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Deregulation of autophagy and vesicle trafficking in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease characterized pathologically by the selective loss of dopaminergic neurons in the substantia nigra and the intracellular accumulation of α-synuclein in the Lewy bodies. While the pathogenic mechanisms of PD are poorly understood, many lines of evidence point to a role of altered autophagy and membrane trafficking in the development of the disease. Emerging studies show that connections between the deregulation of autophagy and synaptic vesicle (SV) trafficking may contribute to PD. Here we review the evidence that many PD related-genes have roles in both autophagy and SV trafficking and examine how deregulation of these pathways contributes to PD pathogenesis. This review also discusses recent studies aimed at uncovering the role of PD-linked genes in autophagy-lysosome function.

Keywords

Parkinson's disease; autophagy; synaptic trafficking; LRRK2

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with more than 10 million people living with the disease worldwide. PD is characterized by the loss of dopaminergic neurons in the substantia nigra overtime, which leads to a variety of motor deficits including tremor and rigidity. While the majority of cases are sporadic, around 5% of cases result from a clear genetic cause [1], and recent advances in genome-wide analyses have uncovered a number of risk factors relevant for sporadic PD [2–7].

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Author contributions

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Conflicts of interest

None.

A major pathological hallmark of PD is the accumulation of aggregated proteins, mainly α-synuclein, in Lewy bodies. This neuropathological characteristic of PD has prompted great interest in understanding the relevance of protein homeostasis pathways in disease pathogenesis. Autophagy is a major degradation pathway for protein aggregates and plays a critical role in the maintenance of protein homeostasis. Important experimental evidence for a role of autophagy in PD and neurodegeneration came from observations in genetic animal models including autophagy-deficient animals. Multiple mouse models lacking a key autophagy gene (e.g., Atg5, Atg7, Ulk1/2) show neurodegeneration typically preceded by axonal dystrophy suggesting an essential role of autophagy in regulating axon homeostasis and preventing neurotoxicity [8–14]. Moreover, animals lacking the core autophagy gene, Atg7 in dopamine neurons display dystrophic neurites, progressive neuronal loss, locomotor deficits, and presynaptic accumulation of α-synuclein and LRRK2 [8]. Results from many genome-wide association studies have also linked autophagy and lysosomal function to PD pathogenesis and a recent meta-analysis has identified 17 additional risk loci, many of which are associated with the autophagy-lysosome pathway [2].

In addition to the autophagy-lysosomal pathway, insights from genetic studies of PD implicate dysfunction of synaptic vesicle (SV) cycling, another neuronal membrane trafficking pathway, as an underlying mechanism of disease development [15, 16]. While previously thought to be independent pathways, recent studies suggest autophagy and SV trafficking converge at presynaptic terminals [17–21]. Here, we review studies linking dysfunction in the autophagy-lysosomal pathway to PD and highlight how the intersection of SV trafficking and autophagy is emerging as an important mechanism of PD pathogenesis.

Disruption of SV endocytosis and macroautophagy by PD mutants

Recent studies suggest the importance of two neuronal membrane trafficking pathways, SV cycling and autophagy, in the development of PD [22–28]. Without proper maintenance of SV cycling, synapses may become dysfunctional over time, leading to a loss of neuronal communication and ultimately to neurodegeneration [29, 30]. A number of PD-linked proteins, including LRRK2, EndophilinA (EndoA), synaptojanin1 (synj1), dynamin, and auxilin, have well-defined roles in SV endocytosis (Figure 1) [31, 32] Intriguingly, more recent evidence suggests that many of these proteins have additional roles in autophagy. Together, these findings suggest that there is an extensive interaction between SV trafficking and autophagy at the presynapse. Alternatively, there may be neuronal synapse-specific autophagy machinery that is particularly compromised in PD. As the endocytic pathway also merges with autophagy [33], it remains unclear whether these proteins are modified in a way that dictates their function in one pathway or another or if these proteins directly control the intersection of SV cycling and autophagy. Here, we discuss these proteins and how their PD-linked mutations lead to the deregulation of these two pathways.

