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Review

VPS35 and the mitochondria: Connecting the dots in Parkinson's disease pathophysiology

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ABSTRACT

Mutations in VPS35 (PARK17), a key molecule in the retromer complex, are a rare cause of autosomal dominant Parkinson's disease (PD), the second most common neurodegenerative disorder. VPS35 exerts crucial functions within the cell in terms of regulating endosomal trafficking. However new data suggest its relevance also in the regulation of mitochondrial dynamics and homeostasis. Herein, we review the crosstalk between VPS35 and the mitochondria, highlighting the potential relevance to PD pathogenesis. VPS35 is not only a critical player in pathways connected to α-synuclein accumulation and clearance, but also plays a key role in ensuring mitochondrial stability and function. The genetic links of VPS35 to PD and the involvement of VPS35 in different PD related pathological mechanisms highlight the potential for targeting VPS35 as a neuroprotective strategy for PD.

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder, has a prevalence of up to 1% in the over-60 population and it is expected to rise in the coming years (de Lau and Breteler, 2006; Dorsey et al., 2018). Clinically, PD is characterized by the classic triad of bradykinesia, rest tremor ("pill-rolling" tremor) and rigidity as well as non-motor symptoms such as cognitive impairment, olfactory dysfunction and dysautonomic features (Kalia and Lang, 2015; Postuma et al., 2015). Key neuropathological hallmarks of PD include the degeneration of dopaminergic (DA) neurons of the Substantia Nigra (SN) and related pathways with the occurrence of Lewy bodies and Lewy neurites, which are intracellular inclusions mainly consisting of aggregated α-synuclein (Spillantini et al., 1997; Braak et al., 2003). Despite an ever-growing amount of clinical and pre-clinical evidence, a detailed understanding of the pathogenesis of PD remains elusive. PD seems to be the result of a complex interplay between genetic and environmental factors. To date, mutations in more than 20 genes have been found to be associated to PD (Blauwendraat et al., 2020). Many of the proteins coded by these genes, most notably Parkin, PINK-1, and α-synuclein, have been implicated in mitochondrial defects (Larsen et al., 2018). In addition, exposure to a distinct group of mitochondrial toxins can lead to a PD-like phenotype and this has led to the development of toxin-based animal models of the disease (Bové et al., 2005). The association of PD with mitochondrial dysfunction stems from the observations of Langston and colleagues of a Parkinson-like syndrome in patients exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a byproduct in synthetic heroin biosynthesis (Ballard et al., 1985). More recently, research is showing how VPS35, a key molecule in the retromer-complex, could act as modulator of mitochondrial dynamics (Tang et al., 2015a; Wang et al., 2016), further underscoring its relevance in multiple pathways connected to PD pathophysiology. In the present review we aim to highlight how VPS35 could serve as a promising drug target for neuroprotection in PD, not only due its central role in α-synuclein accumulation (Dhungel et al., 2015; Tang et al., 2015a; Eleuteri and Albanese, 2019), but also for its regulatory effects on mitochondrial fusion and fission.

2. Mitochondrial impairment in PD

Mitochondria are membrane-bounded organelles that exist in dynamic networks within the cells. They are traditionally regarded as the powerhouse of the cell, producing adenosine triphosphate (ATP) through oxidative phosphorylation. However, the role of mitochondria extends far beyond the production of ATP, including involvement in many roles essential to cell survival, e.g. calcium signaling, iron

Abbreviations: VPS35, vacuolar sorting protein 35; PD, Parkinson's disease; DN, dopaminergic neurons; SN, substantia nigra; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; PINK1, PTEN-induced putative kinase 1(PINK1); LRRK2, leucine-rich repeat kinase 2; MD, mitochondrial dynamic; Mfn1, Mitofusion 1; Mfn2, Mitofusion 2; Drp1, dynamin-related protein 1

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metabolism and apoptosis regulation among others (Nunnari and Suomalainen, 2012). Diseases affecting mitochondrial function can give rise to dysfunction in virtually any organ (Gorman et al., 2016). Specifically concerning PD, both in genetic and sporadic forms, mitochondrial impairment is thought play an important role (Larsen et al., 2018). Toxins that induce mitochondrial dysfunction have been used to generate animal models of PD. Chemicals such as MPTP (Blum et al., 2001), rotenone (Betarbet et al., 2000) and TaClo (Liu et al., 2018; Yang et al., 2019) directly inhibit mitochondrial complex I of the electron transfer chain, while others, such as paraquat and 6-OHDA, act through reactive oxygen species (ROS) generation, damaging DNA and inducing apoptosis (Blum et al., 2001; Manning-Boğ et al., 2003). Various mechanisms in PD are thought to contribute to the generation of ROS, including the metabolism of dopamine, calcium homeostasis imbalances, dysfunction in PD-causing gene products (e.g. DJ-1, PINK1, parkin or alpha-synuclein), aging as well as mitochondrial dysfunctions (Dias et al., 2013; Puspita et al., 2017). The mitochondria themselves act as both a pivotal site for ROS production, being normally produced during the electron transfer chain, and a target of ROS-induced damages (Puspita et al., 2017), potentially affecting mitochondrial DNA and structures (Blesa et al., 2015).

