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The endosomal pathway in Parkinson's disease

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ABSTRACT

Parkinson's disease is primarily a movement disorder with predilection for the nigral dopaminergic neurons and is often associated with widespread neurodegeneration and diffuse Lewy body deposition. Recent advances in molecular genetics and studies in model organisms have transformed our understanding of Parkinson's pathogenesis and suggested unifying biochemical pathways despite the clinical heterogeneity of the disease. In this review, we summarized the evidence that a number of Parkinson's associated genetic mutations or polymorphisms (*LRRK2, VPS35, GBA, ATP13A2, ATP6AP2, DNAJC13/RME-8, RAB7L1, GAK*) disrupt protein trafficking and degradation via the endosomal pathway and discussed how such defects could arise from or contribute to the accumulation and misfolding of α-synuclein in Lewy bodies. We propose that an age-related pathological depletion of functional endolysosomes due to neuromelanin deposition in dopaminergic neurons may increase their susceptibility to stochastic molecular defects in this pathway and we discuss how enzymes that regulate ubiquitin signaling, as exemplified by the ubiquitin ligase Nedd4, could provide the missing link between genetic and acquired defects in endosomal trafficking. This article is part of a Special Issue entitled 'Neuronal Protein'.

Contents

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting 1% of people over the age of 60. Clinically it is characterized primarily by a movement disorder causing resting tremor, bradykinesia, rigidity, postural instability and diverse non-motor symptoms including dementia, which in community-based studies, was reported in up to 80% of patients with long disease duration (Hely et al., 2008) This latter finding indicates that PD is a diffuse neurodegenerative disorder. Similarly, detailed neuropathological studies have shown that one of the cardinal histological features, the intraneuronal inclusions called Lewy bodies (LB), are detected in numerous cortical areas and often correlate with the extent of cognitive decline (Schneider et al., 2012). Despite this diffuse evolution, the presentation to health services is commonly due to the loss of a critical number of dopaminergic neurons in the substantia nigra (Lees et al., 2009) whereas in the minority of patients, dementia may be the predominant or presenting feature (often termed PD dementia).

Recent advances in sequencing technologies have transformed our molecular understanding of Parkinson's disease and suggested unifying themes despite its clinical heterogeneity, largely due to emerging genetic–pathological correlations (Tofaris, 2012). A major challenge ahead is the validation of the molecular mechanism(s) by which these genes cause the aforementioned clinical and pathological characteristics and accumulation of α-synuclein in LB, which is a sine qua non feature of the commonest form of sporadic PD. In this respect, it is imperative to ask whether an integrated cellular pathway based on molecular genetics and studies in model organisms can explain the relatively selective neuronal vulnerability initially and the diffuse evolution of

