REVIEW

THE VPS35 PROTEIN AND THE ROLE OF ITS IMPAIRMENTS IN MITOCHONDRIAL DYSFUNCTION IN PARKINSON'S DISEASE

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The VPS35 is an essential protein that plays multifunctional roles in various biological processes. It is a core component of the retromer complex, involved in protein recycling from endosomes to the trans-Golgi network (TGN) and the plasma membrane. Besides its role as the retromer complex component, VPS35 interacts with many proteins and regulates mitochondrial homeostasis, mitochondrial dynamics (fusion and fission), and other important processes in various cell compartments. In the context of Parkinson's disease (PD) convincing evidence exists that VPS35 mutations, particularly [D620N], have a significant impact on normal retromer functioning, mitochondrial dysfunction, and impairment of neuronal health and survival. In this review we briefly consider structure and functions of the retromer complex, the role of VPS35 in mitochondria, and finally analyze physical and functional interactions of this protein with PD-important proteins associated with mitochondria.

Keywords: VPS35; retromer complex; Parkinson's disease; neurodegeneration; mitochondria; mitochondrial dysfunction

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INTRODUCTION

Parkinson's disease (PD) is the second-most common and the most rapidly growing neurodegenerative disorder in the world [1–3]. The modelling study projects that by 2050 PD will have become a greater public health challenge for our society [4]. The hallmarks of PD are the degeneration of the nigrostriatal dopaminergic (DA) system and the intracellular inclusions rich in alpha-synuclein (Lewy bodies) [5–9]. PD is characterized either by motor impairments (tremor, bradykinesia, rigidity), or by non-motor symptoms (anxiety, depression, cognitive loss, sleep disturbance) [10–12]. After discovery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydopyridine)-induced parkinsonism, the impairment of mitochondrial function is considered to be the distinctive feature or even the reason of PD. The underlying action of MPTP is the inhibition of mitochondrial complex I under the action of toxic MPP^+ (1-methyl-4-phenylpyridinium) ion [13]. Results of numerous studies point to an important role of mitochondrial dysfunction in the pathogenesis of PD [14, 15]. The impairment of ubiquitin-proteasome system is also one of the central pathological mechanisms of PD [16–18]. Many proteins undergoing atypical mono- and polyubiquitination (or implicated in such ubiquitination) and involved in different biological pathways are related to PD [19].

Although most cases of PD are idiopathic, since the first PD gene (encoding alpha-synuclein) was discovered in 1997 [20], the genetics and pathogenetics of PD developed rapidly [21–25]. At present, about 100 distinct genes or loci associated with this heterogeneous disease have been identified [26]. As Robert Nussbaum (a well-known geneticist, whose work on hereditary PD led to the identification of alpha-synuclein) has mentioned, the importance of finding these rare mutations of hereditary PD "confirms William Harvey's observation from 350 years ago that studying rarer forms of a disease is an excellent way to understand the more common forms of that disease" [27].

In 2011, the list of PD-associated genes was supplemented by the *VPS35* gene, which was identified by two independent groups as the gene linked to rare familial late-onset PD [28, 29]. To date, more than ten mutations of this gene are known, but only one of them (D620N, the substitution of aspartic acid to asparagine at position 620) was confirmed pathogenic in relation to PD [30, 31]. This relatively rare mutation [32] has been identified in the populations of several countries (Austria, Germany, Switzerland, USA, UK, Japan, Tunisia, Yemen, and the Caucasus) [28, 29, 32–37].

Using a germline D620N VPS35 knockin mouse model and viral-mediated gene transfer rat model, the pathogenic effects of the D620N mutation were

demonstrated at physiological expression levels. D620N mutations were sufficient to reproduce key neuropathological hallmarks of PD: the progressive degeneration of *substantia nigra* DA neurons and axonal pathology [38, 39].

1. THE RETROMER COMPLEX STRUCTURE AND FUNCTION

The protein encoded by *VPS35* (vacuolar protein sorting) was first discovered in *Saccharomyces cerevisiae* in 1992 [40]. This highly conservative protein assembles with 4 other peripheral membrane proteins to form the retromer complex involved in protein recycling from endosomes to the trans-Golgi network (TGN) and the plasma membrane [41] (Fig. 1). The mammalian retromer complex has a very similar structure. The structure of its core component VPS35, as well as that of the whole retromer complex, is described in detail [42–47]. In brief, the VPS35 molecule has a flexible right-handed alpha-helical solenoid structure to make it possible to conform to curved membranes of endosomes and vesicles. VPS35 forms a heterotrimer with VPS26 and VPS29. These proteins bind to the N-terminal (residues 1–172) and C-terminal (residues 307–796) regions of VPS35, respectively. VPS29 has structural similarity to divalent metal-containing phosphoesterases; it can coordinate metals in a similar manner but has no detectable phosphoesterase activity. Thus, the phosphoesterase fold probably acts as a protein interaction scaffold for retromer assembly [45]. VPS26 exists in two paralogues, VPS26a and VPS26b, each of them forming retromer complexes, which differ in their cellular localization and cargo-sorting preferences [44, 48–52].

