viruses, and in the case of the SARS-CoV-2 virus, selenos binds directly to the coronavirus replication machinery. However, if these different roles are distinctly separate, or to what extent they overlap, remains an important open question. Also, it remains unknown which of these cellular functions utilizes selenos 'only' as recruiter, and which of them requires its putative enzymatic activity. Despite the all the accumulated experimental insights, it is currently not possible to pinpoint selenos's specific cellular roles and achieve a mechanistic understanding of its multifaceted contributions to cellular life.

A quintessential first step to make inroads and identify these roles is to establish what proteins selenos directly interacts with and what specific features of selenos enable it to bind and interact with the different multiprotein complexes. Furthermore, it is essential to determine the structure and membrane topology of selenos since structure informs on function. Isolating the enzymatic substrates of selenos will confirm its enzymatic activity *in vivo* and identify the relevant pathways. This might also provide an explanation why this versatile disordered protein needs to be a selenoprotein.

Declaration of competing interest

All authors have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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