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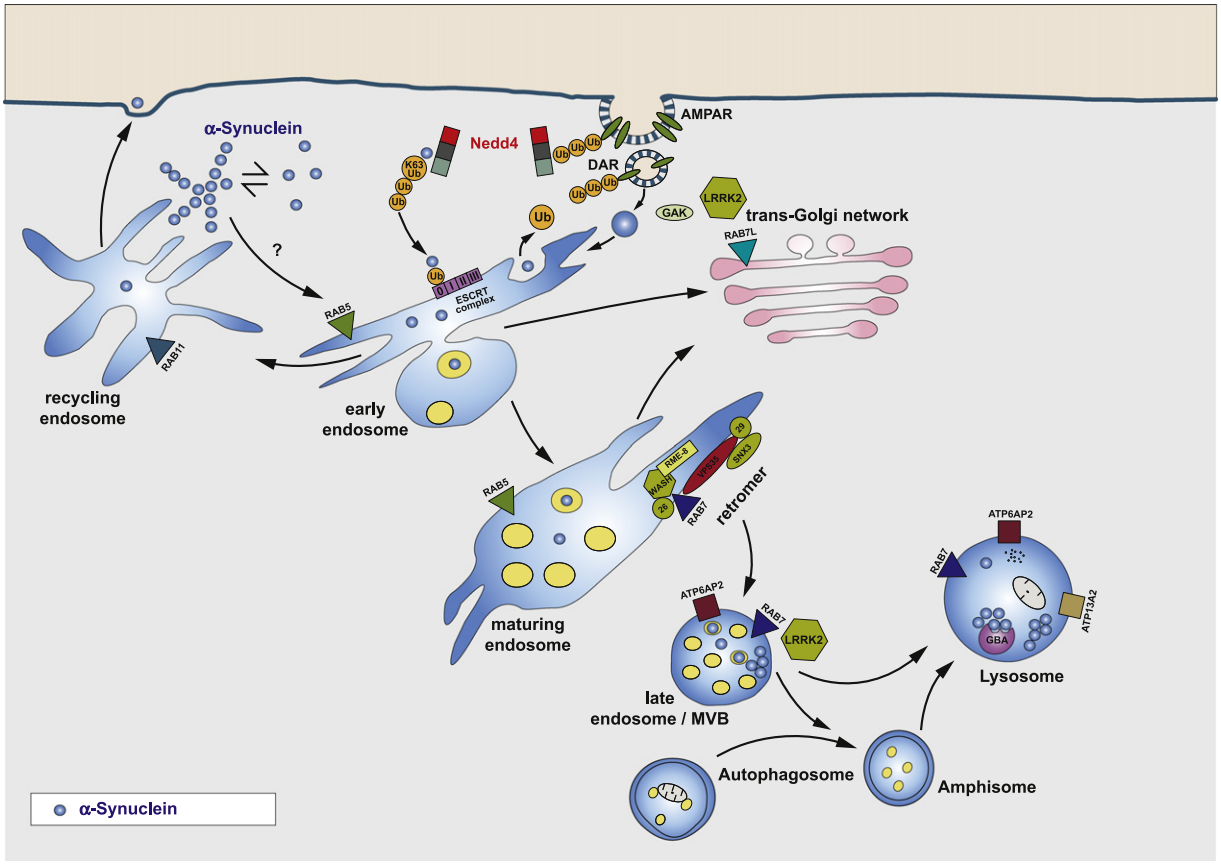

Fig. 1. The endosomal pathway and molecular mechanisms by which it could be disrupted in PD. Conjugation of a Lys-63 linked ubiquitin (Ub) chain to intracellular α-synuclein or transmembrane receptors, e.g. dopamine (DAR) or AMPA receptor (AMPAR), by E3 Nedd4, serves as a trafficking-signal to the endosome via the ESCRT complex. The Ub chain is removed by deubiquitinases and the cargo enters the endosome. From the endosome, cargo can be recycled to the plasma membrane or trafficked to the lysosome. Endosomal maturation is characterized by the loss of the small GTPase Rab5 and acquisition of Rab7. The endosomal retromer complex induces actin polymerization and is required for protein sorting. It is composed of a protein complex that includes VPS35 and RME-8. Late endosome/multivesicular body (MVB) to lysosome fusion requires SNARE proteins and is associated with increased acidification, mediated by the V-ATPase complex; ATP6AP2 is an accessory protein of this complex. Heterozygous mutations in the lysosomal enzyme glucocerebrosidase (GBA) increase the risk of PD. In addition mutations in the lysosomal P-type ATPase ATP13A2, a cation pump, lead to α-synuclein accumulation. LRRK2 interacts with and disrupts endocytosis, GAK-Rab7L trans-Golgi complex formation and late endosome–lysosome trafficking. Impaired endosomal trafficking of α-synuclein may trigger its accumulation and fibrillation in the vicinity of or within endosomal/lysosomal compartments, disrupting multiple points within the pathway.

the disease eventually. In this review we summarized the evidence that protein trafficking via the endosomal pathway fulfills these criteria in Parkinson's disease pathogenesis and discussed novel therapeutic targets within these protein networks.

2. The endosomal pathway

Endosomal trafficking is essential for the maintenance of cellular homeostasis and thus organismal viability as evidenced by the lethal phenotype of critical enzymes that regulate its multiple functions (Zeigerer et al., 2012). Endosomes are a critical hub for the re-use or breakdown of membrane-bound proteins, trafficking of Golgi-associated proteins and the extracellular release of proteins in exosomes (Fig. 1). Neurons are heavily dependent on such processes to fulfill their specialized functions in neurotransmission and ensure that the fine balance between recycling and degradation of synaptic vesicles or specific protein cargoes such as neurotransmitter or growth factor receptors is tightly maintained throughout lifespan.