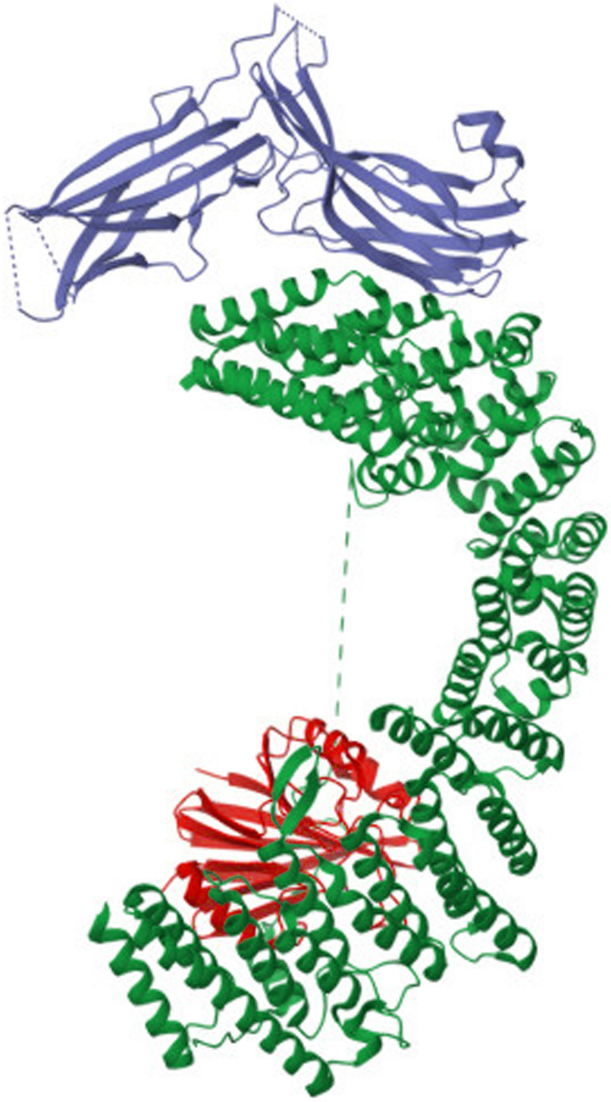

Figure 1. Spatial structure of the human retromer complex: VPS29 (red) and VPS26C (blue) bound to VPS35L (green). Reproduced from Protein Data Bank database (ID: 8SYN); entered into the database by the authors: Chen Z., Chen B., Burstein E., Han Y. (date of entry: 2023-11-01). The color version of the figure is available in the electronic version of the article.

Vps35, along with Vps26 and Vps29, forms the so-called cargo recognition complex of the retromer, which cooperates with sorting nexins to mediate cargo selection and membrane curvature, respectively [53, 54]. The main function of the retromer complex is to sort and transport proteins from endosomes back to the TGN or directly to the plasma membrane, preventing their degradation in lysosomes, ensuring reuse of vital molecules and sending them to their correct destinations, crucial for cell signaling, nutrient uptake, and neuronal health [55–58]. The retromer complex recruits the pentameric WASH complex (via its FAM21 subunit) to endosomes. WASH in turn facilitates endosomal protein sorting by activating the Arp2/3 complex, which leads to initiation of F-actin polymerization, crucial for forming branched actin networks. It helps concentrate specific proteins (cargo) into these actin-supported tubules for retrograde transport back to the TGN or plasma membrane, preventing them from being sent to lysosomes [59–61] (Fig. 2). Although it was generally accepted that WASH complex was attached to the endosomal membrane via the interaction of its subunit FAM21 with the retromer subunit VPS35, Dostál et al. observed the presence of the WASH complex and F-actin on endosomes even in the absence of VPS35. Thus, the WASH complex binds to the endosomal surface in both a retromer-dependent and a retromer-independent manner [62]. However, studies have shown that PD-associated D620N mutation of *VPS35* gene impairs the recruitment of WASH complex to endosomes and inhibits the autophagosome formation and subsequent degradation of autophagy substrates [63].