The effects of the above-mentioned toxins recapitulate some of the abnormalities found in PD patients, including the state of increased oxidative stress observed in the brain in PD patients (Beal, 1995; Jenner et al., 2003), showing how an increased oxidative damage plays a capital role in the disease pathogenesis. Analysis from post-mortem PD patient brain shows reduced activity of mitochondrial complex I in the substantia nigra (SN) (Schapira et al., 1990), which also has been observed in other tissues (Mann et al., 1992). Data from cybrid cell lines further point towards a decrement of complex I activity and implicate a role for mitochondrial DNA (mtDNA) alterations (Swerdlow et al., 1996). An increase in mtDNA point mutations and deletions has been found in the SN of Incidental Lewy body disease and early PD (Lin et al., 2012). However, the association of these mutations with mitochondrial complex I impairment is not entirely clear (Palin et al., 2013). Mitochondrial defects have been investigated also through functional magnetic resonance spectroscopy showing a similar level of mitochondrial impairment in early onset PD and late onset PD, further worsened in patients harboring a PTEN-induced putative kinase 1 (PINK1) mutation (Rango et al., 2020). The potential role of mtDNA mutations in PD pathogenesis is suggested by the finding that some patients who harbor mutations in the polymerase gamma (POLG) gene, which leads to the accumulation of somatic mtDNA mutations, develop a parkinsonian phenotype clinically (Davidzon et al., 2006; Hsieh et al., 2019) and show loss of dopaminergic SN neurons at pathology (Reeve et al., 2013). Thus, a great deal of genetic and environmental data implicates a role for mitochondrial dysfunction in PD, and raise the possibility that somatic mtDNA mutations may contribute to this mitochondrial dysfunction in PD (Clark et al., 2011).

2.1. Genetic forms of PD and mitochondrial dysfunction: a focus on PARKIN-PINK1 mediated mitophagy

Many PD-related genes have functions directly or indirectly linked to mitochondrial homeostasis. Two key PD-related genes connected to mitochondrial impairment are *PRKN (coding for the protein Parkin)* and *PINK1* (PARK2 and PARK6, respectively). Loss of function mutations in *PRKN* and *PINK1* lead to autosomal recessive (AR) PD (Kitada et al., 1998; Valente et al., 2004). PRKN and PINK1 play a key role in mitophagy, the process by which the cell selectively disposes of damaged mitochondria (Palikaras et al., 2018). This process can be carried out through ubiquitin dependent or non-ubiquitin dependent pathways (Khaminets et al., 2016). Mitochondria maintain a stable membrane potential due to the proton gradient generated by its membrane complexes I-IV for the production of ATP (Zorova et al., 2018). Aging, ROS accumulation, or other stressors may cause mitochondria to depolarize, initiating the pathways necessary for its degradation (Zorova et al., 2018). PINK1 and Parkin work as a mitochondrial quality control system, enhancing ubiquitin-dependent mitophagy (Palikaras et al., 2018). In healthy mitochondria, PINK1, localized in the outer mitochondrial membrane (OMM), is internalized via TOM23 and cleaved by Presenilins-associated rhomboid-like protein (PARL) at the level of the internal mitochondrial membrane (IMM) (Jin et al., 2010; Sekine and Youle, 2018). On the other hand, in dysfunctional mitochondria, PINK1 accumulates in the OMM, recruiting the E3 ligase Parkin leading to the ubiquitination of mitochondrial proteins, and consequently to mitochondrial degradation via formation of the phagosome (Chan et al., 2011; Yoshii et al., 2011). Other PD-related genes also have been connected to mitochondrial dysfunction, in particular DJ-1 (McCoy and Cookson, 2011), LRRK2 (Singh et al., 2019) and HTRA2 (Strauss et al., 2005; Vande Walle et al., 2008).

2.2. Interactions between α-synuclein and the mitochondria

There is a large body of evidence suggesting that the accumulation and toxicity of α-synuclein is a pivotal pathologic step of PD pathophysiology (Lashuel et al., 2013). This view is supported by the identification of autosomal dominant (AD) PD caused by missense mutations, as well as multiplication, of the α-synuclein gene SCNA (Polymeropoulos et al., 1997; Singleton et al., 2003; Chartier-Harlin et al., 2011). Interestingly, α-synuclein itself has been implicated in the mitochondrial dysfunction seen in PD patients. Aggregated α-synuclein causes mitochondrial complex I inhibition in cellular and animal models (Chinta et al., 2010; Reeve et al., 2015), potentially by blocking mitochondrial protein import via TOM20 (Di Maio et al., 2016). In addition, mice lacking α-synuclein appear to be protected against MPTP toxicity (Dauer et al., 2002; Drolet et al., 2004). Other data emphasize the role of α-synuclein in mitophagy. For example, mice overexpressing human A53T α-synuclein display abnormal mitophagy and high mitochondrial fragmentation (Chinta et al., 2010; Chen et al., 2015).

