Parkinson's disease: convergence on synaptic homeostasis

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Abstract

Parkinson's disease, the second most common neurodegenerative disorder, affects millions of people globally. There is no cure, and its prevalence will double by 2030. In recent years, numerous causative genes and risk factors for Parkinson's disease have been identified and more than half appear to function at the synapse. Subtle synaptic defects are thought to precede blunt neuronal death, but the mechanisms that are dysfunctional at synapses are only now being unraveled. Here, we review recent work and propose a model where different Parkinson proteins interact in a cell compartment-specific manner at the synapse where these proteins regulate endocytosis and autophagy. While this field is only recently emerging, the work suggests that the loss of synaptic homeostasis may contribute to neurodegeneration and is a key player in Parkinson's disease.

Keywords autophagy; common factors in Parkinson's disease; endocytosis; protein homeostasis; synaptic decay

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Introduction

Cells, also neurons, accumulate cellular debris, dysfunctional organelles, and proteins. However, the post-mitotic nature of neurons makes it impossible for them to dilute cellular debris through cell division. Moreover, neurons have an extensive cytoplasm: The volume of the cell body is often < 1% of the volume of the entire neuron. These features together with the need for intense metabolic activity during stimulation to sustain neurotransmission make neurons especially dependent on efficient mechanisms that control protein homeostasis.

Synapses are often at a far distance from the cell body where proteins are synthesized and protein degradation has been shown to take place (reviewed in Hara *et al*, 2006; Kaushik & Cuervo, 2015). However, recent work indicates the existence of synapse-specific mechanisms that regulate protein turnover. These may be of

particular importance in the context of neurodegenerative diseases (reviewed in Vijayan & Verstreken, 2017; Jin *et al*, 2018) that are often characterized by misfolded, aggregated, and dysfunctional proteins [e.g., α -Synuclein and LRRK2-containing Lewy bodies in Parkinson's disease (PD; Spillantini *et al*, 1997; Zhu *et al*, 2006)]. Neurodegeneration is often thought to start at synaptic contact sites, as these are the first cellular compartments that appear to be affected (Cheng *et al*, 2010; Burke & O'Malley, 2013). We therefore hypothesize that deciphering the mechanisms that function in synaptic protein homeostasis at synapses is critical to understand these diseases.

We will argue that connections between synaptic protein homeostasis and the mechanisms of PD are particularly strong. The origin of PD is in many cases unknown: toxins, pesticides, and dysregulation of complex genetic interactions are thought to account for about 90–95% of cases. Familial monogenic mutations account for about 5–10% of the PD cases, and there are about 20 different genes that cause PD when mutated ("PD genes"). Some of the mutations are inherited in a dominant fashion while others are inherited recessively (see Table 1). Loss- and gain-of-function studies for most of these 20 genes have been conducted, and phenotypic analyses indicate that more than half of these "PD-genes" regulate synaptic function and protein turnover (see Table 1). These synaptic and protein turnover defects also appear pathologically relevant, because they are seen when pathogenic mutants of these "PD genes" were knocked in or over expressed in flies or mice (Table 1 and references therein). However, additional studies where pathogenic mutations are knocked into the endogenous locus or studies with human neurons derived from patients are needed to better model and understand these defects across the genetic space of PD. Nonetheless, the available data indicate that many of the genes mutated in PD encode proteins that regulate mechanisms of synaptic function.

Several of the genes implicated in PD encode proteins that are enriched at the presynaptic compartment, including DNAJC6/Auxilin, Synaptojanin 1 (Synj1), leucine-rich repeat kinase 2 (LRRK2), Endophilin A1 (EndoA), and α -Synuclein (Table 1). α -Synuclein is also often found aggregated in PD (in Lewy bodies), and dominant mutations or triplications cause the disease (Hope *et al*, 2004; Zarranz *et al*, 2004). Some studies suggest that the aggregation of proteins such as α -Synuclein may itself also alter

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Table 1. Proposed function of familial Parkinson's disease genes.

Symbol	Gene/ Protein	Mutation(s)	Inheritance	Biological process	Synaptic function
PARK1/4	<i>SNCA/α-Synuclein</i>	A30P, E46K, H50Q, G51N, A53T, and multiplications	AD	Clathrin-mediated endocytosis Neurotransmitter release Exosome release Chaperone-mediated autophagy	Yes ^a
PARK8	<i>DARDARIN/ LRRK2</i>	N1437H, R1441H/G/C, Y1699C, G2019S, I2020T	AD	Clathrin-mediated endocytosis Autophagy Neurotransmitter release Endo-lysosomal trafficking Exosome release	Yes ^b
PARK17	<i>VPS35/Vps35</i>	D620N	AD	Autophagy Endo-lysosomal trafficking Golgi complex trafficking	Yes ^c
PARK2	<i>parkin/Parkin</i>	Numerous duplication and missense mutations	AR	Clathrin-mediated endocytosis Mitochondrial quality control neurotransmitter release Ubiquitination Tumorigenesis	Yes ^d
PARK6	<i>PINK1</i>	Numerous deletions and point mutations	AR	Mitochondrial function Mitochondrial quality control	Yes ^e
PARK7	<i>PARK7/DJ-1</i>	dup 168–185, A39S, E64D, D149A, Q163L, L166P, M261I	AR	Mitochondrial function mitochondrial quality control of reactive oxygen species transcription regulation	Yes ^f
PARK9	<i>ATP13A2/ ATP13A2</i>	M810R, G877R, missense, small insertions, and deletions	AR	Endo-lysosomal pathway Exosome release	ND
PARK14	<i>PLA2G6</i>	P806R, R301C, D331N	AR	Membrane trafficking Phospholipid metabolism Mitochondrial function	ND
PARK15	<i>FBXO7</i>	T22M, L34R, R378G, and frameshift mutation	AR	Ubiquitination Proliferation	ND
PARK19	<i>DNAJC6/Auxilin</i>	Q734X	AR	Clathrin-mediated endocytosis Golgi-lysosome trafficking	Yes ^g
PARK20	<i>SYNJ1/ Synaptojanin 1</i>	R258Q, R459P	AR	Clathrin-mediated endocytosis Synaptic autophagy	Yes ^h
PARK21	<i>DNAJC13/ RME-8</i>	N855S	AD	Clathrin-mediated endocytosis Endosomal sorting/trafficking	ND

AD, autosomal dominant; AR, autosomal recessive.