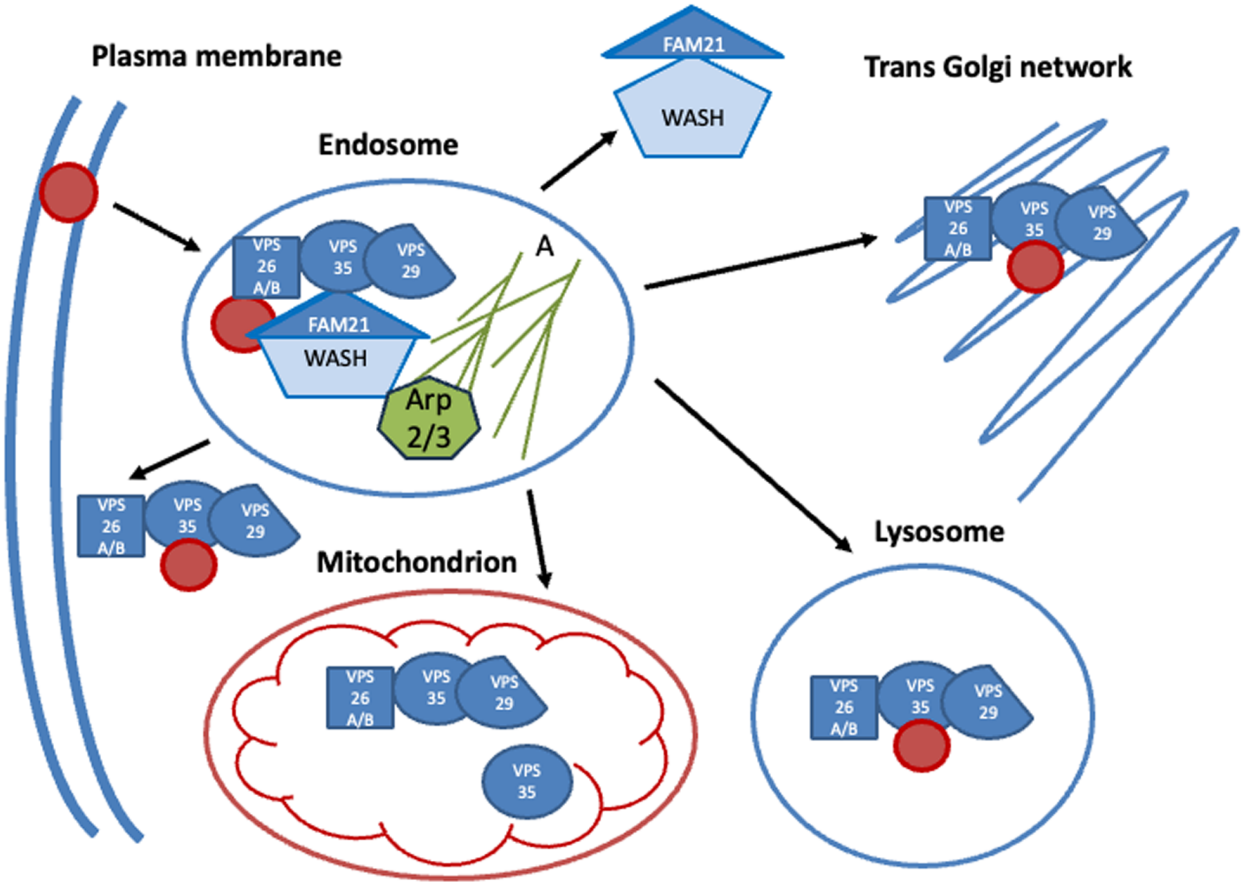

Figure 2. The functioning of VPS35 protein as a part of the retromer complex. Blue is the retromer complex, pentagon is pentameric complex WASH with its subunit FAM21, which makes the connection with the retromer. Red circle is the designation of protein "cargo", green heptagon is the heptameric Arp2/3 complex, activated by WASH and promoting the creation of branched actin chains (A). Other explanations are given in the text. The color version of the figure is available in the electronic version of the article.

Although VPS35 binds VPS26 and VPS29 with K_d values around 1–2 (nM) and 100–250 (nM), respectively (rather tight) [64], evidence shows that the subunits of the mammalian retromer complex can exist and function independently or in distinct subcomplexes, revealing unique roles beyond their collective function in endosomal cargo sorting [65, 66].

The role of D620N mutation of *VPS35* gene in neurodegeneration is undeniable. As for the other proteins of retromer complex, the results of DNA sequence analysis of 702 PD patients have shown that mutations within the *VPS26a*, *VPS26b*, and *VPS29* genes are rare and do not play a major role for PD risk [67]. Nevertheless, Seong et al. have demonstrated that VPS26b performs a protective function against MPTP-induced neurotoxicity in DA human neuroblastoma SH-SY5Y cells. The exposure to MPTP significantly reduced the expression of VPS26b in SH-SY5Y cells. The upregulation of VPS26b expression has a positive effect on maintaining neuronal function [68]. These data are consistent with our experiments on the MPTP mouse model. In this model, mitochondria of experimental animals, in addition to VPS35, alpha-synuclein, DJ-1 protein, contained VPS26b. Notably, VPS26b was found in the brain mitochondria of mice exposed to MPTP or MPTP and neuroprotector isatin, and not of the animals of the control group [69].

Next, we will focus our attention on VPS35 protein, which, besides its well-known function (as a component of the retromer complex), devoted to the retrograde transport of transmembrane protein-cargo, is essential for the mitochondrial function and interacts (directly or indirectly) with different PD-associated protein partners.

2. VPS35 AND MITOCHONDRIA

Mitochondria are the organelles that play the central role in PD [13–15, 70–74]. They have numerous important functions beyond the ATP production, such as regulation of reactive oxygen species (ROS), calcium signaling, apoptosis, heme and lipid metabolism, participating in cell growth and differentiation [75–78]. Mitochondrial dysfunction is a characteristic feature of toxic models of PD with the use of MPTP,

6-hydroxydopamine (6-OHDA), rotenone, and paraquat. These neurotoxins directly inhibit mitochondrial complexes I and IV, or affect mitochondrial functions increasing ROS production by other mechanisms [79–85].

Using the MPTP cell model, Bi et al. demonstrated the effect of PD-associated mutation on the cell-protective function of VPS35. Wild-type VPS35 protected N27 cells against MPTP, while in the case of the VPS35 D620N mutant this protection was lower. This finding was confirmed with the use of viral expression of wild-type and mutated human VPS35 in DA neurons of rat embryos [86]. Using the induced pluripotent stem cell-derived neurons from a patient with the D620N mutation of VPS35, Hanss et al. demonstrated the decreased autophagy and lysosomal mass associated with an accumulation of alpha-synuclein, mitochondrial dysfunction with decreased membrane potential, impaired mitochondrial respiration, and increased production of reactive oxygen species associated with a defect in mitochondrial quality control via mitophagy [87].

2.1. VPS35 and Mitochondrial Dynamics

Mitochondrial dynamics dysfunction plays an essential role in neurodegeneration [88–93].

VPS35 participates in the mitochondrial-derived vesicles (MDV) formation. MDV bud off mitochondria to transport components (enzymes, proteins, lipids, nucleic acids) to lysosomes or peroxisomes, or outside the cell. These structures play crucial role in mitochondrial quality control, cellular communication, immune response, and metabolic regulation [94, 95]. They are stimulated as an early response to oxidative stress [95, 96]. Retromer modulates the formation of MDVs and mediate their transport to the peroxisomes [94, 97] or lysosomes [98].