LRRK2

Missense mutations of LRRK2 are linked to the most common inherited forms of PD [34, 35]. LRRK2 protein is reportedly localized to synaptic compartments where it interacts with a variety of SV endocytic proteins and appears to regulate SV trafficking and distribution

[36–38]. Multiple studies have shown that the loss of LRRK2 or the expression of PD mutant G2019S slows the kinetics of SV endocytosis, but these same studies find differential effects of LRRK2 on SV exocytosis [36, 39–41]. Additionally, loss of function or hyperactivation of LRRK2 kinase function leads to deregulation of autophagy [42–46]. Multiple PD-linked pathogenic mutations of LRRK2 result in the hyperactivation of its kinase function, suggesting that chronic or improper phosphorylation of LRRK2 substrates may underlie PD development through alterations in SV cycling and autophagy [47].

Despite a variety of studies linking LRRK2 to autophagy, two questions remain unanswered. First, it remains unclear, whether LRRK2 positively or negatively regulates autophagy. Second, LRRK2 has been implicated in regulating multiple steps of autophagy, including initiation and termination, resulting in uncertainty as to the precise role of LRRK2 in autophagy. Major attempts to address the function of LRRK2 have utilized pharmacological inhibitors as well as manipulations that increase LRRK2 activity, namely the overexpression of LRRK2 G2019S, a PD-linked mutation that leads to hyperactivation of LRRK2 kinase activity. Adding to the complexity, alterations in the activity of LRRK2 in either direction result in similar outcomes. Specifically, both the silencing of LRRK2 through gene knockdown and the overexpression of LRRK2 hyperactive kinase mutant result in impaired macroautophagy-mediated degradation in cell lines [48, 49]. Identification of direct LRRK2 targets that mediate autophagy regulation may provide insight into these unsolved issues.

EndophilinA

While associated with PD through its interaction LRRK2, EndoA (encoded by SH3GL2) was also recently identified as a novel risk factor for sporadic PD [2]. EndoA is a protein critical for clathrin-mediated endocytosis at nerve terminals [50, 51]. Studies performed in *Drosophila* have shown that EndoA phosphorylation is increased upon LRRK2 G2019S expression. Interestingly, both the LRRK2 kinase loss-of-function and gain-of-function impair synaptic endocytosis [36]. Subsequent studies have found that LRRK2-mediated phosphorylation of EndoA biases the membrane-deforming capabilities of this protein to form high curvature membranes that recruit ATG3 and thus initiate autophagosome formation. The loss of EndoA results in degeneration of the fly eye which, importantly, is not rescued by either non-phosphorylatable or phosphomimetic EndoA [20]. These results again suggest that a balance in EndoA phosphorylation state is necessary to maintain healthy cells. This balance would be altered by either the loss of LRRK2, resulting in non-phosphorylated EndoA, or overactivation of LRRK2 kinase resulting in chronic phosphorylation of EndoA. This finding may help explain how alterations in the activity of LRRK2 in either direction disrupt dynamic phosphorylation, which may underlie defects in autophagy and other pathways. While these studies require future validation in mammalian systems, they strongly argue that a careful examination of the effect of chronic phosphorylation of verified LRRK2 substrates is necessary to understand the various roles of LRRK2 more completely.

Past studies of EndoA have shown that the triple knock-out of all three EndoA isoforms in mice results in neurodegeneration. RNA-SEQ analysis revealed changes in pathways including synaptic transmission and protein homeostasis. The most striking finding was an

increase in the ubiquitin-proteasome system (UPS) E3 ligase, FBXO32. Studies revealed a direct interaction of FBXO32 and EndoA on autophagosomes. EndoA triple knockout mice showed a reduction in LC3B, Atg5, and autophagosomes while the loss of FBXO32 in flies caused defective autophagosome formation, mimicking EndoA loss. The authors suggest that a disruption in either EndoA-autophagy or FBXO32-UPS overburdens the remaining pathway, disrupting protein homeostasis, and initiating neurodegeneration [19].