From the above observations, it becomes clear, firstly, that mitochondrial derangement plays a relevant role in PD and, secondly, that a number of connections between different pathological pathways may converge on the mitochondria **(**Fig. 1**).**

3. VPS35 and the mitochondrion

3.1. Summary on VPS35 function in PD

Vacuolar protein sorting 35 (*VPS35*) is an evolutionary conserved protein in eukaryotic cells that acts as the central hub of the retromer cargo recognition complex. The retromer is composed of a heterotrimeric core complex formed by Vacuolar Protein Sorting (VPS35, VPS26 and VPS29) involved in protein transportation, and by a membrane-targeting dimer of nexins (i.e. SNX1, SNX2, SNX5, SNX6, SNX32), necessary for the adhesion of the complex to the endosomal membrane. VPS35 is localized at the level of the early endosome and is well characterized as a controller of the retrograde trafficking of cargo proteins from early endosome to the trans-Golgi network (Hierro et al., 2007; Harbour et al., 2010; Trousdale and Kim, 2015). Two separate studies link point mutations in *VPS35* to late-onset PD (Vilariño-Güell et al., 2011; Zimprich et al., 2011). Many VPS35 variants of uncertain significance also have been described in the literature (Verstraeten et al., 2012), but it remains unclear if any of these influence susceptibility to PD. The *VPS35* gene (PARK17, OMIM-601501) localizes on chromosome 16q11.2 and spans 29.6 kb divided in 17 exons (Deng et al., 2013). To date only the D620N (c.1858G > A) mutation has been demonstrated to be pathogenic with a relatively low frequency of 1.3% in familial cases and 0.3% in sporadic PD (Guella et al., 2012; Kumar et al., 2012). The clinical presentation of PARK17 PD patients is comparable to that of classical PD except for an earlier mean age of onset (mean age: 50.3 ± 7.3) (Sheerin et al., 2012).