VPS35 is involved in mitochondrial dynamics also via its influence on key proteins of mitochondrial fusion and fission. Mitochondrial homeostasis is determined by the actions of dynamin-family members: dynamin-related protein 1, or dynamin-like protein 1 (DRP1 or DLP1), involved in mitochondrial fission, and mitofusins (Mfns), membrane-anchored GTPases essential for mitochondrial fusion [99–102]. Genetic experiments with mouse model have revealed that VPS35 expression in DA neurons is necessary for mitochondrial fusion and function, which is crucial for the neuron survival. VPS35 facilitates mitochondrial fusion by promoting the trafficking and degradation of mitochondrial E3 ubiquitin ligase 1 (MUL1, also known as MULAN), which ubiquitinates Mfn2, contributing to its degradation, mitochondrial fragmentation, and DA neuron loss. Expression of wild type of VPS35, but not the PD-associated mutant D620N, in VPS35-deficient cells restores Mfn2 decrease and mitochondrial damage [103] (Fig. 3).

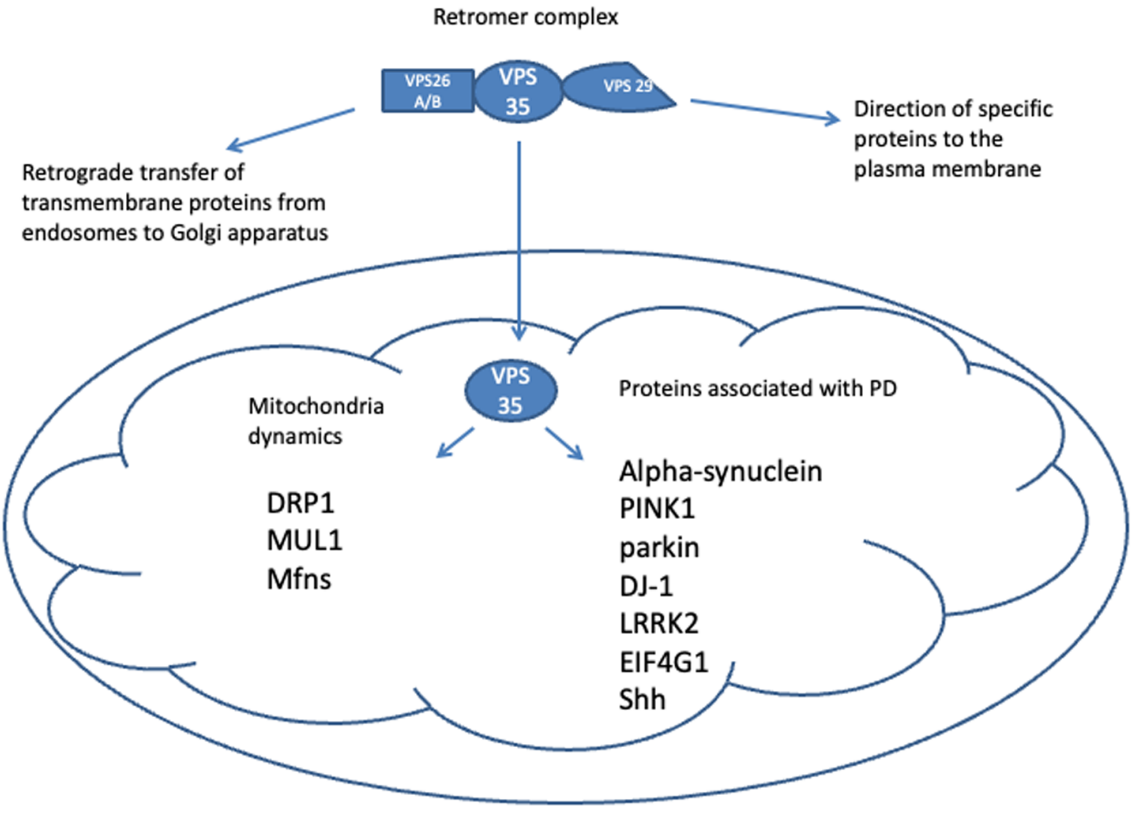

Figure 3. Protein VPS35 partners, involved in PD and associated with mitochondria.

VPS35 also takes part in mitochondrial fission. The PD-associated D620N mutation of VPS35 caused mitochondrial fragmentation and cell death in cultured neurons *in vitro*, in mouse *substantia nigra* neurons *in vivo*, and in human fibroblasts from an individual with PD. VPS35 mutants showed increased interaction with DLP1, which enhanced turnover of the mitochondrial DLP1 complexes via the mitochondria-derived vesicle-dependent trafficking to lysosomes [104]. Mitochondrial dysfunction and neuronal loss could be prevented by inhibition of mitochondrial fission. The VPS35–DLP1 interaction increased during oxidative stress [98, 104]. A highly conserved FLV motif was identified in the C-terminus of DLP1, its mutation significantly reduced VPS35–DLP1 interaction. A decoy peptide design based on this FLV motif blocked the VPS35-DLP1 interaction and inhibited the recycling of mitochondrial DLP1 complexes. Moreover, VPS35 D620N mutant-induced mitochondrial fragmentation was rescued by the treatment of this decoy peptide in both M17 cells overexpressing D620N or PD fibroblasts bearing this mutation [104].