^aRibeiro et al (2002), Chandra et al (2005), Burré et al (2010), Westphal and Chandra (2013), Zaltieri et al (2015).

^bPiccoli et al (2011), Matta et al (2012), Piccoli et al (2014), Arranz et al (2015), Islam et al (2016), Soukup et al (2016), Pan et al (2017).

^cMunsie et al (2014), Inoshita et al (2017).

^dChung et al (2001), Huynh et al (2003), Beccano-Kelly et al (2014).

^eVerstreken et al (2005).

^fUsami et al (2011).

^gEdvardson et al (2012), Yim et al (2010).

^hCremona et al (1999), Gad et al (2000), Verstreken et al (2003), Schuske et al (2003), Mani et al (2007).

pathways that guard synaptic homeostasis, e.g. by “clogging” protein turnover systems, thus causing a further buildup of dysfunctional proteins and organelles (Polymeropoulos et al, 1997; Kramer & Schulz-Schaeffer, 2007). The data also indicate an important role for the cell biology of the presynaptic terminal in the pathogenesis of PD. A model emerges where defects in pathways that regulate protein turnover at synapses and aggregated or dysfunctional proteins at synapses (e.g. α-Synuclein) both contribute to synaptic demise in PD. In this review, we discuss the mechanisms that synapses use to survey their proteome and we point out the many direct connections to pathways of PD. We propose that defects in

the regulation of protein turnover pathways at synapses are a common feature in the disease.

Synaptic decay in the pathology of Parkinson's disease

Parkinson's disease is a neurodegenerative condition that affects over 6 million people worldwide. The disease not only results in typical motor symptoms, but also in several debilitating non-motor symptoms that are gaining attention (Chen et al, 2015). The disease slowly progresses and there is no cure, resulting in steep care costs.

The motor symptoms in PD result from the degeneration of substantia nigra pars compacta (SNc) dopaminergic neurons (DA), but the disease is more widespread and many other neurons in the brain also suffer (Visanji *et al*, 2013).

Evidence suggests that synaptic decay in PD precedes neuronal demise, suggesting this is an early pathological event. At the time motor symptoms are manifest, about 30% of SNc and about 50–60% of the DA terminals are already lost (Scherman *et al*, 1989; Fearnley & Lees, 1991; Ma *et al*, 1997; Greffard *et al*, 2006; Beach *et al*, 2008; Cheng *et al*, 2010). Thus, at the onset of the disease (here taken as the occurrence of motor symptoms), the loss of DA synaptic terminals exceeds the loss of DA cell bodies. In paraffin-embedded tissue blots with Lewy body pathology, the majority of α -Synuclein aggregates accumulate at presynaptic terminals (Kramer & Schulz-Schaeffer, 2007) and additional neuroanatomical studies of post-mortem patient brain samples from familial PD cases support the idea that synaptic decay precedes neuronal death (Hornykiwicz, 1998; Cheng *et al*, 2010; Burke & O'Malley, 2013). These observations support a “dying back” hypothesis where synaptic demise, including presynaptic dysfunction, occurs before overt neuronal death.

Much of the research in PD has concentrated on DA loss in the SNc (Hirsch *et al*, 1988). The loss of these neurons causes typical PD motor symptoms, and this correlates with axonal degeneration in nigrostriatal pathways (Kordower *et al*, 2013; Caminiti *et al*, 2017). The SNc DA neurons are extremely ramified, and it has been suggested this is one of the reasons these neurons degenerate while other types of neurons survive. The axon arborizations of SNc DA neurons can reach a total length of four and a half meters and give rise to more than two million synaptic contacts, all connected to one cell body (Bolam & Pissadaki, 2012). In comparison, DA neurons of the ventral tegmental area (VTA) have significantly fewer synapses (< 30,000) and they do not degenerate in the context of PD. The axonal compartment of SNc neurons is comparatively very large, and we speculate that such an extensive neuronal arbor would significantly rely on local protein quality control mechanisms. Alterations in the synaptic protein turnover machinery may therefore have a more profound effect in SNc neurons compared to their less ramified counterparts in the VTA, providing possible explanations why the SNc neurons are so vulnerable. SNc neurons are not the only ones affected, and several other neuronal subtypes also die or are dysfunctional in PD. These are not necessarily extremely ramified, suggesting that other parameters than “extreme neuronal morphology” may contribute to neuronal dysfunction in PD and additional work is needed to understand this “cell type specificity” in the context of neurodegenerative disease.

Several genes implicated in PD encode proteins that are enriched at the presynaptic terminal. Mutations in these genes likely cause defects in synaptic mechanisms that (eventually) manifest as defects in neurotransmitter release. A straightforward model would be that such synaptic function defects eventually elicit synaptic and neuronal demise. There are indeed several examples where mutations in genes encoding presynaptic proteins that mediate neurotransmitter release also cause neurodegeneration. For example, mutations in *DNAJC5* (encoding CSP α) cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis (ANCL), a severe neurodegenerative condition (Benitez *et al*, 2011; Nosková *et al*, 2011). Also, CSP α knock-out mice and flies display