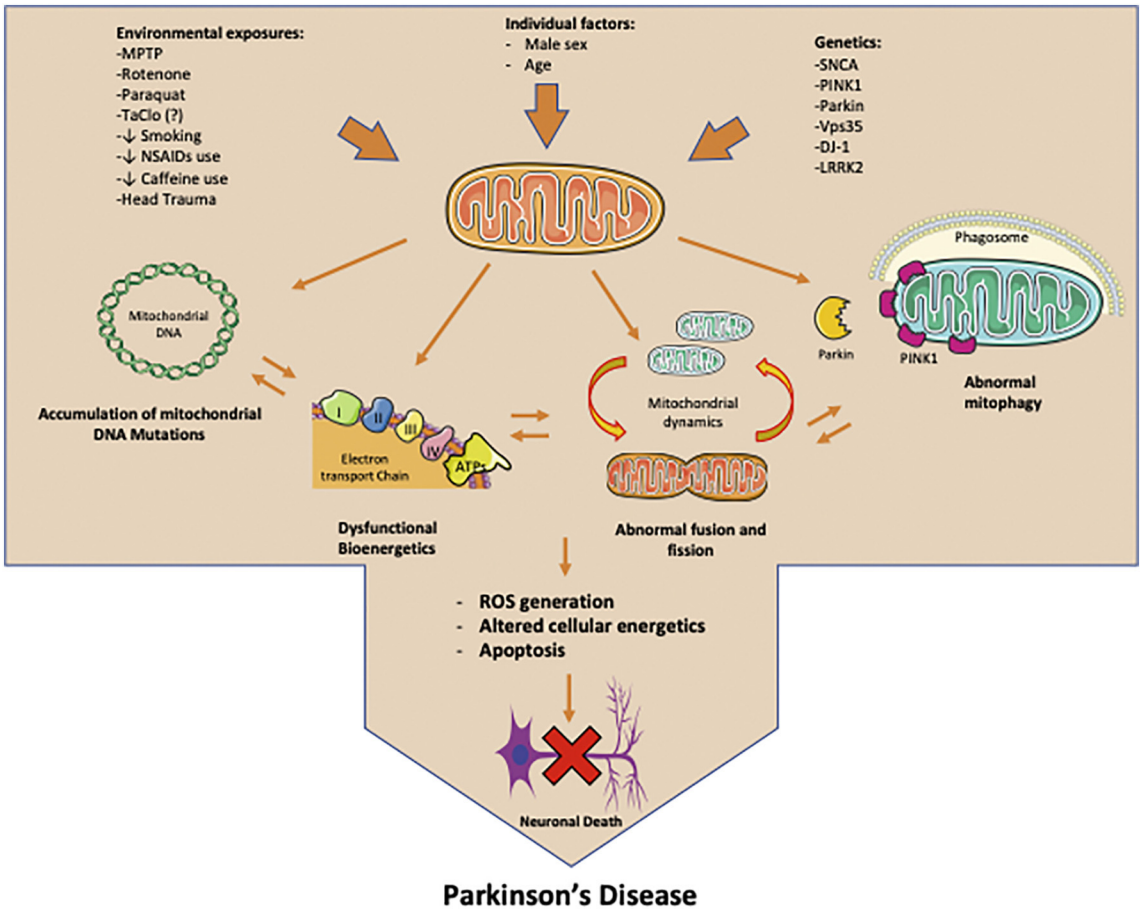

Fig. 1. Mitochondrial physiology derangement is a key feature of Parkinson's disease. Environmental exposures (such as toxins or even head trauma), Individual factors and the underlying genetics of each individual may predispose to PD and are implicated in mitochondrial impairments. MtDNA mutations, dysfunctional bioenergetics as well as abnormal mitochondrial dynamics and mitophagy lead to an increased generation of ROS ultimately leading to dysregulated apoptosis and consequent neurodegeneration (Adapted from Servier Medical Art images, creative common license).

Regarding the possible mechanism by which mutations in VPS35 lead to PD, different data highlight the possibility that there is loss of VPS35 function in both sporadic PD and in PD associated with the VPS35-D620N mutation. VPS35 protein is mislocalized in PD patient brains and found in LBs (Dhungel et al., 2015). Additionally, VPS35-D620N-expressing cells show a reduction at the endosomal level with an increase in perinuclear localization (Zavodszky et al., 2014). The VPS35-D620N mutation impairs autophagy by dysrupting ATG9A trafficking and reducing the localization of WASH complex to the endosomes (Zavodszky et al., 2014). VPS35-D620N in knock-in (KI) mice show a robust and widespread tau-positive pathology, indicating a gain of function or dominant-negative mechanism. (Chen et al., 2019). Moreover, VPS35-D620N KI mice, or mice with knock-down of VPS35, show altered LRRK2-mediated Rab protein phosphorylation, indicating that VPS35 could play a major role in controlling LRRK2 kinase activity, and showing again how the VPS35-D620N mutation could result in a gain of function (Mir et al., 2018). Conversely, expression of the LRRK2 G2019S mutation leads to a deficiency of VSP35 in mouse N2A neuroblastoma cells (MacLeod et al., 2013). Furthermore, VPS35 levels are decreased within SN dopaminergic neuron in *sporadic* PD patients brains (MacLeod et al., 2013) or mislocalized at the level of Lewy bodies (Dhungel et al., 2015).

VPS35, and the retromer complex in general, have a variety of functions within neurons that me be relevant in the context of PD, in particular in regulation and maintenance of synapses (Temkin et al., 2011; Wang et al., 2013; Loo et al., 2014) and control of dopamine transporter (DAT) recycling (Wu et al., 2017). Over the last decade, research efforts also have focused on the relationship between VPS35 and α-synuclein clearance (Miura et al., 2014; Dhungel et al., 2015; Tang et al., 2015b). It has been demonstrated that VPS35 exerts a regulatory effect on: (i) lysosomal function; Sortilin and CI-MPR, essential proteins for the lysosome-mediated degradation pathways also related to trafficking and maturation of Cathepsin D, are recognized VPS35 cargo-proteins (McGlinchey and Lee, 2015), (ii) macroautophagy; specifically VPS35 controls the recruitment of the WASH complex (Zavodszky et al., 2014), (iii) chaperone mediated autophagy, in which VPS35 is essential in retrieving the receptor LAMP2A (Tang et al., 2015b). A complete and thorough discussion of all the VPS35-PD related pathways is beyond the scope of this review and is discussed elsewhere (Eleuteri and Albanese, 2019).

3.2. *VPS35 and mitochondrial dysfunction*

In a landmark study it was shown that the retromer complex mediates the formation of mitochondria-derived vesicles (MDVs) directed towards the peroxisome (Braschi et al., 2010). MDVs constitute a mitophagy-independent quality control system for the mitochondria, transporting selected cargo proteins to the lysosome or to the peroxisome for degradation (Soubannier et al., 2012; Sugiura et al., 2014). VPS35 has been shown to regulate the subpopulation of MDVs targeting the peroxisome; however, it could have a major role also in lysosome-targeting vesicles (Braschi et al., 2010; Wang et al., 2016). Notably, PARKIN and PINK1 also play a role in the formation of MDVs (McLelland et al., 2014). The retromer may also play an important role

Table 1
Summary of the VPS35-mitochondria interaction.