2.2. VPS35 and other PD-Related Proteins Associated with Mitochondrial Dysfunction

Interaction of VPS35 with the protein products of other PD-related genes, also participating in the regulation of mitochondrial dysfunction and mitophagy, is of special interest. These include: alpha-synuclein (PARK1), PTEN-induced kinase 1 (PINK1, PARK6), E3 ubiquitin ligase Parkin (PARK2), DJ1 protein (PARK7), leucine-rich repeat kinase 2 (LRRK2, PARK 8), phospholipase A2 Group VI (PLA2G6, Park14), eukaryotic translation initiation factor 4 gamma 1 (EIF4G1, PARK18), Sonic hedgehog protein. The impairment of VPS35 function is linked to mitochondrial and autophagy-lysosomal pathways dysfunction and altered neurotransmitter receptor transport [31, 55, 58, 105–108].

2.2.1. Alpha-Synuclein. The alpha-synuclein gene was the first identified gene associated with PD. Normally alpha-synuclein, mainly localized in presynaptic terminals, enhances the fusion of synaptic vesicles with the presynaptic membrane. This protein has structural and functional homology with the 14-3-3 family proteins, chaperones, which are widely distributed in the brain and are involved in the regulation of apoptosis, cell cycle, division, gene expression, and other cellular processes [109]. Mutations in the gene of alpha-synuclein were discovered in families with dominant forms of PD, and it was the first to link genetics to the disease. In pathology, alpha-synuclein aggregates and accumulates in presynaptic terminals (thus inhibiting dopamine release) and in the cytoplasm of neurons in the form of Lewy bodies which can be called a hallmark of PD [6, 7, 20, 27, 110–112]. Alpha-synuclein is localized not only in cytosol, but also in mitochondria-associated endoplasmic reticulum (ER) membranes. Convincing evidence exists that that pathogenic point mutations in human alpha-synuclein result in its reduced association with those membranes, coincident with a lower degree of apposition of ER with mitochondria and an increase in mitochondrial fragmentation [113]. Experiments with dynamin-family members have shown that normally alpha-synuclein modulates mitochondrial morphology and operates downstream of the mitochondrial fusion/fission machinery, and that these processes are impaired by pathogenic mutations in alpha-synuclein [113].

On the other hand, *in vitro* and *in vivo* studies from various laboratories have demonstrated that aggregated or mutant alpha-synuclein can associate with the inner mitochondrial membrane, where it binds to and inhibits mitochondrial complex I, leading to reduced mitochondrial function, lower ATP production in DA neurons, and increased production of reactive oxygen species with the increase in mitophagy [114–119].

Recent studies of Liu et al. have shown that highly expressed alpha-synuclein is transferred to mitochondria via membrane receptors such as TOM20 (translocase of outer mitochondrial membrane 20) and cause mitochondrial dysfunction and mitochondrial oxidative stress, leading to neuronal injury [120]. The mitochondria-targeted oligomeric alpha-synuclein induced degradation of the main protein-conducting channel of the TOM complex (TOM40) via the ubiquitin-proteasome system pathway and caused mitochondrial dysfunction in PD patient-derived NPSC (neural stem/progenitor cell) lines and patient brain tissues [121]. It is hypothesized that alpha-synuclein can bind directly to mitochondrial DNA or influence its transcription by interacting with RNAs or transcription factors [122].

It should be noted that cell and animal model studies have shown that there is a strong link between VPS35 dysfunction and Lewy bodies-like inclusions formation [123, 124]. Most of the authors report that VPS35 mutations impair the lysosomal/autophagy pathway, which enhances the alpha-synuclein load, leading to increased aggregation. They suggest that VPS35 regulates alpha-synuclein degradation by impacting the endosomal-lysosomal system, autophagy, and the ubiquitin-proteasome system [6, 38, 99, 113, 117, 119, 123–135].

Expression of one of PD-associated Vps35 variants, with a loss-of-function mutation R524W, in HeLa cells caused the accumulation of intracellular alpha-synuclein-positive aggregates [134]. Using the *Drosophila* model, Miura et al. have shown that *VPS35* knockdown influenced the trafficking of cathepsin D, a lysosome protease involved

in alpha-synuclein degradation, and caused the accumulation of alpha-synuclein in the lysosomes of the brain, locomotor impairments and mild compound eye disorganization in flies expressing human alpha-synuclein [129].

Impaired vision is a common non-motor manifestation of PD. Rod-specific deletion of the *VPS35* gene in a mouse model develops retinal degeneration with similarities to PD and cone-rod dystrophy. Mouse retinas with VPS35-deficient rods exhibited synapse progressive degeneration with the related formation of Lewy body-like inclusions and phospho-alpha-synuclein aggregation in late endosomes [124].

Analyzing human induced pluripotent stem cell-derived neurons from PD patients with the VPS35 D620N mutation, Bono et al. observed DA neuron extensive apoptotic cell death and endosomal dysfunction. They also found alpha-synuclein accumulation in tyrosine hydroxylase-positive DA neurons (DA neurons expressing tyrosine hydroxylase, the key enzyme of dopamine synthesis) [127].

VPS35-deficient mice exhibited PD-relevant deficits including accumulation of alpha-synuclein in DA neurons, loss of DA transmitter and DA neurons in *substantia nigra pars compacta* and striatum, and locomotor behavior impairments. VPS35-deficient DA neurons or DA neurons expressing PD-linked VPS35 mutant D620N had impaired endosome-to-Golgi retrieval of Lamp2a (lysosome-associated membrane glycoprotein 2a) and accelerated Lamp2a degradation. Expression of Lamp2a in VPS35-deficient DA neurons reduced alpha-synuclein, supporting the view for Lamp2a as a receptor of chaperone-mediated autophagy critical for alpha-synuclein degradation. These results revealed a crucial pathway, VPS35-Lamp2a-alpha-synuclein, preventing PD pathogenesis [128]. Niu et al. reported that the VPS35 D620N knockin mice demonstrated, along with the other aspects typical of PD (motor deficits, significant changes in the levels of DA and DA metabolites in the striatum, robust neurodegeneration of the DA neurons in the *substantia nigra* and DA terminals in the striatum, mitochondrial fragmentation and dysfunction, increased neuroinflammation), accumulation and aggregation of alpha-synuclein in DA neurons [131].