neurodegeneration and activity-dependent loss of synaptic terminals (Fernández-Chacón *et al*, 2004; Garcia-Junco-Clemente *et al*, 2010). However, these data do not exclude roles of CSP α beyond its function in neurotransmission. Indeed, there is evidence that disproves a simple linear correlation between synaptic dysfunction and synaptic demise. The loss of essential presynaptic proteins, Munc13–1/2 or the SNARE synaptobrevin-2/VAMP2, very strongly blocks synaptic transmission, yet this does not cause neurodegeneration (Schoch *et al*, 2001; Varoqueaux *et al*, 2002; Peng *et al*, 2013). Conversely, the loss of other essential proteins that reside at the presynaptic terminal, Munc18-1 and the SNARE SNAP-25 (and CSP α), also blocks synaptic transmission and this does cause neurodegeneration (Santos *et al*, 2017). Here, the authors were able to draw a correlation with Golgi abnormalities: They observed such abnormalities in Munc18-1 and SNAP-25 loss of function animals, but not in Munc13–1/2 or synaptobrevin-2/VAMP2 loss-of-function animals (Santos *et al*, 2017). However, how Golgi abnormalities cause neurodegeneration is elusive, and Golgi abnormalities are not universal among animals with mutations in synaptic proteins associated with neurodegeneration (EndoA, Synj1, DNAJ6, CSP α , etc. see below). Nonetheless, these results do indicate that presynaptic proteins that regulate neurotransmitter release can have divergent roles beyond their function in synaptic transmission. In other words, mere defects in neurotransmitter release do not (entirely) explain synaptic degeneration. We will argue that also the proteins mutated in PD have functions in pathways other than their (indirect) role in the regulation of transmitter release. In particular, we will review how these proteins regulate protein or organellar homeostasis, often uniquely at synapses. This idea mostly stems from studies of genes causative to familial forms of PD (Burré *et al*, 2010; Nemani *et al*, 2010; Zimprich *et al*, 2011; Edvardson *et al*, 2012; Matta *et al*, 2012; Krebs *et al*, 2013; Quadri *et al*, 2013; Soukup *et al*, 2016; Vanhauwaert *et al*, 2017). However, given that α -Synuclein aggregates, a proxy for protein homeostasis defects, are observed both in familial and sporadic cases of PD, this idea is most likely also relevant to the sporadic cases of the disease.

Mechanisms that control protein homeostasis at synapses

Protein homeostasis is under the control of different cellular mechanisms, and in some cases, synapses have specific adaptations (Labbadia & Morimoto, 2015; Vijayan & Verstreken, 2017). Protein homeostasis encompasses the activity of chaperones that fold and refold proteins in an ATP-dependent manner. Some of these chaperones are abundant (Hsp90) and even enriched (Hsc70/HSPA8) at synapses (Wang *et al*, 2017). When refolding by chaperones is not possible, proteins can be turned over by degradation. Synaptic membrane proteins are endocytosed and sorted at endosomes to be trafficked to lysosomes. Different routes of endosomal sorting have been found in neurons, and at synapses, the synaptic GTPase-activating protein Skywalker/TBC1D24 and the small GTPase Rab35 are involved (Uytterhoeven *et al*, 2011; Fernandes *et al*, 2014; Fischer *et al*, 2016; Sheehan *et al*, 2016). In addition, proteins and organelles can be degraded by autophagy. There are various types of autophagy, but common to all is that proteins or organelles are delivered to the lysosome for degradation. In most cellular compartments, the ubiquitin–proteasome system also plays a prominent

role, but this process does not seem to be responsible for the local turnover of the majority of presynaptic proteins (Hakim *et al*, 2016).

Of all protein turnover pathways, autophagy has been most strongly implicated in PD. Below, we review the different types of autophagy (reviewed in Galluzzi *et al*, 2017) and how they are connected to the proteins mutated in this disease:

- 1 In macroautophagy, a large vesicle invaginates as to engulf part of the cytoplasm and/or organelles by a double-membrane structure. This autophagosome fuses with the lysosome to degrade and recycle the contents. Autophagosomes were recently shown to form at presynaptic endings and to be transported back to the cell body (Hernandez *et al*, 2012; Maday & Holzbaur, 2014; Binotti *et al*, 2015; Soukup *et al*, 2016; Oerlundk *et al*, 2017; Vanhauwaert *et al*, 2017). Macroautophagy can be non-selective or selective. In selective macroautophagy-tagged organelles, e.g., mitochondria with ubiquitinated proteins on their outer membrane are engulfed and degraded (Pickrell & Youle, 2015; Yamano *et al*, 2016; Galluzzi *et al*, 2017). Several proteins implicated in PD are in direct control of macroautophagy at synapses and in macroautophagy of a specific organelle, the mitochondria (mitophagy). We discuss this in more detail below.
- 2 During endosomal microautophagy and chaperone-mediated autophagy, the chaperone Hsc70/HSPA8 recognizes specific protein motifs (similar to KFERQ) and brings proteins with these motifs to the endosomal membrane. This function of Hsc70 is independent from its role as a protein-refolding chaperone (Uytterhoeven *et al*, 2015). At the endosomal membrane, targeted proteins are either directly translocated over the endosomal membrane by the LAMP2a pore complex (chaperone-mediated autophagy; Bandyopadhyay *et al*, 2008) or the endosomal membrane invaginates as to engulf the targets (endosomal microautophagy; Sahu *et al*, 2011; Uytterhoeven *et al*, 2015; Mukherjee *et al*, 2016). Interestingly, synaptic proteins are significantly enriched for this “KFERQ” recognition motif (Uytterhoeven *et al*, 2015), and proteins central to PD (α -Synuclein, LRRK2, Tau) also contain this motif (Cuervo *et al*, 2004; Wang *et al*, 2009; Orenstein *et al*, 2013). This indicates that Hsc70-mediated autophagy may be important for the turnover of synaptic proteins also in the context of PD. More direct connections between proteins that mediate Hsc70-mediated autophagy and PD are currently lacking, but the possibility exists to exploit this process to regulate the levels of these pathogenic proteins as discussed elsewhere (Kaushik & Cuervo, 2015).