Pathway involved	Molecules involved	Mechanism	Reference(s)
Mitochondria-derived vesicles (MDVs)	MDV cargo proteins	VPS35 implicated in the formation of MDVs directed to the peroxisome or the lysosome for the degradation of mitochondrial proteins	(Braschi et al., 2010; Wang et al., 2016)
Apoptosis	Bcl-XL	The retromer facilitates the transport of the anti-apoptotic molecule Bcl-XL to the OMM	(Farmer et al., 2019)
Membrane stability	Ceramides and their precursors	The retromer prevents the accumulation of ceramides in mitochondrial membrane	(Lin et al., 2018, 2019)
Mitochondrial fusion	Mfn2, MUL1	VPS35 removes MUL1 from the OMM preventing the ubiquitination of Mfn2	(Tang et al., 2015a)
Mitochondrial fission	Drp1	VPS35 removes inactive Drp1 complexes from the OMM allowing the formation of active Drp1 complexes	(Wang et al., 2016, 2017)

in apoptosis by facilitating the transport of Bcl-XL, an important anti-apoptotic protein, to the OMM, potentially accounting for why retromer deficient cells are more prone to apoptosis (Farmer et al., 2019). Recent data connect VPS35 with *PLA2G6* (PARK 14), a gene which encodes the phospholipase A2, a protein involved in lipid metabolism. *PLA2G6* mutations are also associated with atypical forms of familial PD (Yoshino et al., 2010). Loss of PLA2G6 affects retromer function, destabilizing VPS35 and VPS26. In turn, a dysfunctional retromer system causes the build-up of ceramide inside plasma membranes and organelles, including mitochondria, ultimately leading to cellular dysfunction and death (Lin et al., 2018, 2019).

See Table 1 for a summary of the VPS35-mitochondria interactions.

3.3. VPS35 and mitochondrial dynamics

Mitochondria are exceptionally dynamic organelles; they constantly fuse and divide (i.e. fusion and fission). These processes are an integral part of mitochondrial homeostasis (Ni et al., 2015; Sironi et al., 2020). Remarkably, mitochondrial dynamics (MD) is critical for energy generation and mitochondrial turnover. Mitochondrial fusion may produce elongated mitochondrial networks with increased ATP production and decreased mitophagy. On the other hand, mitochondrial fission can be asymmetrical, i.e. it can produce a depolarized daughter that will be eliminated via mitophagy, together with a more normal daughter that persists (Twig and Shirihai, 2011; Larsen et al., 2018). In order to fuse, two adjacent mitochondria require the interaction of proteins Mitofusin 1 and 2 (Mfn1 and Mfn2) in the OMM and Opa1 for the IMM (Hoppins et al., 2007). Both Mitofusions (Mfn1 and Mfn2) are required for fusion and their deletion causes important developmental impairments in animal models (Chen et al., 2003). Their mRNA levels differ throughout the body, with Mfn2 preferentially expressed in brain, muscles, adrenal glands, and brown adipose tissue (Eura et al., 2003; Schrepfer and Scorrano, 2016). On the other hand, a major mitochondrial protein mediating fission in mammalian cells is the GTPase dynamin related protein 1 (Drp1, also known as Dlp1, i.e. dynamin-like protein 1) (Smirnova et al., 2001). Drp1 polymerizes into ring- or spiral-like structures around the mitochondrial membrane constricting it and inducing the fission of the mitochondrion (Hoppins et al., 2007). Another relevant player in MD is the mitochondrial ubiquitinase ligase 1 (MUL1, also known as MAPL, i.e. mitochondrial anchored protein ligase), an E3 ligase located in the OMM able to ubiquitinate Mfn2 promoting its degradation (Braschi et al., 2009). Notably, MUL1 also is involved in mitochondrial fission, being responsible for SUMOylation of Drp1, possibly leading to the stabilization of Drp1 complexes (Wasiak et al., 2007).

Recent data indicate that VPS35 is a putative modulator of MD. Experiments by Tang and colleagues have demonstrated that VPS35 affects fusion through regulation of Mfn2 by controlling the trafficking of MUL1 to the mitochondrial membrane (Tang et al., 2015a). It was observed that VPS35 is crucial for the removal of MUL1 from the OMM showing how, in dopaminergic neurons of mice depleted of VPS35, the concentration of MUL1 increases, leading to a MUL1-dependent ubiquitination of Mfn2, further leading to Mfn2 degradation and consequent inhibition of mitochondrial fusion (Tang et al., 2015a). Thus, loss of VPS35 leads to increased MUL1 on the OMM with consequent ubiquitination and degradation of Mfn2, and thus to decreased mitochondrial fusion.