However, in the *VPS35* D620N knockin mouse model Chen el al. demonstrated the progressive degeneration of nigrostriatal pathway DA neurons but did not find any evidence for alpha-synuclein-positive neuropathology in aged *VPS35* knockin mice. *VPS35* D620N expression also failed to modify the lethal neurodegenerative phenotype of human A53T-alpha-synuclein transgenic mice. The A53T alpha-synuclein mutation is the cause of the development of familial PD, increasing alpha-synuclein neurotoxicity and tendency to aggregation. Interestingly, VPS35 D620N expression in the mouse model induced robust tau-positive somatodendritic pathology throughout the brain as indicated by abnormal hyperphosphorylated and conformation-specific tau [38]. Exploring the neuroprotective capacity of increasing VPS35 expression in a viral-based human wild-type alpha-synuclein rat model of PD, these authors found that the overexpression of wild-type VPS35 was not sufficient for protection against alpha-synuclein-induced nigral DA neurodegeneration. This suggests a limited interaction of VPS35 and alpha-synuclein in neurodegenerative models of PD [130].

2.2.2. EIF4G1. Functional genetic interaction was reported between two PD genes, *VPS35* and *EIF4G1*. The *EIF4G1* gene encodes eukaryotic translation initiation factor 4-gamma (eIF4G1) which is a key component of the eIF4F complex, essential for the initiation of protein synthesis by recruiting mRNA to the ribosome. The eIF4G1 protein is a scaffold that coordinates activities of other components of the complex and directly binds the 40S ribosomal subunit to promote efficient translation [136]. The eIF4G1-mediated mitochondrial translation is required for development and cognitive functions, such as learning and memory [137]. Mutations in the *EIF4G1* gene (Park18) have been linked to an inherited form of PD [138, 139]. Dhungel et al. discovered a powerful genetic and functional interaction between *VPS35* and *EIF4G1*, in yeast, worms, and mouse models. The authors defined the mechanism by which these genes interact and showed that VPS35 protected against alpha-synuclein-induced neurodegeneration in a mouse model [123]. Their results provide evidence that *EIF4G1* upregulation causes defects associated with protein misfolding. The interactions between VPS35, EIF4G1, and alpha-synuclein were also shown [123].

2.2.3. Parkin, PINK, and DJ-1. Mutations in the *PINK1* and *PARKIN* genes are the most common causes of recessive early-onset PD [140]. Proteins encoding by these genes, E3 ubiquitin ligase Parkin and PTEN-induced putative kinase 1 (PINK1), are crucial for mitochondria quality control through a process that tags damaged mitochondria for degradation [141]. PINK1 acts as a sensor for mitochondrial damage, accumulating on the outer membrane of dysfunctional mitochondria to recruit and activate Parkin. PINK1 phosphorylates both Parkin and ubiquitin, which triggers a feedforward loop of ubiquitination and phosphorylation of proteins, leading to mitophagy [142]. Mutations in *PINK1* and *PRKN* disrupt mitophagy as well as mitochondrial fission and fusion [143–145].

VPS35 interaction with Parkin was confirmed in *Drosophila* models when Parkin-induced deficits were attenuated by overexpressing of VPS35 [146]. Experiments with human neural cells (SH-SY5Y) and *Drosophila* neurons have demonstrated that Parkin mediates the atypical (K6) poly-ubiquitination of VPS35 [147, 148]. As the VPS ubiquitination by Parkin is not typical of that which serves for subsequent proteasomal degradation (when the poly-ubiquitin chain attachment is K48-linked), it may be important for retromer-mediated endosomal sorting [147].

To investigate a possible pathogenic mechanism among VPS35, PINK1, and Parkin in PD, Ma et al. used heterozygous SH-SY5Y cells carrying the PD-associated D620N variant of VPS35. The cells were treated with a protonophore carbonyl cyanide *m*-chlorophenylhydrazone (CCCP) to induce the PINK1/Parkin-mediated mitophagy. Mitochondria in the VPS35-D620N cells were desensitized to the CCCP induced collapse in mitochondrial potential, as they displayed altered fragmentation and were unable to accumulate PINK1 at their surface upon this insult. Parkin recruitment to the cell surface was inhibited and initiation of the PINK1/Parkin-dependent mitophagy was impaired. Thus, PD-associated VPS35 mutation causes mitochondrial dysfunction and suggest a converging pathogenic mechanism among VPS35, PINK1, and Parkin in PD [149].

Another functional interaction of Parkin with VPS35 is associated with the retromer-mediated endosomal sorting. In the brain of *Parkin* knockout mice, the levels of components of the retromer-associated WASH complex were markedly decreased. The latter suggests that Parkin may modulate WASH complex-dependent retromer sorting. *Parkin* gene silencing in primary cortical neurons selectively disrupted the vesicular sorting of the autophagy receptor ATG9A, a WASH-dependent retromer cargo. In the case of DA neurodegeneration induced by the expression of D620N VPS35 in mice, Parkin was not required for disease manifestation thus suggesting downstream location of VPS35 relative to Parkin [147].