Macroautophagy and mitophagy

The proteins encoded by several “PD genes” have specific and direct actions in the regulation of macroautophagy (LRRK2, Synj1, DNAJC6, PINK1, Parkin, etc. see below). These observations were made based on loss- and gain-of-function studies of these “PD genes” in genetic model organisms as well as using induced neurons derived from patients (iPS). In addition, variation in genes that encode core components of the autophagic machinery, the proteins Atg5 and Atg7, is reported risk factors for PD (Chen *et al*, 2013a, 2013b). Lastly, recent work also found that variation in the *EndoA1*

gene constitutes a risk factor for PD (Chang *et al*, 2017). We and others showed that EndoA plays a prominent role in synaptic autophagy in fruit flies and mice (Murdoch *et al*, 2016; Soukup *et al*, 2016). Together these studies suggest that there is a common underlying theme where several of the genetic factors associated with PD encode proteins that affect the process of macroautophagy (Plowey *et al*, 2008; Winslow *et al*, 2010; Sánchez-Danés *et al*, 2012; Bravo-San Pedro *et al*, 2013; Zavodszky *et al*, 2014).

Macroautophagy has been extensively studied in yeast and mammalian cells. The key players involved in macroautophagy are also expressed in neurons, suggesting that the core macroautophagy pathway is also important in neurons (Bains *et al*, 2009; Wong *et al*, 2011; Krüger *et al*, 2012; Sánchez-Danés *et al*, 2012; Viscomi *et al*, 2012). The process of macroautophagy (and thus also mitophagy) in yeast cells and mammalian cells starts by inhibition of the mTOR complex 1 resulting in the activation of the Atg1/ULK1 complex. This leads to the translocation of multiprotein complexes like—phosphatidylinositol 3-kinase (Vps34)—to preautophagosomal membranes. An important next step is the generation of phosphatidylinositol 3-phosphate (PI(3)P)-rich membranes by Vps34. Binding of WD40 repeat domain phosphoinositide-interacting (WIPI) proteins to PI(3)P/PI(3,5)P₂-rich membranes facilitates the elongation of the isolation membrane and LC3 lipidation on the fully formed autophagosome (Proikas-Cezanne *et al*, 2015). Elongation is dependent on several proteins: Atg5, Atg12, and Atg16 forming an E3-like ligase complex that specifically binds to proteins of the WIPI family. Next, the ubiquitin-like conjugating enzyme Atg3, together with Atg4 and Atg7, conjugates LC3/ATG8 to phosphatidylethanolamine (PE) on the mature autophagosome. Following elongation and maturation, the autophagosome fuses with the lysosome, a process mediated by SNAREs (soluble N-ethylmaleimide-sensitive factor activating protein receptors; Menzies *et al*, 2017). Macroautophagy is important for neuronal survival as the knock-out of essential autophagy genes (e.g. *atg7*) in flies and mice causes neuronal defects, including neurodegeneration (Komatsu *et al*, 2006; Juhász *et al*, 2007). The exact steps that occur downstream of defective macroautophagy leading to the death of a cell remain elusive. However, it is conceivable that both the accumulation of dysfunctional proteins and organelles and the lack of fresh biomolecules for the synthesis of new proteins contribute to the deregulation of cellular homeostasis. Furthermore, as detailed below, there are also synapse-specific adaptations to the process of macroautophagy and several lines of recent evidence indicate that this synapse-specific process of macroautophagy is disrupted by mutations in “PD genes”.

Macroautophagy ends by the fusion with lysosomes, thus degrading the contents. Lysosomes have been implicated in maintaining synaptic homeostasis (Sambri *et al*, 2017), and lysosomal dysfunction has been repeatedly associated with neurodegeneration, also in the context of PD (Dehay *et al*, 2012; Dodson *et al*, 2012; Usenovic *et al*, 2012; Miura *et al*, 2014; Mazzulli *et al*, 2016). ATP13A2 and glucocerebrosidase regulate lysosomal function and autosomal-recessive mutations in ATP13A2 cause PD, while heterozygosity for GBA predisposes to PD (Aharon-Peretz *et al*, 2004). In fact, the restoration or (hyper-)acidification of lysosomes has been proposed as a therapeutic approach for PD. For example, acidic nanoparticles that promote the acidification of lysosomes are able to rescue lysosomal defects in ATP13A2-mutant cells and in

glucocerebrosidase-mutant cells. Moreover, intracerebral injection of these particles even diminishes dopaminergic neuron loss in a PD toxin model (Bourdenx *et al*, 2016). Hence, autophagic dysfunction and lysosomal dysfunction, and thus defects in intracellular degradation pathways, are often seen disrupted in models of PD (and other forms of neurodegeneration). It is plausible that defects in lysosomal activity contribute to the accumulation of α -Synuclein that is aggregation prone and of other (dysfunctional) proteins (Williamson *et al*, 2010; Ganley *et al*, 2011; Korolchuk *et al*, 2011; Takáts *et al*, 2014). In this context, it is noteworthy that specific post-translational modifications in α -Synuclein are also further inhibiting the ability of this protein to be degraded at lysosomes, thus contributing to its own aggregation (Smith *et al*, 2005). What remains unexplained is how dysfunction in such broad processes such as lysosomal function or autophagy elicits defects in a number of defined cell types. In addition, it is not known why other aggregation-prone proteins besides α -Synuclein are not aggregating consistently in PD.

Classical macroautophagy is non-selective and triggered by amino acid deprivation. In neurons, the process is also triggered by neuronal activity, indicating there are neuron-specific pathways that initiate the process (Soukup *et al*, 2016). Macroautophagy can also be selective when it is triggered by “tagged targets”, for example the ubiquitination of outer mitochondrial membrane proteins. In addition to the classical macroautophagy machinery, different proteins, including Pink1, Parkin, and Fbxo7, regulate the targeted macroautophagy of mitochondria or mitophagy (Narendra *et al*, 2008; Geisler *et al*, 2010; Vives-Bauza *et al*, 2010; Yamano *et al*, 2016). Autosomal-recessive mutations in the genes that encode these proteins cause PD (Lücking *et al*, 2000; Bonifati *et al*, 2005; Ibáñez *et al*, 2006). Defects in mitochondrial turnover would eventually lead to an accumulation of dysfunctional mitochondria, and dysfunctional mitochondria are also often observed in tissue from sporadic PD patients (Parker *et al*, 2008). In addition, the effects of specific toxins on mitochondria recapitulate features of PD in humans and animal models, thereby further underlining the connection between dysfunctional mitochondria and PD (Przedborski & Jackson-Lewis, 1998).