Other data point towards the role that VPS35 plays in regulation of Drp1. Wang et al. demonstrated that VPS35 enhances mitochondrial Drp1 turnover, promoting the formation of MDVs directed to the lysosome in order to remove inactive Drp1 from the OMM. They observed in different cell lines that the PD-associated VPS35-D620N mutation resulted in an increased interaction between VPS35 and inactive Drp1, freeing the membrane from inactive complexes and promoting the polymerization of new active Drp1, hence boosting fission and fragmentation of the mitochondria (Wang et al., 2016, 2017). Notably, they also reported an increased VPS35-Drp1 interaction in conditions of increased oxidative stress, which is a feature frequently observed in PD brains (Beal, 1995; Jenner et al., 2003). Thus, loss of VPS35 leads to the retention on the OMM of inactive Drp1, and therefore to decreased mitochondrial fusion.

Fig. 2 offers a schematic view of the VPS35/retromeric modulation of Mitochondrial Dynamics.

In the study performed by Wang and colleagues, overexpression of wild-type or D620N mutant VPS35 caused mitochondrial fragmentation while VPS35 depletion promoted mitochondrial fusion (Wang et al., 2016). In contrast, Tang et al. reported that VPS35 depletion gave rise to fragmented mitochondria (Tang et al., 2015a). Notably, in both studies the overexpression of mutant D620N VPS35 gave rise to mitochondrial fragmentation. These disparate results may be attributable to differences in the cellular models used or in the techniques performed to maniuplate VPS35. More research is needed to address these issues.

VPS35 also may interact with Parkin. Analysis performed on *Drosophila* models overexpressing VPS35 showed a rescue of parkin-induced deficits (Malik et al., 2015). The interaction between VPS35 and Parkin is further supported by other studies showing that VPS35 is a target of parkin-mediated ubiquitination (Martinez et al., 2017; Williams et al., 2018). Curiously, this process doesn't promote VPS35 proteasomal degradation and it may be implicated in modulating retromer-mediated endosomal sorting (Williams et al., 2018).

4. Discussion and future perspectives

To date, only symptomatic therapies are available for PD, and many are based on dopaminergic enhancement (Espay et al., 2017). Some clinical studies aimed at identifying neuroprotective strategies have centered on the mitochondria and energy metabolism, such as trials of coenzyme Q10 (Flint Beal et al., 2014) or creatine (Kieburtz et al., 2015), but they failed to demonstrate clinical benefits. The newly discovered role of VPS35 in mitochondrial dynamics opens interesting connections with other key PD pathological processes. VPS35 already is regarded as a candidate target for its action on α-synuclein (Eleuteri and Albanese, 2019), and in this review we present a mounting body of