Mutations in *DJ-1*, just like in *PINK1* and *PARKIN*, cause recessive parkinsonism in humans. Normally, DJ-1, which is involved in various signaling pathways, together with the PINK1/Parkin regulates mitochondrial function and mitophagy by acting as a sensor and antioxidant for oxidative stress. Oxidative stress increases, DJ-1 becomes oxidized, localizes to the mitochondria, and helps to limit excessive ROS production [150]. Besides that, DJ-1 is involved in mitochondrial dynamics, regulation of apoptosis, and dopamine homeostasis [150–154].

While a direct physical interaction between DJ-1 and VPS35 has not been detailed, studies have shown that they are linked through their involvement in mitochondrial dysfunction. VPS35 mutations lead to an increase in the activity of mitochondrial E3 ubiquitin ligase MUL1, promoting MFN2 degradation, which causes mitochondrial fragmentation, and the subsequent neuronal loss seen in PD [103]. DJ-1 promotes mitochondrial fusion and MFN2 stability, which helps to maintain mitochondrial integrity and protect against cellular damage [155].

2.2.4. LRRK2. The *LRRK2* (*Park8*) gene encodes leucine-rich repeat kinase 2, also known as dardarin. LRRK2 is a multifunctional protein possessing kinase and GTPase activities. LRRK2 plays a crucial role in neuronal functions such as development, maturation, synaptic transmission, in the processes of autophagy. LRRK2 regulates neuroinflammation by influencing the function of brain immune cells like microglia, macrophages, and astrocytes [156, 157]. Although LRRK2 is primarily found in the cytoplasm, certain evidence exists that it can be associated with intracellular membranes, including the outer mitochondrial membrane, where it plays a role in regulating mitochondrial function. It affects mitochondrial dynamics, calcium handling, and mitophagy [158, 159]. As *LRRK2* mutations are the most common genetic cause of familial PD and this enzyme is involved in a broad range of cellular activities, the underlying of mechanisms of LRRK2-PD is of special interest [160].

The most frequent pathogenic mutation in the *LRRK2* gene, G2019S, found in the kinase domain, results in increased LRRK2 kinase activity [161]. The increased LRRK2 activity may contribute to PD pathology by causing the dysregulation of microtubule dynamics, vesicle trafficking, synaptic transmission, and the accumulation of aggregated alpha-synuclein. The mitochondrial dysfunction, caused by LRRK2 pathogenic mutations, is supported by evidence from a wide range of experimental models, including simple organisms like *C. elegans* and *Drosophila*, as well as more complex systems like rodent and human cell lines and brain tissue from PD patients. These models show how mutations lead to mitochondrial damage, impaired dynamics, and increased susceptibility to cellular stress [158, 162].

LRRK2 functions are involved in Rab GTPase phosphorylation, with its kinase activity directly phosphorylating a subset of Rab (Ras analog in brain) proteins which seem to play a central role in mitochondrial quality checking and disposal through PINK1/Parkin-mediated mitophagy and alternative pathways [163]. This in turn affects their downstream functions in intracellular trafficking, organelle maintenance, and cellular stress responses [164] The experiments with the mouse embryonic fibroblasts, mouse tissues (the lung, kidney, spleen, and brain), neutrophils and monocytes isolated from PD patients

with a heterozygous VPS35 [D620N] mutation reveal that the VPS35 [D620N] mutation elevates LRRK2-mediated phosphorylation of various Rab proteins. Thus, VPS35 controls LRRK2 activity and the VPS35 [D620N] mutation results in a gain of function, potentially causing PD through hyperactivation of the LRRK2 kinase [108, 165].

Besides that, VPS35 [D620N] mutation causes lysosome dysfunction increasing LRRK2 kinase activity and thus affecting a pathway involving VPS35, LRRK2, phospho-Rabs, the phospho-Rab effector protein RILPL1, and lysosomal integral membrane protein TMEM55B [166].

2.2.5. Sonic hedgehog protein. The Sonic hedgehog signaling pathway plays a crucial role in the development of the central nervous system. As Sonic hedgehog (Shh) protein is involved in the survival and function of DA-producing neurons, its dysregulation has been implicated in several neurodegenerative diseases, including PD, where it influences glial activation, neuroinflammation, and neuronal survival [167, 168]. *Shh* knockout in DA neurons results in PD-like locomotor deficits in mouse models [169].

Although the Shh protein travels from the ER to the Golgi and then to the cell membrane for secretion and it is not localized in mitochondria, activation of the Shh signaling pathway affects multiple aspects of neuronal mitochondria. Experiments with animals and cells have shown that Shh significantly increased mitochondrial mass, reduced mitochondrial fission, promoted mitochondrial elongation. It also increased mitochondrial membrane potential and respiratory activity and protected neurons against oxidative stress caused by the mitochondrial toxin rotenone or hydrogen peroxide [170]. Studies in rodent and cell models have demonstrated the pathogenic LRRK2 or PINK1 influence on the ciliogenesis and thus the ability of cells to respond to cilia-dependent Shh signaling [171-173]. Primary cilia are sensory antennae on neurons that play a crucial role in PD by coordinating ciliary signaling pathways, particularly the Shh pathway. In PD, primary cilia can become dysfunctional leading to abnormal signaling, impaired autophagy, and altered mitochondrial function, especially in DA neurons [174]. Increased Shh activity due to ciliary dysfunction may lead to the development of mitochondrial dysfunction typical of PD [171-173].