Following internalization at the plasma membrane by either clathrin-dependent or clathrin-independent endocytosis, the cargo is delivered to the early endosome where sorting occurs. These trafficking steps are highly selective and involve a series of membrane fusion/fission events, mediated by specific GTPases. Early endosome to late endosome maturation is a continuum, associated with an increase in the number of intraluminal vesicles (multivesicular bodies, MVBs), luminal acidification and endosome movement from the cell periphery towards the nucleus. The transport of endosomes takes place on polarized microtubules via dynein and kinesin motor proteins. This morphological maturation is associated with a molecular switch in GTPase composition with loss of Rab5 expression and acquisition of Rab7 (Huotari and Helenius, 2011; Jean and Kiger, 2012). Recycling to the plasma membrane is achieved either by a slow route mediated by Rab11 or directly from the early endosome involving Rab4. The retromer complex is a key player in endosomal retrieval of membrane proteins (Seaman et al., 1997). It is located on the endosomal membrane where it recognizes cargo and recruits the WASH complex, which together with Arp2/3 induces the actin polymerization required for protein sorting (Derivery et al., 2009; Gomez and Billadeau, 2009). The WASH complex is comprised of five proteins, strumpellin, FAM21, SWIP, ccdc53 and WASH (Derivery and Gautreau, 2010). The retromer is comprised of a cargo-selective complex (CSC), which is a trimer of VPS35, VPS26 and VPS29, and a sorting nexin dimer (SNX), either SNX1 or SNX2 with SNX5 or SNX6 (Seaman, 2005; Wassmer et al., 2007). The interaction of FAM21 with VPS35 in the CSC is required for the endosomal recruitment of the WASH complex (Harbour et al., 2010, 2012; Helfer et al., 2013; Jia et al., 2012). The CSC is recruited by Snx3 and Rab7, suggesting that the retromer is only active during the midpoint of endosome maturation, when both Snx3 and Rab7 are expressed (Seaman, 2012).

Lysosomes are the common degradative end-point at which the endosomal and autophagic pathways converge (Fig. 1). Late endosomes

fuse directly with lysosomes in a three-step process: tethering which is Rab7-dependent, trans-SNARE complex formation (involving late endosomal syntaxin 7 (Stx7), Vti1b, and Stx8 and lysosomal vesicle-associated membrane protein 7, VAMP7) and membrane fusion (Mullock et al., 1998; Pryor et al., 2004). The fusion of the autophagosome with the lysosome is a similar process, requiring SNARE complexes (autophagosomal Stx17, synaptosomal-associated protein 29 (SNAP29) and endosomal/lysosomal membrane VAMP8), the homotypic fusion and protein sorting (HOPS)-tethering complex and Rab7 (Jager et al., 2004; Itakura et al., 2012; Jiang et al., 2014).

Correct delivery of individual protein-substrates or protein-complexes to endosomes typically involves the conjugation of a poly-ubiquitin chain linked via Lysine-63 (K63) or multiple mono-ubiquitins, which act as sorting signals. This in turn triggers the assembly of a highly conserved machinery, the Endosomal Complex Required for Transport (ESCRT) which captures the ubiquitin conjugates on the endosomal membrane. ESCRT complexes are comprised of four distinct assemblies (named ESCRT 0, I, II, III) which recognize the cargo, associate with the endosomal membrane and sort protein-substrates in intraluminal vesicles (Raiborg and Stenmark, 2009). Dedicated ubiquitin ligases and deubiquitinating enzymes play a critical regulatory role in this process, as conjugation of ubiquitin chains determines the processing of protein-substrates or the stability of various ESCRT components.