Synaptojanin1

Several studies have identified SYNJ1/PARK20 as an early onset Parkinsonian gene [52–54]. As discussed above, synj1 is an EndoA binding partner that acts in SV endocytosis [55–58]. One study examining changes in the proteome and phosphoproteome of brains from LRRK2 hyperactive kinase mutation R1441C expressing flies revealed major changes in SV proteins [59]. Further investigation into these alterations identified synj1 as a putative LRRK2 substrate [59]. Additional studies revealed a distinct phosphorylation site in synj1 (T1205) *in vitro* using purified LRRK2 G2019S and showed this phosphosite is critical for the interaction of synj1 with EndoA [39]. Aside from its interaction with LRRK2, mutations in the SAC1 and 5′phosphatase domain of synj1 are also linked to hereditary early-onset PD [52–54, 60]. While synj1 is known for its role in SV endocytosis, recent studies have found an additional role of synj1 in autophagy. One PD linked mutation, R258Q, in the synj1 SAC1 domain leads to an imbalance in lipid production that results in the accumulation of WIPI2/Atg18a, a PI(3)P/PI(3,5)P2 binding protein. This accumulation blocks autophagosome maturation at the *Drosophila* neuromuscular junction and in patient-derived neurons. Interestingly, SV endocytosis remains intact in synj1 RQ mutant flies [61]. However, other investigations in RQ knock-in mice have found a disruption in SV endocytosis, an accumulation of clathrin-coated intermediates, and dystrophic terminal changes [62]. Prior to this study, the role of the SAC1 domain in endocytosis was not well documented; though, it was known that the 5′phoshatase domain is necessary for SV endocytosis [56]. Whether there is a direct role of the SAC1 domain of synj1 in autophagy or if these deficiencies are due to an endocytic defect needs further study. Additionally, recent studies in zebrafish show that a 5′ phosphatase synj1 mutation, D732A, blocks autophagy in photoreceptor neurons [18]. Again, the contribution of disrupted endocytosis to the deregulation of autophagy remains uncertain in this system and requires further study to parse apart the exact role of synj1 in endocytosis versus autophagy. Nonetheless, these studies show synj1 PD-linked mutations disrupt autophagy and, together with the EndoA findings, raise an interesting potential of synapse-specific autophagy machinery that is disrupted in PD.

Dynamin

The dynamin family of GTPases is critical for membrane scission during endocytosis events including SV endocytosis [63]. Recent studies have shown genetic and biochemical interaction between dynamin isoforms and LRRK2. For example, LRRK2 has been shown to interact with dynamins 1–3 in HEK cells and, more specifically, with dynamin 1 in neuronal cultures [64]. Additionally, genetic variability within dynamin 3 was shown to modify the age of onset of PD in LRRK2 G2019S carriers [65]. While the role of the dynamin family in autophagy remains unclear, one recent study has shown dynamin 2 plays

a role in the activation of mTORC1 through the endocytosis of amino acids in HEK cells [66]. This again highlights the interconnectivity of endocytosis and autophagy and underpins the need for additional studies to understand the role of this important endocytic protein in neuronal autophagy and to determine the functional role of its interaction with LRRK2.

Rab GTPases

A recent landmark study has shown that multiple members of the Rab family of small GTPases are physiological substrates of LRRK2 [23]. As critical regulators of membrane trafficking, Rab GTPases are likely candidates to regulate neuronal autophagy and SV cycling [67–69]. Interestingly, mouse models harboring LRRK2 hyperactive kinase mutations display defects in synaptic and autophagic function, suggesting chronic phosphorylation of Rab GTPases may underlie these alterations [36, 42, 43]. Indeed, the Rab GTPases identified as LRRK2 substrates, Rab8, 10, and 12, all have putative roles in autophagy and endocytic recycling, particularly in the context of neurological disease conditions [22, 24–28, 67, 70–76]. Further, all three of these Rab proteins have been shown to associate with SVs through mass spectrometry analysis of the protein composition of purified SVs [69]. The exact role of these proteins in neurons and the effect of LRRK2-mediated phosphorylation on their function remains a topic of great interest, which is expected to garner considerable insight into how alterations in neuronal trafficking pathways contribute to PD pathogenesis.

Auxilin

Aside from LRRK2 and its interactors, additional genes implicated in PD have roles in SV trafficking. Specifically, mutations in DNAJC6 have been associated with juvenile Parkinsonism and early-onset PD [54, 77, 78]. DNAJC6 encodes auxilin, a protein enriched in nerve terminals where it functions in clathrin uncoating during endocytosis [79–82]. The effects of its PD-linked mutations on synaptic endocytosis are currently unknown and warrant further study.