Parkin is a cytoplasmic E3 ubiquitin ligase, while Pink1 is a kinase that regulates mitochondrial function and also phosphorylates Parkin and ubiquitin (Ziviani *et al*, 2010; Kondapalli *et al*, 2012; Shiba-Fukushima *et al*, 2012). Pink1-dependent Parkin phosphorylation results in the ubiquitination of target proteins, such as those at the surface of mitochondria, and this is a trigger for autophagosomes to engulf these “tagged” mitochondria (Ziviani *et al*, 2010; Glauser *et al*, 2011). Further details on this process can be found in these excellent reviews: (Pickrell & Youle, 2015; Yamano *et al*, 2016; Galluzzi *et al*, 2017). In the context of DA neuronal terminals, mitophagy may be a necessary mechanism to survey the mitochondria in the vast expanse of the neuronal arbor of these cells, as to maintain a proper energy supply or to buffer calcium at the extremities of these neurons. Indeed, an intricate mechanism that regulates the transport of neuronal mitochondria exists and is under the control of Miro, another protein that is also phosphorylated by Pink1 (Wang *et al*, 2011). Mitochondrial motility regulates mitochondrial autophagy: When mitochondria stop moving (when they are less functional), autophagy is induced (Ahrafi *et al*, 2014). It has however been difficult to observe mitophagy at synapses in neurons *in vivo* and the functional relevance

of the process in relation to neuronal survival and neuronal function is also elusive. While it is conceivable that a chronic failure to remove mitochondrial debris will cause harm to the cellular and synaptic environment, it is important to note that Pink1, Parkin, and Fbxo7 have also mitophagy-independent functions. Pink1 and Fbxo7 regulate the activity of complex I of the electron transport chain (Gautier *et al*, 2008; Morais *et al*, 2009; Chan *et al*, 2011; Vos *et al*, 2012; Delgado-Camprubi *et al*, 2017), while Parkin can ubiquitinate other targets besides proteins at the outer mitochondrial membrane (Cao *et al*, 2014). Hence, *PINK1*, *parkin*, and *Fbxo7* are pleiotropic genes affecting different pathways, making it difficult to assess the function of mitophagy in isolation *in vivo*.

Synaptic autophagy

Autophagy digests parts of the cytoplasm, but at the relatively small presynaptic contacts, where the process is active as well (Maday *et al*, 2012; Maday & Holzbaur, 2014; Soukup *et al*, 2016; Oerlundk *et al*, 2017; Vanhauwaert *et al*, 2017), it is important to tightly control autophagy as to prevent unwanted breakdown on proteins and organelles. Different proteins encoded by genes that are associated with PD (causative and risk factors) are in direct control of this process, and their loss of function or pathogenic mutants severely affect synaptic autophagosome formation in flies, mice, and induced human neurons.

Live imaging indicates LC3/Atg8-labeled structures, likely autophagosomes, form at synaptic terminals and they are transported along axons to the cell body (Hernandez *et al*, 2012; Maday *et al*, 2012; Ashrafi *et al*, 2014; Binotti *et al*, 2015; Wang *et al*, 2015; Soukup *et al*, 2016). Transport leads to acidification, and lysosomal fusion results in degradation (Maday *et al*, 2012; Maday & Holzbaur, 2014, 2016). Recent work indicates that proteins uniquely present at the presynaptic terminal control the local formation of autophagosomes. For example, Bassoon, a protein that resides in the presynaptic density, directly binds to Atg5, and this association controls the formation of autophagosomes at presynaptic terminals. Hence, this defines a presynaptic-specific mechanism of autophagy (Oerlundk *et al*, 2017). It is currently not known whether these synaptic autophagosomes engulf specific targets (e.g. mitochondria) or whether the process is non-selective. One study reports synaptic-like vesicles inside these structures (Binotti *et al*, 2015) and another suggests a connection between macroautophagy induction, the number of synaptic vesicles, and neurotransmitter release (Hernandez *et al*, 2012). Nonetheless, live imaging, electron microscopy, and correlative light and electron microscopy indicate that electrical activity (and amino acid deprivation) causes the formation of Atg8/LC3-Atg18- and Lamp1-positive autophagosomes at synapses.

LRRK2

Variation in the *LRRK2* gene is a risk factor for PD, and dominant mutations in the *LRRK2* gene are the most common cause of genetic forms of PD (Zimprich *et al*, 2004; Satake *et al*, 2009). The most frequent mutation found causes the expression of a protein with a gain of kinase function (*LRRK2*^{G2019S}), but other pathogenic mutations do not appear to increase kinase activity (Greggio *et al*, 2006; Greggio & Cookson, 2009). *LRRK2* is enriched at the presynaptic compartment and it phosphorylates regulators of vesicle trafficking,

including (among others) Rab proteins, NSF, and EndoA (Piccoli *et al*, 2011; Matta *et al*, 2012; Cîrnușu *et al*, 2014; Arranz *et al*, 2015; Yun *et al*, 2015; Belluzzi *et al*, 2016; Ito *et al*, 2016; Soukup *et al*, 2016; Steger *et al*, 2016). Rab proteins regulate (synaptic) vesicle trafficking; NSF is an ATPase required for synaptic vesicle cycling, and EndoA is required for synaptic vesicle endocytosis. These observations suggest that LRRK2 may be a regulator of membrane trafficking at the presynaptic compartment.

Several studies report macroautophagy defects LRRK2 PD models where pathogenic mutants are over expressed (Plowey *et al*, 2008; Sánchez-Danés *et al*, 2012; Bravo-San Pedro *et al*, 2013; Manzoni *et al*, 2013). Additional work now shows that this function of LRRK2 in autophagy at synapses requires LRRK2 kinase activity. LRRK2 acts through the phosphorylation of EndoA, and this is independent from the role of EndoA in endocytosis (Soukup *et al*, 2016). As EndoA is a presynaptic-enriched protein (as is Bassoon), these findings indicate that the process of synaptic autophagy is independently controlled by presynaptic proteins.