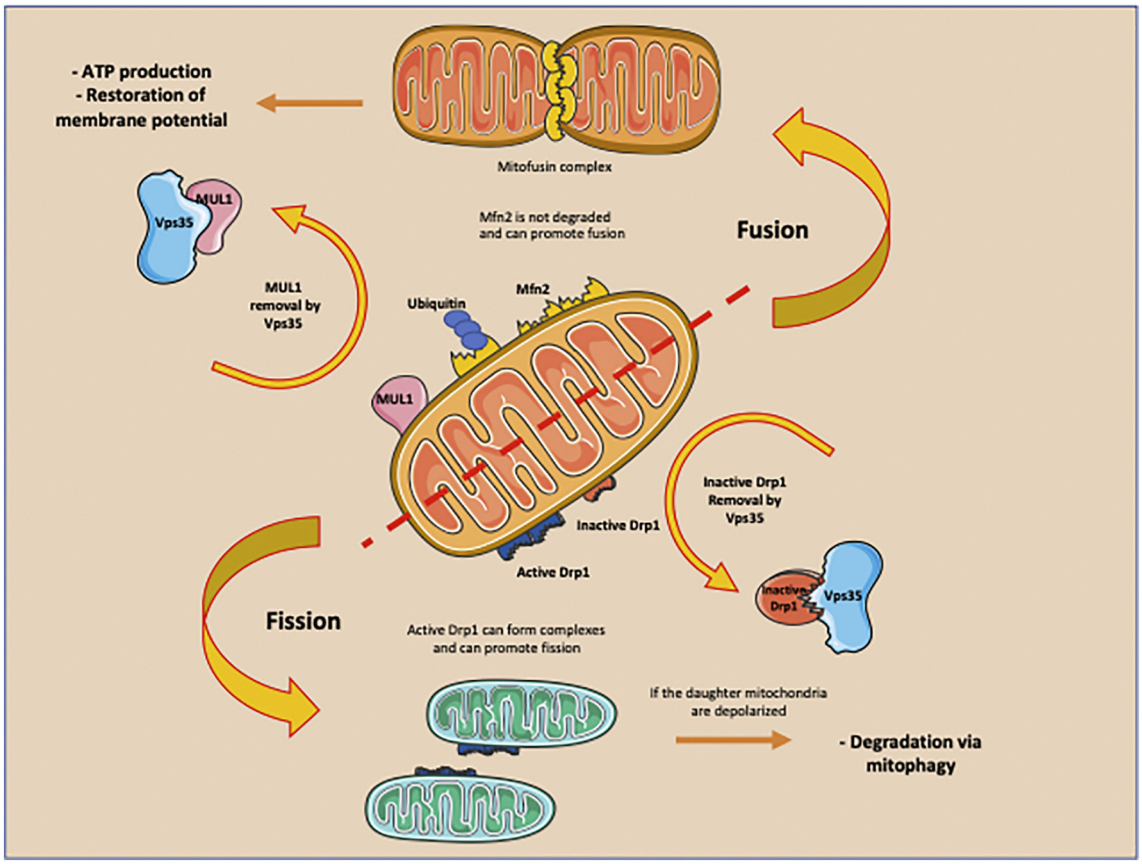

Fig. 2. A schematic representation of the role of VPS35 in mitochondrial dynamics. VPS35 removes MUL1 from the OMM, preventing Mfn2 ubiquitination and degradation, hence promoting fusion. VPS35 also has a role in the removal of inactive Drp1 complexes that, once removed, may allow the polymerization of active Drp1 ultimately leading to mitochondrial fission. Elongated mitochondrial network can provide the cell with more ATP and potentially restore transient mitochondrial depolarization while, after fission, the depolarized daughter mitochondria may be degraded by mitophagy (Adapted from Servier Medical Art images, creative common license).

evidence connecting VPS35 with mitochondrial homeostasis. It is known that MD is directly linked to mitochondrial turnover, specifically, mitochondria that undergo fission can generate smaller, depolarized, mitochondria that will face mitophagy. Conversely, the fusion of two mitochondria allows the mix of their contents, potentially restoring membrane potential (Twig and Shirihai, 2011; Larsen et al., 2018). Interestingly, as noted in this review, VPS35 indirectly regulates both fusion and fission, so that loss of VPS35 may impair both of these pathways. Many PD genes identified through the years have functions directly or indirectly linked to mitochondrial homeostasis. Other genetic causes of PD, such as loss of function mutations in PARKIN and PINK1, point to a central role for disruption of mitochondrial homeostasis in the pathogenesis of PD (Pickrell and Youle, 2015), and thus upregulation of VPS35 is a promising strategy for potential neuroprotection in PD. Genetic studies suggest that common variants within the same genes associated with monogenic PD-associated mutations, such as LRRK2, SCNA or PRKN, could confer an altered susceptibility to sporadic PD (Nalls et al., 2011; Oczkowska et al., 2014). Consequently, important advances in PD pathogenesis could derive from the study of rare genetic forms of the disease, which may reveal new potential treatments exploitable in the context of sporadic PD.

The multiple interconnections of VPS35 with other PD-associated genes and its roles as a regulator of protein trafficking and autophagy and as a mediator of mitochondrial function highlight VPS35 as a therapeutic target in the setting of PD-associated mitochondrial dysfunction. Cells with deficient or mutated VPS35 have morphologically abnormal mitochondria (Tang et al., 2015a; Wang et al., 2017); however, the effect of VPS35 modulation concerning mitochondrial homeostasis remains to be fully elucidated. Given the important role of VPS35 in both fusion and fission, it will be crucial to better understand the impact of VPS35 modulation on mitochondrial homeostasis, with particular reference to tissue and/or model-specific differences in the relative roles of one pathway over the other. To address this, the tissue specific expression of additional molecular players in the VPS35-MD interaction should also be evaluated.

The studies outlined here show how VPS35 represents an important regulator of crucial pathways involved in PD pathogenesis controlling the accumulation and clearance of alpha-syn (Miura et al., 2014; Dhungel et al., 2015; Tang et al., 2015b), mitochondrial dynamics (Tang et al., 2015a; Wang et al., 2017) and synaptic functions (Temkin et al., 2011; Wang et al., 2013; Loo et al., 2014). Consequently boosting VPS35 function in neurons could represent a disease modifying strategy in the treatment of PD. Currently, different approaches have been evaluated to increase VPS35 levels in the neurons and to develop a potential drug candidate. A strategy that may be promising for the treatment of an endosomal-related disorder such as PD but also Alzheimer's disease (Berman et al., 2015) is the development of a pharmacological approach aimed at stabilizing the retromer complex and precisely regulating VPS35 levels in cells using the thiophene thiourea derivatives R33 and R55 (Mecozzi et al., 2014). Alternatively, VPS35 could be directly modulated in the brain by gene therepy through viral vectors, i.e. adenovirus or lentivirus (Goverdhana et al., 2005), or through gene editing techniques such as CRISPR/Cas9 (Epstein and Schaffer, 2017). Hovewer, pathways for mitochondrial homeostasis are ubiquitous and mediate vital functions in nearly all cells, so tight dose and regional titration might be necessary in order to safely achieve a