A key interaction between Shh and VPS35 occurs when VPS35 dysfunction (specifically the D620N mutation) leads to lysosomal dysfunction, which activates LRRK2. LRRK2, in turn, disrupts the Shh neuroprotective pathway. This cascade of events indicates a complex interplay where VPS35 dysfunction exacerbates PD by indirectly interfering with the neuroprotective effects of Shh signaling, leading to enhanced neurodegeneration.

In the context of the Shh pathway, VPS35, and mitochondria, it should be noticed that Shh signaling and VPS35 as a part of the retromer complex play important roles in mitochondrial dynamics and functioning, although the understanding of their relationship on the health of the DA signaling requires further study [175].

2.2.6. PLA2G6. The enzyme iPLA$_2$β (calcium-independent phospholipase A$_2$β), encoded by the *PLA2G6* gene, selectively hydrolyses glycerophospholipids to release free fatty acids. Mutations in *PLA2G6* have been associated with several neurodegenerative disorders, autosomal recessive early-onset parkinsonism among them [176–178]. iPLA$_2$β deficiency leads to the activation of microglia, the release of key mediators of inflammation — cytokines, such as tumor necrosis factor alpha and interleukin 1 beta, iron accumulation, mitochondrial dysfunction, lipid dysregulation, and other pathological changes contributing to the neurodegenerative symptoms [179]. The experiments in *Drosophila* have shown that loss of the function of a homologue of the *PLA2G6* gene, *iPLA2-VIA*, results in reduced survival, locomotor deficits and organismal hypersensitivity to oxidative stress. Furthermore, it leads to a number of mitochondrial abnormalities, including mitochondrial respiratory chain dysfunction, reduced ATP synthesis, abnormal mitochondrial morphology, and increased lipid peroxidation. These findings have been confirmed using cultured fibroblasts taken from two patients with mutations in the *PLA2G6* gene [180].

The calcium-independent phospholipase enzyme and VPS35 interact directly as part of the retromer complex. Lin et al. have shown that loss of iPLA2-VIA does not affect the phospholipid composition of brain tissue but rather causes an elevation in ceramides. iPLA2-VIA binds the retromer subunits VPS35 and VPS26 and enhances retromer function to promote protein and lipid recycling. Loss of iPLA2-VIA impairs retromer function, leading to a buildup of ceramides, lysosomal dysfunction, and ultimately neurodegeneration [181].

CONCLUSIONS

VPS35 is an important protein, which has a wide range of interacting proteins, including mitochondrial ones (Fig. 4). It acts as the central scaffolding unit of the retromer complex, interacting with proteins VPS26 and VPS29; however, VPS35 also functions independently.

The functional impairments observed in cell and animal models with the mutant VPS35 provide valuable information of sporadic PD.

VPS35 interacts with many proteins and regulates mitochondrial homeostasis, mitochondrial dynamics (fusion and fission), and other important processes

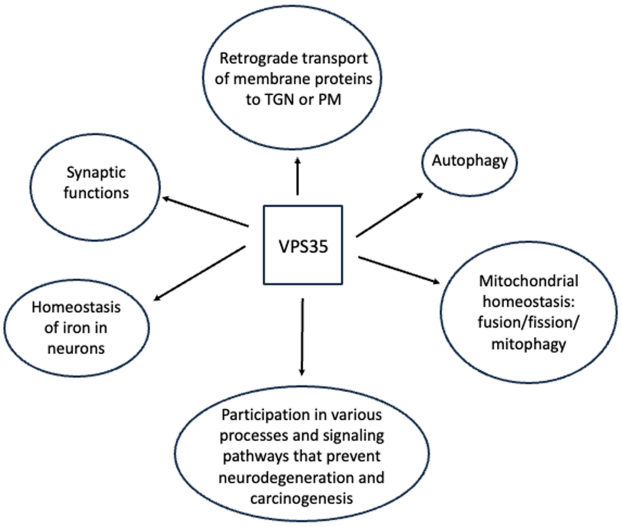

Figure 4. Functions of VPS35 protein within and outside the retromer complex.

in different compartments of the cell. Although there is no yet specific treatment of patients with PD caused by VPS35 genetic impairments [182], functional changes, observed in animal and cell models with mutant VPS35, provide valuable information about sporadic PD.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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БЕЛОК VPS35 И РОЛЬ ЕГО НАРУШЕНИЙ В МИТОХОНДРИАЛЬНОЙ ДИСФУНКЦИИ ПРИ БОЛЕЗНИ ПАРКИНСОНА

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VPS35 — важный белок, играющий многофункциональную роль в различных биологических процессах. Он является ключевым компонентом ретромерного комплекса, участвующего в рециркуляции белков из эндосом в транссеть Гольджи (ТСГ) и плазматическую мембрану. Помимо своей роли в качестве компонента ретромерного комплекса, VPS35 взаимодействует со многими белками и регулирует митохондриальный гомеостаз, митохондриальную динамику (слияние и деление) и другие важные процессы в различных клеточных компартментах. В контексте болезни Паркинсона (БП) существуют убедительные доказательства того, что мутации VPS35, в частности [D620N], оказывают значительное влияние на нормальное функционирование ретромера, митохондриальную дисфункцию и ухудшение здоровья и выживаемости нейронов. В этом обзоре мы кратко рассмотрим структуру и функции ретромерного комплекса, роль VPS35 в митохондриях и, наконец, проанализируем физические и функциональные взаимодействия этого белка с важными для БП белками, связанными с митохондриями.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: VPS35; ретромерный комплекс; болезнь Паркинсона; нейродегенерация; митохондрии; митохондриальная дисфункция

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