EndoA

EndoA can deform membranes and is critical for synaptic vesicle endocytosis (Ringstad *et al*, 1999; Verstreken *et al*, 2002; Milosevic *et al*, 2011). The EndoA dimer contains several amphiphilic helices that insert into the membrane to bend it. LRRK2 phosphorylates EndoA at Serine 75 and Threonine 73 that are located in one of these membrane insertion domains (Matta *et al*, 2012; Arranz *et al*, 2015). The negatively charged phosphogroups affect the ability of EndoA to associate with the membrane (Matta *et al*, 2012; Ambrosio *et al*, 2014) resulting in very highly curved membranes. Conversely, non-phosphorylated EndoA inserts deeper causing shallower membrane curvature that may be more compatible with the process of endocytosis (Ambrosio *et al*, 2014). Hence, LRRK2 kinase function controls a switch in EndoA allowing the protein to create zones of high (EndoA is phosphorylated) or low (EndoA is not phosphorylated) membrane curvature. The highly curved membrane zones that are created by phosphorylated EndoA are involved in synaptic autophagy (Soukup *et al*, 2016). It is known that several autophagic proteins, including Atg14, Atg1, and Atg3, associate with highly curved membranes (Fan *et al*, 2011; Ragusa *et al*, 2012; Nath *et al*, 2014). Indeed, the curved membrane zones created by phosphorylated EndoA allow Atg3 to bind to nascent autophagosomes also *in vivo* (Fig 1; Soukup *et al*, 2016). Hence, kinase activating LRRK2 mutations and phosphomimetic EndoA promote synaptic autophagy, while LRRK2 loss-of-function mutants and phosphodead EndoA blocks the process. These data indicate that LRRK2 and EndoA are critical gatekeepers of autophagy at synapses. Similar observations were made in mice where EndoA was also found to reside on autophagosomal membranes (Murdoch *et al*, 2016). In mice, the loss of EndoA1 and EndoA2 causes neurodegeneration at post-natal day 18. In flies, expression of phosphomimetic and phosphodead EndoA also cause neurodegeneration (Milosevic *et al*, 2011; Murdoch *et al*, 2016; Soukup *et al*, 2016). Corroborating this finding, both kinase activating mutations and mutations that do not affect kinase activity have been found in LRRK2 [(Jaleel *et al*, 2007) and reviewed in (West *et al*, 2007; Kumar & Cookson, 2011; Rudenko *et al*, 2012)]. This suggests that the balance between phosphorylated and dephosphorylated substrates of LRRK2 may be of essence, possibly also in the context of synaptic autophagy.

EndoA is emerging as a central nexus of synaptic biology in the context of PD. Not only is EndoA phosphorylated by LRRK2, but the protein also binds to Parkin and Synj1 (Schuske *et al*, 2003; Verstreken *et al*, 2003; Trempe *et al*, 2009; Cao *et al*, 2014; Fig 2) and variation at the *EndoA1* locus (*SH3GL2*) is a risk factor for PD (Chang *et al*, 2017). Mutations in either *parkin* or *SYNJ1* cause an autosomal-recessive early-onset form of PD, and mutations in *Synj1* are in general more severe (Krebs *et al*, 2013; Quadri *et al*, 2013; Olgiati *et al*, 2014; Kirola *et al*, 2016). Parkin is an ubiquitin ligase that regulates mitophagy, but as stated above, it also has other targets than the proteins at the outer mitochondrial membrane, including EndoA (Trempe *et al*, 2009; Cao *et al*, 2014). Finally, there are several curious observations made at the transcriptional level that further connect EndoA to PD. There is a reciprocal regulation of gene expression of *SNCA* (the gene that encodes α -Synuclein) and *SH3GL2* (the gene that encodes EndoA1; Westphal & Chandra, 2013). Furthermore, there is a similar reciprocal regulation of gene expression of *parkin* and *SH3GL2* (Cao *et al*, 2014). The molecular mechanisms for this regulation are still unclear, but these observations suggest that high α -Synuclein or Parkin load result in low EndoA1 levels, and thus less synaptic autophagy.

Synj1

The tightest binding partner of EndoA is Synj1, a lipid phosphatase. Synj1 has been mostly studied in the context of synaptic vesicle endocytosis (Micheva *et al*, 1997; Gad *et al*, 2000; Schuske *et al*, 2003; Verstreken *et al*, 2003). Synj1 contains two lipid phosphatase domains, a 5-phosphatase domain that dephosphorylates, among others, phosphatidylinositol (4,5) biphosphate (PI(4,5)P₂) and a SAC1 domain that dephosphorylates PI(4)P and PI(3)P as well as other lipids. PI(4,5)P₂ is critical in synaptic vesicle endocytosis (and several other processes including ion channel function), where it serves as a docking platform for endocytic adaptor proteins, allowing protein complexes in the endocytic pit to be assembled. Once synaptic vesicles are formed, Synj1-dependent PI(4,5)P₂ dephosphorylation results in the uncoating of newly formed synaptic vesicles, thus fueling the vesicle cycle. In mice, mutations that block 5-phosphatase activity, but leave SAC1 function intact, result in severe defects in synaptic vesicle endocytosis (Mani *et al*, 2007), pointing to the important role of the 5-phosphatase domain in synaptic endocytosis (Fig 3). In contrast, PI(4)P and PI(3)P are mechanistically less well connected to synaptic vesicle endocytosis, and mutations in the SAC1 domain appear to more mildly affect synaptic vesicle recycling (Mani *et al*, 2007). These data suggest the lipid phosphatase domains of Synj1 have divergent roles.

Most of the PD mutations in Synj1 (R258Q and R459P) reside in the SAC1 domain. These mutations block SAC1 function while leaving the 5-phosphatase activity intact (Krebs *et al*, 2013). Flies expressing only Synj1^{R228Q} (the corresponding pathogenic mutation to R258Q in flies) show largely normal synaptic endocytosis at excitatory glutamatergic neurons and histaminergic photoreceptors (Vanhouwaert *et al*, 2017). In contrast, inhibitory neurons of Synj1^{R258Q} knock-in mice show an accumulation of coated vesicles, suggesting slowed vesicle recycling. This effect did appear more pronounced in inhibitory neurons because excitatory neurons displayed less accumulation of endocytic proteins when stimulated (Cao *et al*, 2017). Inhibitory neurons tend to have higher firing rates than excitatory neurons, and they thus require more efficient

Figure 1. Schematic representation of the autophagic function of LRRK2, EndoA, and Synj1 at the presynaptic terminal.