Parkin

Mutations in Parkin, an E3 ubiquitin ligase, result in juvenile-onset PD [83]. While the role of Parkin in mitophagy has been extensively studied [84, in this issue], the role of Parkin in regulating synaptic proteins remains under investigation Several synaptic proteins have been shown to be Parkin substrates and/or interactors [85–90]. In particular, Parkin has been shown to ubiquitinate EndoA, synj1, and dynamin, proteins critical in regulating SV endocytosis, as well as another PD-risk factor, Synaptotagmin XI (Syt11) that will be discussed later in this review [87, 90]. The effect of Parkin ubiquitination of these proteins is yet to be investigated; however, marked Parkin upregulation is seen in the brains of both EndoA triple KO mice and synj1-RQ knock-in mice [62, 90]. One potential explanation for this finding is that Parkin upregulation functions as a compensatory mechanism to counteract autophagy defects in these mutant mice [19]. Altogether, these findings suggesting a complex interplay between Parkin and SV endocytic proteins and further corroborate a link between SV endocytosis, autophagy, and PD pathogenesis.

α-synuclein

Mutations or copy number variations of SNCA, the gene encoding α-synuclein, are associated with familial PD [91, 92] while the accumulation of α-synuclein in Lewy bodies is a pathological hallmark of sporadic and many genetically linked PD cases. While wild-type α-synuclein is degraded by chaperone-mediated autophagy (CMA), mutated α-synuclein impairs CMA [93]. Additionally, aggregates of α-synuclein impair autophagosome clearance during macroautophagy [94] and overexpression of α-synuclein inhibits Rab1a activation, which is necessary for macroautophagy [95]. However, knockdown of α-synuclein also disrupts macroautophagy [96], suggesting that α-synuclein plays a role in macroautophagy. As α-synuclein was shown to be associated with SVs, many studies have investigated its potential role in SV trafficking; however, the exact function of α-synuclein in SV cycling is still under debate. Many early studies pointed to a role of this protein in regulating SV exocytosis, while more recent studies also implicate α-synuclein in SV endocytosis; this point of controversy was recently reviewed elsewhere [97].

Summary

While the many proteins described here have strong connections to both autophagy and SV cycling, the majority of the studies performed have investigated the role of these proteins in the two pathways independently. While limited, recent evidence has just begun to reveal how SV proteins modulate autophagy activity at the presynapse [98]. A detailed investigation of the link between these two pathways will allow for a greater understanding of PD pathogenesis and facilitate the targeted correction of PD-related disruptions in neuronal membrane trafficking.

Lysosomal dysfunction in PD

Evidence suggests that many PD-linked genes may affect the degradative capacity of autophagy by impairing lysosomal function. In this section, we review recent investigations into the role of LRRK2 and other PD-linked genes in regulating lysosomal function. Although LRRK2 is expressed highly in astrocytes, few studies have investigated its role in these cells. Recently, Henry et al. showed the expression of various LRRK2 PD mutants (G2019S, R1441C, or Y1699C) results in enlarged lysosomes with decreased degradative capacity. Although the study is carried out in astrocytes, the high expression of LRRK2 in these cells has drawn interest in examining the role of LRRK2 in astrocytes. Ultrastructural analysis of cortical neurons transfected with LRRK2 G2019S show enlarged electron-dense structures reminiscent of swollen lysosomes suggesting a general role of LRRK2 in regulating lysosomal function across neural cell types [99]. Further mechanistic investigation into this finding suggested that G2019S expression reduces lysosomal pH and results in increased expression of another PD gene, ATP13A2. The application of LRRK2 kinase inhibitors blocks this effect suggesting these results are kinase-dependent. Intriguingly, both G2019S and sporadic PD patient brains show decreased LAMP2 intensity in the prefrontal cortex while only G2019S patients show enhanced ATP13A2 expression [100]. ATP13A2 is a lysosomal ATPase linked to a juvenile form of Parkinsonism with dementia [101]. Expression of mutant ATP13A2 in cells results in lysosomal impairment, decreased cathepsin D activity, and α-synuclein accumulation [102]. Intriguingly, ATP13A2