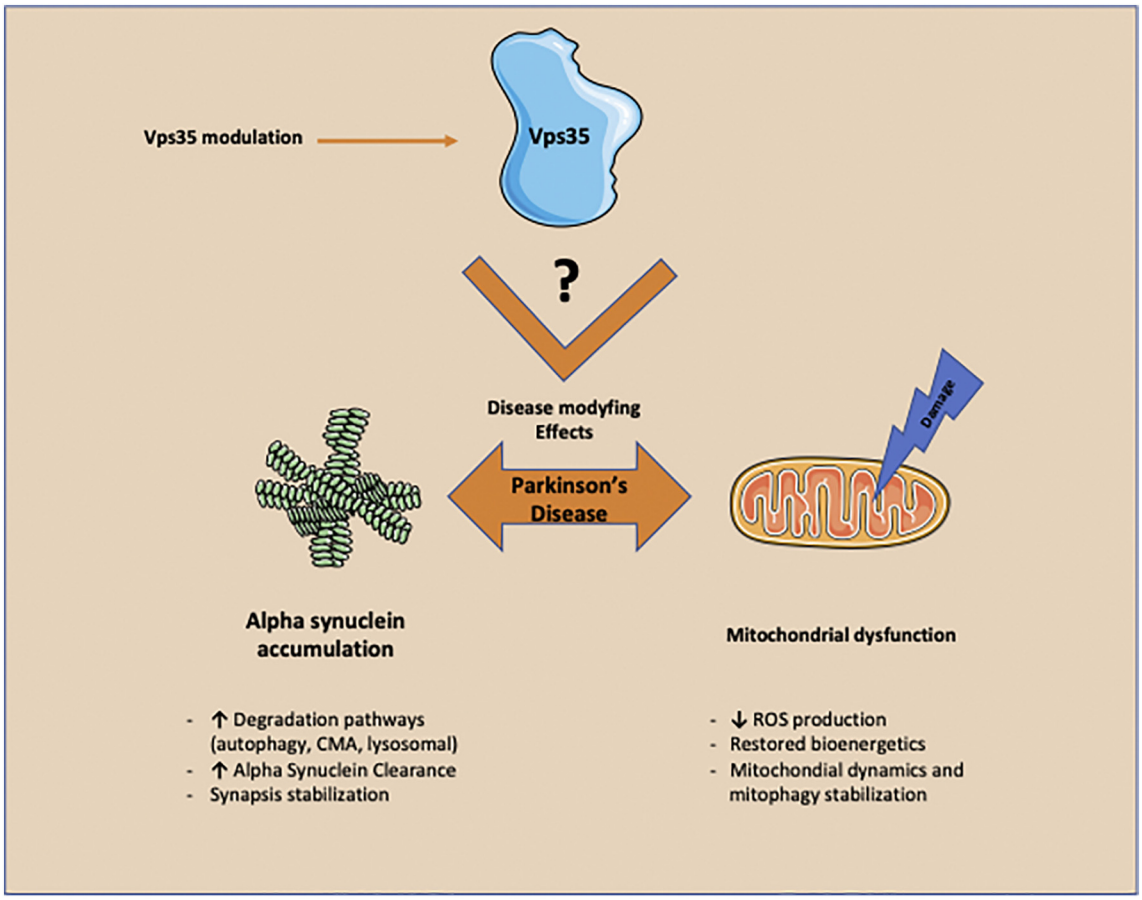

Fig. 3. Hypothetical drug exploiting the "double nature" of VPS35. Stabilization of the retromer complex could potentially act both on α-synuclein clearance pathways and PD-related mitochondrial dysfunction. Abbreviation: CMA: chaperone mediated autophagy; ROS: reactive oxygen species (Adapted from Servier Medical Art images, creative common license).

therapeutic effect in patients. Furthermore, PD is a heterogeneous disorder with respect to pathophysiology, and VPS35-targeted therapies may have different effects in different patient subtypes. Therefore, although the predictive value of rodent PD models with regards to neuroprotective strategies may be limited, it is prudent to evaluate the impact of increasing VPS35 in multiple different genetic and pharmacological rodent PD models to assess its neuroprotective role against mitochondrial, endosomal and lysosomal dysfunctions. The results may provide insights as to which group of PD patients may be most likely to benefit from a VPS35-based treatment.

In conclusion, the double nature of VPS35 (Fig. 3) in regulating α-synuclein accumulation and as an important player in mitochondrial homeostasis may offer an invaluable opportunity to develop VPS35-targeted therapies in order to tackle these two pathophysiological hallmarks of PD in order to achieve neuroprotection. Additional studies are needed to clarify if there may be subgroups of PD patients who are preferentially responsive to a VPS35-based treatment.

Author contribution

GC, DKS and SE conceived the idea, CG and SE wrote the initial draft of the manuscript; GC,DKS and SE critically reviewed and edited the manuscript.

Declaration of Competing Interest

G.C., S.E. and D.K.S have nothing to disclose.

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