(A) Lrrk/LRRK2 phosphorylation of the Endophilin A1 (EndoA1) dimer leads to highly curved membranes, e.g., such as those seen on nascent autophagosomes. Atg3 insertion on highly curved membranes promotes lipidation [conjugation to phosphatidylethanolamine (PE)] of Atg8 on these membranes and thereby the formation of autophagosomes. (B) Synaptojanin 1 (Synj1) SAC1 phosphatase function acts on phosphatidylinositol 3-phosphate at autophagosomal membranes to induce WIPI2/Atg18a cycling, necessary for proper autophagic flux.

synaptic vesicle endocytosis. Hence, it is conceivable that the more extreme (activity) conditions of inhibitory neurons reveal an endocytic defect of the Synj1^{R258Q} mutation, not seen in the fly system or at excitatory neurons.

Beyond endocytosis, recent work also starts to shed light on a different function of Synj1, in the regulation of synaptic autophagy (George *et al*, 2014, 2016; Vanhauwaert *et al*, 2017). In transgenic fly Synj1^{R228Q} neurons where endocytosis is largely normal, synaptic autophagy is blocked. This phenotype is also recapitulated in neurons generated from patient-derived induced pluripotent stem (iPS) cells with a Synj1 R258Q mutation. In this context, it would

also be interesting to analyze autophagic function at the synapses of Synj1^{R258Q} knock-in mice. Nonetheless, the data in flies and induced patient neurons indicate the role of Synj1 in autophagy is evolutionary conserved (Vanhauwaert *et al*, 2017).

Synj1^{R228Q} mutant fruit flies also show dopaminergic neuron loss, similar to some of the other PD fruit fly models and the EndoA phosphomutants (Bayersdorfer *et al*, 2010; Hindle & Elliott, 2013; Navarro *et al*, 2014; Soukup *et al*, 2016; Marcogliese *et al*, 2017), indicating Synj1 domain function is needed for these neurons to survive. Mechanistic work indicates that the SAC1 domain of Synj1 is needed to dephosphorylate PI(3)P, and likely also PI(3,5)P₂, on synaptic

Figure 2. LRRK2 and Parkin interaction with Synj1, EndoA1, and Dynamin 1.

Endophilin A1 (EndoA1) is a binding partner of Synj1 and Dynamin 1, and these proteins have been shown to function in autophagy and endocytosis. While it is clear that EndoA1 binding to Dynamin 1 and Synj1 is required to promote endocytosis, the functional relationship of these proteins in autophagy remains enigmatic. Synj1, EndoA1, and Dynamin 1 are phosphorylated by LRRK2 and ubiquitinated by Parkin. LRRK2-dependent phosphorylation of EndoA1 is required for its function in autophagy, and LRRK2-dependent phosphorylation of Synj1 and Dynamin 1 has been shown to affect endocytosis. However, the functional consequence of Parkin-dependent ubiquitination of Synj1, EndoA1, and Dynamin 1 in autophagy and endocytosis remains to be elucidated.

autophagosomal membranes (Vanhouwaert *et al*, 2017). These phosphoinositides, produced by Vps34 and Fab1, respectively, are critically required during the initial steps, and likely in the maturation steps, of autophagy (Rusten *et al*, 2007; Juhász *et al*, 2008; Thoresen *et al*, 2010; Stjepanovic *et al*, 2017). However, as the autophagosome matures, these phosphoinositides need to be dephosphorylated to lower the affinity of specific autophagic factors such as Atg18a/WIP1, allowing autophagosome formation to move forward. Synj1 appears critical in this process and regulates, together with a handful of other proteins such as Bassoon and EndoA, the formation of autophagosomes at synapses (Fig 1B). EndoA and Synj1 also regulate synaptic vesicle endocytosis, but defects in endocytosis and autophagy are not mutually exclusive and connections between the two processes have been described (Ravikumar *et al*, 2010; Kononenko *et al*, 2017).

Auxilin and RME-8

The recent discovery of PD mutations in DNAJ6 (Auxilin) and DNAJC13 (RME-8) provides further connections between PD, the mechanisms of autophagy, and synaptic vesicle endocytosis (Ahle & Ungewickell, 1990; Ungewickell *et al*, 1995; Scheele *et al*, 2001; Hirst *et al*, 2008; Yim *et al*, 2010; Edvardson *et al*, 2012; Vilariño-Güell

et al, 2013). There are autosomal-recessive mutations that cause PD and affect the Auxilin Clathrin-binding domain. In contrast, there is an autosomal-dominant mutation that causes PD in RME-8, and this mutation affects the region between two IWN repeats in the protein. Auxilin and RME-8 are both co-chaperones that at a step following endocytosis and together with Hsc70 and are independently involved in synaptic vesicle and early endosome uncoating (Fig 3; Chang *et al*, 2004; Girard *et al*, 2005; Eisenberg & Greene, 2007; Xhabija & Vratsis, 2015). This is interesting, because Hsc70 is the same protein that is involved in chaperone-mediated autophagy and in endosomal microautophagy. In fact, the latter two processes were shown to target LRRK2 and α -Synuclein to mediate their degradation (see above). The precise effect of the pathogenic mutations in Auxilin and RME-8 has not yet been tested, but they are thought to cause a loss-of-protein function (Edvardson *et al*, 2012; Vilariño-Güell *et al*, 2013). In line, Auxilin loss of function in flies causes locomotion defects and the loss of dopaminergic neurons (Song *et al*, 2017). It is in this context likely that pathogenic Auxilin and RME-8 mutants affect both endocytosis and Hsc70-dependent autophagic processes; but this remains to be determined.