3. Endosomal defects in Parkinson's pathogenesis

Given the complexity of endosomal fusion and delivery systems, it is not surprising that many of these steps have been implicated in neurodegenerative or neurodevelopmental diseases. However the discovery of both genetic mutations (e.g. *α-synuclein, VPS35, LRRK2, DNAJC13/RME-8*) in late-onset familial PD which is clinically similar to sporadic disease and polymorphisms in genome-wide studies (e.g. *GAK, Rab7L1*, Nalls et al., 2014), that disrupt endosomal trafficking, strongly supports the notion that endosomes are especially important in this disease. Changes in endo-lysosomal enzyme activities have also been reported in the CSF of patients with sporadic PD (van Dijk et al., 2013).

The discovery of families with *α-synuclein* gene multiplications indicates that increased levels of this protein are sufficient to cause PD with LB (Tofaris and Spillantini, 2007; Ross et al., 2008). Cellular studies in diverse model systems suggest that one potential mechanism by which α-synuclein expression perturbs cellular function is by disrupting membrane fusion events in the endosomal pathway. In this respect, yeast cells, which are heavily dependent on endocytic and secretory pathways, have been informative (Outeiro and Lindquist, 2003). Overexpression of α-synuclein in this model results in dose-dependent toxicity, accumulation of vacuoles and aggregation of α-synuclein with multiple Rab GTPases (Soper et al., 2011; Gitler et al., 2008; Soper et al., 2008). In addition, α-synuclein interacts with prenylated Rab acceptor protein (PRA1) (Lee et al., 2011), found in the Golgi and late endosomes and regulates the cycling of Rab GTPases during exocytosis and endocytosis (Abdul-Ghani et al., 2001). Co-transfection of α-synuclein and PRA1 caused defects in vesicle trafficking, possibly by the inhibition of Rab recycling (Lee et al., 2011). Fusion of the late endosomes with lysosomes or phagophores requires the SNARE complex (Nichols and Pelham, 1998) which is also important for synaptic vesicle fusion. Studies in mammalian systems showed that α-synuclein directly binds to the SNARE protein synaptobrevin-2 (VAMP2) and is required for SNARE complex assembly at the synapse (Burre et al., 2010, 2014). Endogenous α-synuclein was protective against neurodegeneration caused by the deletion of the SNARE chaperone cysteine-string protein α (CSPα) (Chandra et al., 2005) whereas its overexpression in a transgenic mouse model caused redistribution of SNARE proteins (Garcia-Reitbock et al., 2010; Lim et al., 2011). In primary neurons, α-synuclein fibrils triggered the accumulation of endogenous α-synuclein in axons and impaired Rab7-positive endosomal transport and fusion with lysosomes (Tanik et al., 2013; Volpicelli-Daley et al., 2014).

Another mechanism by which α-synuclein misfolding may impair endosomal function stems from the knowledge that low pH accelerates its fibrillation by reducing the net positive charge on the carboxyl-terminus of the protein (Uversky et al., 2001; Buell et al., 2014). Acidification of endosomes and lysosomes is key to their maturation and function: early endosomes have a pH of 6.8–6.1, late endosomes 6.0–4.8 and lysosomes around 4.5 (Maxfield and Yamashiro, 1987). Interestingly, mutations affecting the levels of ATP6AP2, an accessory protein of the V-ATPase complex that is required for acidification (Forgac, 2007), cause X-linked parkinsonism with spasticity (Korvatska et al., 2013). It is therefore possible that impaired endosomal trafficking of α-synuclein may trigger its accumulation and fibrillation within endosomal compartments.

An autosomal dominant D620N mutation in the VPS35 subunit of the retromer has been linked to late-onse PD (Zimprich et al., 2011; Vilarino-Guell et al., 2014; Ando et al., 2012). In rat primary neurons and *Drosophila*, the expression of D620N VPS35 caused dopaminergic neuron degeneration (Tsika et al., 2014; Wang et al., 2014), and in patient-derived fibroblasts, *Drosophila* and HEK cells, the mutation caused α-synuclein accumulation in late endosomes/lysosomes, likely due to a disruption in the trafficking of cathepsin D, the main lysosomal enzyme which degrades α-synuclein (Sevlever et al., 2008; Follett et al., 2014; Miura et al., 2014). This phenotype can be explained by the fact that mutant VPS35 has decreased affinity for FAM21, and therefore shows reduced association with the WASH complex (McGough et al., 2014) impairing its endosomal recruitment and thus perturbing endosomal/lysosomal trafficking (Zavodszky et al., 2014).