has recently been linked to another PD risk factor gene, Syt11 [103]. Knockdown of Syt11 phenocopied the lysosomal defects observed upon loss of ATP13A2 while double knockdown of these two genes did not further impair functionality suggesting they act in the same pathway [17]. Further studies suggest Syt11 may control the clearance of autophagosomes by regulating autophagosome-lysosome fusion [17]. Syt11 has also been linked to SV endocytosis in dorsal root ganglion and hippocampal neurons [104]. Knockdown studies suggest Syt11 ensures precision in synaptic vesicle endocytosis by limiting membrane retrieval sites [104]. Overall, these findings suggest a network of PD genes that converge on SV trafficking and the autophagy-lysosome pathway.

Additional genes linked to PD have roles in regulating lysosomal function. These include β-glucocerebrosidase (GBA), LAMP2A, and sphingomyelin phosphodiesterase-1 (SMPD1). Mutations in these genes tend to reduce lysosomal function and lead to increased α-synuclein levels. Aside from increasing levels of α-synuclein through a lack of degradation, lysosomal dysfunction has also been linked to an increase in the propagation of α-synuclein [105]. Indeed, decreased enzymatic activity of GBA has been shown to increase the propagation of α-synuclein aggregates [106]. While homozygous mutations in GBA are known to cause Gaucher's disease, a lysosomal storage disorder, heterozygous mutations in GBA were found to greatly increase the risk of PD [107]. As LAMP2A is the major receptor for CMA, it is not surprising that decreased levels of LAMP2A result in impaired clearance of α-synuclein, a known CMA substrate [105]. LAMP2A was found as a risk factor in sporadic PD [7], and mistrafficking of LAMP2A has been implicated as a pathogenic mechanism in VPS35 linked familial PD [108]. VPS35 is associated with retromer trafficking from endosomes to the trans-golgi network. Mutations in VPS35 result not only in the mistrafficking of LAMP2A but also of Atg9A, which leads to impaired autophagy [109]. Intriguingly, a recent study in *Drosophila* has shown that the loss of VPS35 results in SV cycling defects that are not rescued by PD-associated mutants [110]. While this finding awaits confirmation in mammalian systems, it adds to the emerging evidence of dysfunction in the coordination of SV cycling and autophagy in PD. Another PD-risk factor, SMPD1 is typically associated with Niemann-Pick lysosomal storage disorder and has been shown to be relevant for lysosomal homeostasis [111]. More recently, a role of sphingolipids in autophagy has been recognized, suggesting yet another link between PD and autophagy/lysosomal function [112].

Conclusion

Recent years have seen an advancement in linking PD pathogenesis to dysfunction within the autophagy-lysosomal system. Now, emerging evidence connects PD to SV cycling, an important neuronal membrane trafficking pathway at presynaptic terminals. The studies over the past few years have shown that these two pathways are not entirely independent and may, in fact, share a number of regulatory proteins. The implication of many of these proteins in PD suggests dysfunction in neuronal membrane trafficking pathways as a key contributor to PD pathogenesis (Figure 2). Although most of these current studies do not directly explain how dysfunctional membrane trafficking leads to neuronal cell death, studies from animal models of PD and other neurodegenerative diseases suggest that changes in SVs and axons represent the earliest detectable phenotypes [44, 99, 113–115].

Additionally, functional imaging in PD patients suggests early changes in dopaminergic terminals in the striatum occur many years before cell loss is observable in the substantia nigra [116]. These findings suggest that the dystrophic changes that occur in axon terminals following defects in autophagy and SV cycling likely represent the initiation of degeneration at the nerve terminal that leads to the “dying-back” or retrograde degeneration of these neurons. This process and its implications in neurodegeneration, especially related to PD, have recently been reviewed elsewhere [117]. As these changes may occur early in the disease, greater understanding of these proteins in regulating autophagy and SV cycling and determination of how deregulation in these membrane trafficking pathways leads to neuronal dysfunction will facilitate the development of interventional therapies aimed at halting PD progression.