A synaptic protein network acting in PD

Different genes that are mutated in PD, or variation in genes which are risk factors for PD, encode proteins that function at the presynaptic terminal. The functions of (many of) these proteins appear to converge on mechanisms of synaptic protein (and organelle) homeostasis. A central nexus is EndoA that directly connects to Parkin, Synj1, and LRRK2 (Figs 2 and 4).

LRRK2 phosphorylates both EndoA (Matta *et al*, 2012; Arranz *et al*, 2015), but also Synj1 at position T1131 and T1205 (Islam *et al*, 2016; Pan *et al*, 2017). LRRK2-dependent EndoA phosphorylation is a trigger for synaptic autophagy (Murdoch *et al*, 2016; Soukup *et al*, 2016), while Synj1 phosphorylation by LRRK2 affects its binding to EndoA. Since the loss of EndoA destabilizes the localization of Synj1 at synapses (Schuske *et al*, 2003; Verstreken *et al*, 2003; Milosevic *et al*, 2011), LRRK2 phosphorylation may potentially affect Synj1 stability. EndoA and Synj1 are also both monoubiquitinated by Parkin (Cao *et al*, 2014; Fig 2). The function of this ubiquitination event remains to be elucidated, but Parkin protein levels are dramatically upregulated in knock-in mice that express pathogenic Synj1 mutations and in EndoA1, 2, 3 triple KO mouse brains (Cao *et al*, 2014, 2017). Thus, the genes most commonly mutated in PD (LRRK2 and parkin) encode proteins that regulate the function of EndoA and Synj1, both unique to the synapse. Similar to the EndoA nexus, Auxilin and RME-8 may also control synaptic protein homeostasis by regulating Hsc70 function. Finally, there are established connections between the Auxilin/RME-8/Hsc70 branch and the LRRK2/EndoA/Synj1 branch: Both Synj1 and Auxilin are known to bind Dynamin 1 (Cestra *et al*, 1999; Newmyer *et al*, 2003; Milosevic *et al*, 2011; Sundborger *et al*, 2011; Geng *et al*, 2016). LRRK2 has been shown to bind Dynamin 1 via its WD40 domain (Piccoli *et al*, 2011) and Parkin monoubiquitinates Dynamin 1 (Cao *et al*, 2014; Fig 2). How these phosphorylation and ubiquitination events regulate Dynamin 1 function and whether Dynamin 1 really constitutes a functional link between different types of (synaptic) autophagy remain to be studied. We propose that deregulation of synaptic

Figure 3. Overview of the synaptic vesicle cycle and neurotransmitter secretion at the synapse.

Following vesicle fusion, Clathrin-mediated endocytosis creates new vesicles from the plasma membrane or from the endosomal membrane. Dynamin 1 is pinching off the nascent Clathrin and protein-coated vesicle. Endophilin A1 (EndoA) recruits the phosphatase Synj1 that, together with Auxilin and Hsc70, mediates the uncoating of proteins (including Clathrin) from new vesicles. Local protein turnover occurs via the endo-lysosomal pathway (in a Rab 35-dependent manner) but also via different autophagic mechanisms (macroautophagy (selective—e.g. mitophagy—and non-selective), microautophagy, chaperone-mediated autophagy). E (endosome); L (lysosome). Synaptic proteins encoded by “PD genes”, and proteins encoded by genes, variation which causes risk of PD, are highlighted in yellow.

autophagy processes is central to cellular and synaptic dysfunction in PD and that several of the genetic factors that cause PD or predispose to the disease converge onto these pathways. Central to our thesis is that proteins commonly studied for their role in endocytosis (EndoA, Synj1, Auxilin, and Hsc70) also have additional functions that relate to protein homeostasis.

Concluding remarks

We propose that the function of many “PD genes” converge on mechanisms of synaptic homeostasis, suggesting this may be a

central factor in PD. It is currently not clear how defects in protein or organelle turnover at synapses cause synaptic and neuronal demise, but one obvious explanation is that an accumulation of dysfunctional proteins results in the gradual failing and demise of synaptic contacts. Mitochondrial homeostasis is in this context also important. These organelles are critical for (synaptic) calcium buffering and for energy production that fuels not only the synaptic vesicle cycle but also synaptic ATP-dependent chaperones and synaptic membrane trafficking events that are required for protein homeostasis. Both mutations in “PD genes” and environmental factors associated with PD are known to cause mitochondrial dysfunction, and it will be interesting to

Figure 4. Functional protein network of synaptic proteins linked to PD. Endophilin A1 (EndoA1) and Dynamin 1 are directly connected to at least three proteins encoded by “PD genes”. Proteins functioning in Clathrin-mediated endocytosis are marked in blue, proteins with a function in (synaptic) autophagy in green, and proteins with a potential function in autophagy in yellow. Protein interactions are visualized with a line, and direct protein interactions are highlighted as a red line. “PD-genes” are displayed in black. Variation in EndoA1 is a risk factor for PD.

assess whether protein homeostasis is disrupted under these conditions.

The model we present starts from genetic factors that are causative to PD or increase the risk of the disease. However, we believe synaptic homeostasis defects may be relevant to sporadic PD as well. First, *LRRK2* is often found mutated in idiopathic PD patients and *Parkin* appears to be often inactivated (Satake *et al.*, 2009; Dawson & Dawson, 2010), suggesting similar molecular/cellular defects in these patients as compared to patients with mutation in *LRRK2* or *parkin*. Second, tissue from sporadic patients often shows decreased mitochondrial function, which, as alluded to above, may indirectly cause defects in synaptic protein homeostasis. Finally, α -Synuclein aggregates are seen in (most) familial and sporadic patients. α -Synuclein is a presynaptic protein, and we propose that defects in protein homeostasis pathways at synapses increase its propensity to aggregate. Thus, the presence of α -Synuclein aggregates in sporadic patients may signify defects in protein turnover mechanisms at synapses. It will be interesting to broaden this analysis to include additional animal models where pathogenic mutations in “PD genes” are knocked in and analyze the mechanisms of protein homeostasis at synapses, as well as to also include material from idiopathic patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

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