Interestingly, mutations in DNAJC13/RME-8, an accessory of the WASH complex, have also recently been linked to PD (Vilarino-Guell et al., 2014). Like VPS35, RME-8 associates to the WASH complex by binding to FAM21 protein (Freeman et al., 2014). RME-8 is associated with both the WASH complex and SNX, which generates membrane tubules. RME-8 may regulate the localization of the WASH complex and SNX dimer, as its knockdown causes an increase in highly branched endosomal tubules and impaired SNX-1 membrane association (Freeman et al., 2014). Interestingly, reduction in VPS35 levels predispose to Alzheimer's pathology (Small et al., 2005) and pharmacological chaperones that stabilize the retromer complex promote its function in APP trafficking (Mecozzi et al., 2014), suggesting that similar approaches may be beneficial in PD.

LRRK2 is a multidomain protein with GTPase and kinase functions and a number of protein/protein interaction motifs (Bosgraaf and Van Haastert, 2003; Marin, 2006; Deng et al., 2008). Autosomal dominant mutations in LRRK2 cause familial PD (Paisan-Ruiz et al., 2004; Zimprich et al., 2004), and have since been found in up to 2% of apparently sporadic cases (Berg et al., 2005), indicating that LRRK2 is the commonest gene defect in PD. LRRK2 was detected in α-synuclein positive brainstem LBs and colocalized with the late endosomal marker Rab7, and less frequently with the lysosomal marker LAMP2, suggesting that it functions in the endo-lysosomal pathway (Higashi et al., 2009). Mutant LRRK2 acts at multiple points within this pathway. Early on, it interacts with Rab5b, a subtype of Rab5, and over- or underexpression in human primary neurons impaired synaptic vesicle endocytosis (Shin et al., 2008), rescued by Rab5b co-expression (Heo et al., 2010). Expression of Rab5 is required for cargo internalization at the plasma membrane (McLauchlan et al., 1998) and it affects endocytosis rates in presynaptic vesicles (Shin et al., 2008). In *Drosophila*, mutations in LRRK2 have been implicated in late endosome maturation and fusion with lysosomes by impairing its interaction with Rab7 (Dodson et al., 2012). Consistent with this notion, in mammalian cells pathogenic LRRK2 mutations reduced Rab7 activity and consequently impaired late endosomal trafficking events (Gomez-Suaga et al., 2014). LRRK2 has been shown to associate with Rab7L1 in endolysosomal and Golgi sorting: Rab7L1 deficiency caused neurodegeneration in mammalian

or *Drosophila* dopaminergic neurons expressing a human LRRK2 mutation, whereas Rab7L1 overexpression rescued the LRRK2 mutant phenotypes (MacLeod et al., 2013). Interestingly these defects were also rescued by the expression of wildtype VPS35 in vitro and in vivo. Furthermore, LRRK2 was shown to directly interact with Rab7L1 and Cyclin G-associated kinase (GAK) forming a complex that promoted the removal of Golgi derived vesicles by autophagy-dependent mechanisms (Beilina et al., 2014). In addition, GAK together with the heat-shock cognate protein 70 (Hsc70) promotes the uncoating of endocytosed clathrin-coated vesicles (Lee et al., 2006). Both Rab7L1 and GAK as well as LRRK2 have been identified as risk factors for sporadic PD by GWAS (Lill et al., 2012; International Parkinson Disease Genomics, C., et al., 2011, Satake et al., 2009; Simon-Sanchez et al., 2009; Tan et al., 2010) and knockdown of GAK in primary rat neurons also increased α-synuclein toxicity (Dumitriu et al., 2011).