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Highlights

- Multiple PD related genes are known to regulate membrane trafficking pathways.
- Autophagy and synaptic vesicle cycling share regulatory proteins.
- Mutations within these common regulators are implicated in PD.
- Disruption in neuronal trafficking pathways may underlie PD pathogenesis.

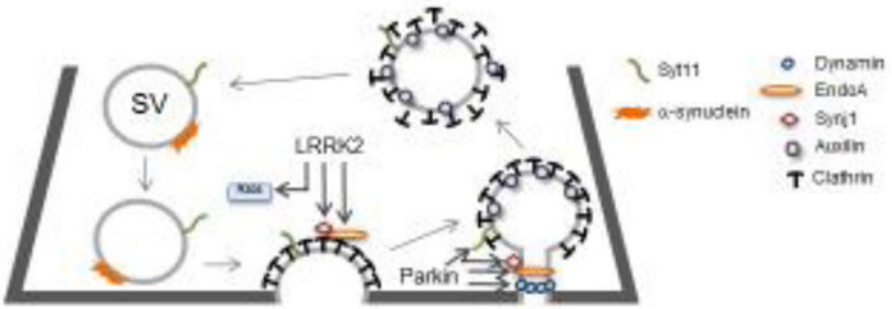

Figure 1. PD linked genes have roles in SV trafficking

Synaptic vesicles release neurotransmitters through highly regulated and tightly coupled rounds of exo- and endocytosis. Many PD-linked genes including α-synuclein, LRRK2, EndoA, synj1, auxilin, syt11, and dynamin are involved in SV cycling, particularly in SV endocytosis. LRRK2 and Parkin, associated with familial PD, are known to post-translationally modify a number of SV endocytosis genes. LRRK2 phosphorylates the SV endocytosis proteins: EndoA, synj1 as well as multiple Rab GTPases that may be involved in SV cycling. Parkin ubiquitinates EndoA, synj1, syt11, and dynamin though more studies are necessary to determine how modification of these proteins influence their function in SV cycling.

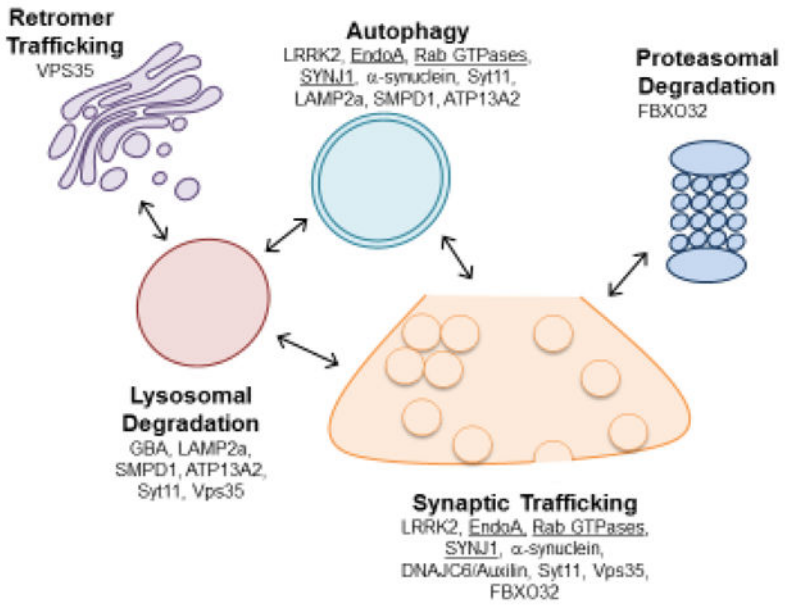

Figure 2. Involvement of PD linked genes in SV trafficking and autophagy degradation pathways

Many genes implicated in PD have roles in multiple neuronal trafficking and degradation pathways. For example, LRRK2 and its substrate, EndoA and synj1, are implicated in the dual regulation of SV trafficking and autophagy. The Rab GTPases, also LRRK2 substrates, are likely to regulate trafficking in a number of these pathways but further study of their roles in neurons is necessary. The other PD genes shown here have been implicated in various pathways and require further study to determine their roles in these pathways and how PD-related mutations alter their function. Putative LRRK2 substrates are underlined.