4. α-Synuclein degradation by the endosomal pathway

Although α-synuclein is degraded by both proteasomes and lysosomes, the latter have emerged as the most relevant degradative pathway in PD pathogenesis (reviewed in Tofaris, 2012). α-Synuclein was found in association with endosomes (Hasegawa et al., 2011; Boassa et al., 2013) and lysosomes extracted from mouse brains (Mak et al., 2010). Endosomal α-synuclein can either be targeted for degradation by lysosomes or enter the recycling endosome and be released in a process involving Rab11a and Hsp90 (Liu et al., 2009; Hasegawa et al., 2011). Interestingly, changes in the expression of Rab11 promoted the extracellular secretion of α-synuclein and decreased its aggregation and toxicity in the *Drosophila* model (Breda et al., 2015). Once delivered to the lysosome, α-synuclein is degraded primarily by Cathepsin D (Sevlever et al., 2008) which when overexpressed in vivo was also protective against α-synuclein toxicity (Qiao et al., 2008; Cullen et al., 2009; Crabtree et al., 2014). Accordingly, in the human brain the expression of the lysosomal proteins LAMP1 and Cathepsin D is reduced in nigral neurons in PD brains (Chu et al., 2009). Mutations in *ATP13A2* (PARK9) cause Kufor–Rakeb syndrome and young onset PD (Di Fonzo et al., 2007). ATP13A2 is a P-type ATPase that is localized across endosomal and lysosomal membranes and functions as a cation pump (Schultheis et al., 2004; Podhajska et al., 2012; Tan et al., 2011). The loss of ATP13A2 function was shown to increase neuronal sensitivity to zinc and impair lysosomal function leading to α-synuclein accumulation (Tsunemi and Krainc, 2014). Importantly, heterozygous mutations in the lysosomal enzyme glucocerebrosidase (GBA) increase the risk of PD by 5-fold (Sidransky et al., 2009; Nalls et al., 2013) at least partly due to decreased degradation and increased toxicity of α-synuclein as evidenced both in cell and animal models (Mazzulli et al., 2011; Sardi et al., 2011; Schondorf et al., 2014). Pharmacological chaperones which promote GBA stability and trafficking to the lysosome (Khanna et al., 2010; Steet et al., 2006) were effective in improving lysosomal function and reducing α-synuclein levels in cellular models (McNeill et al., 2014) and transgenic mice overexpressing human α-synuclein leading to improved motor function (Richter et al., 2014). Collectively these data strongly suggest that α-synuclein is degraded by a lysosomal pathway and promoting this activity also mitigates toxicity that is associated with increased α-synuclein levels.

Different types of autophagy have been implicated in the lysosomal clearance of α-synuclein and activation of autophagy in vivo under pathological conditions of α-synuclein overexpression is protective (Decressac et al., 2013). However, the relevance of autophagy, if any, for the basal turnover of neuronal α-synuclein remains to be clarified. It is noteworthy that mice with neuron-specific inactivation of critical autophagy genes develop neurodegeneration with diffuse ubiquitin-positive inclusions which are not typically positive for α-synuclein, indicating that multiple other autophagy substrates may contribute to the phenotype (Hara et al., 2006; Komatsu et al., 2006; Ahmed et al., 2012).

Enzymes with relative substrate selectivity could also promote the lysosomal degradation of α-synuclein without the potentially harmful effects from generalized activation of lysosomal protein breakdown. It is now evident that enzymes in the ubiquitin pathway serve this function and boosting their activity is protective in animal models. Conjugation of a specific type of ubiquitin chain (Lys-63 linked) to protein-substrates serves as a trafficking-signal to the endosome via ESCRT as discussed earlier and under certain conditions the autophagosome, via p62 and related ubiquitin-receptors. This post-translational modification occurs in a three-step catalytic process, involving a ubiquitin activating enzyme E1, a ubiquitin conjugating enzyme E2 and a ubiquitin ligase E3. There are more than 650 ubiquitin ligases (E3s), which regulate substrate specificity. Once a substrate enters the relevant degradative pathway, the ubiquitin chain is removed by one of the 90 deubiquitination enzymes (DUBs) that control the cellular flux of ubiquitin and further proof-read the degradation process.

We first identified one of the 650 E3s, Nedd4, as an important ubiquitin ligase in Parkinson's pathogenesis (Tofaris et al., 2011). Nedd4 (Neuronally-expressed developmentally down-regulated gene 4) serves a critical function in the endosomal–lysosomal pathway, promoting the degradation of membrane-associated proteins (Rotin and Kumar, 2009). Nedd4, as its name suggests is down-regulated during development, and up-regulated in response to oxidative stress (Hoshikawa et al., 2003), traumatic head injury (Sang et al., 2006) and neurodegeneration (Kwak et al., 2012) indicating that its expression in neurons is tightly regulated. In our initial studies, we showed that Nedd4 and its yeast ortholog Rsp5 directly and robustly ubiquitinated α-synuclein in vitro, identified the sequence on α-synuclein that is recognized by Nedd4, the lysine residues that are targeted for ubiquitination and demonstrated that this process involved K63-linked ubiquitin chains. Our data indicated that in mammalian cells Nedd4 overexpression promoted the degradation of α-synuclein by the ESCRT-mediated endosomal–lysosomal route and that in yeast Rsp5 protected against α-synuclein toxicity (Tofaris et al., 2011). More recently, we have shown that Nedd4 overexpression protects against α-synuclein accumulation in *Drosophila* and rat models of α-synucleinopathy, whereas endogenous Nedd4 in *Drosophila* is especially critical for the dopaminergic neuronal response to α-synuclein toxicity (Davies et al., 2014). A role for Nedd4 in the human condition is supported by our neuropathological observations that Nedd4 is upregulated in a subpopulation of pigmented neurons containing LBs (Tofaris et al., 2011), the identification of a coding SNP as a risk factor for idiopathic PD (Srinivasan et al., 2009), and the finding that Nedd4 mRNA expression is increased in brain regions with LB pathology (Dumitriu et al., 2012). Thus, our data that Nedd4 is protective against human α-synuclein toxicity in evolutionarily distant model systems (yeast, *Drosophila*, rat) strongly suggest that activation of this conserved ubiquitination pathway should be considered as a target for neuroprotective therapies. In agreement with our earlier observations, a recent chemical genetic screen has identified a small molecule that binds to and activates Nedd4 as a neuroprotective agent in yeast and iPSc-derived cortical neuronal models of α-synuclein toxicity and also showed that Nedd4 overexpression is protective in the A53T iPSc-derived neuronal model (Chung et al., 2013). Our earlier observation that the ubiquitin ligase activity of Nedd4 and its yeast ortholog Rsp5 is necessary for protection at least partly by a direct effect on α-synuclein (Tofaris et al., 2011; Davies et al., 2014) has been confirmed and extended by recent studies, which showed that Nedd4 also promoted the endosomal processing of internalized α-synuclein (Sugeno et al., 2014) and identified mutants in yeast that enhanced α-synuclein ubiquitination (Wijayanti et al., 2014). Additional α-synuclein-independent protective effects are also possible. For example, Nedd4 promotes the ubiquitination and recycling of neurotransmitter receptors at the synapse such as the AMPA receptor (Hou et al., 2011), which interestingly is also regulated, downstream to Nedd4, by the retromer (Munsie et al., 2014). In addition, Nedd4 has recently been

shown to ubiquitinate cytosolic misfolded proteins following heat-stress (Fang et al., 2014).

Collectively, these data strongly suggest that enzymes in the ubiquitin pathway such as Nedd4 that regulate the trafficking of α-synuclein to endosomes could provide a molecular mechanism that links the accumulation of α-synuclein in LB, often in a ubiquitinated form (Tofaris et al., 2003) to the downstream genetic defects in endosomal–lysosomal function. Importantly, their enzymatic activity and relative substrate selectivity could be targeted for therapies in sporadic PD. It should be noted that direct E3 activation is not easily achieved pharmacologically. Thus, despite early promising results in compound screens (Chung et al., 2013), future studies to better understand the function of Nedd4 in neurons and mechanisms of its regulation, may facilitate the identification of additional nodes for pharmacological intervention in this protective ubiquitination pathway.

5. Concluding remarks

In this review we have highlighted recent advances suggesting a central role for endosomal processing in PD pathogenesis. Molecular genetics indicate that disease causing mutations cluster within this pathway (Fig. 1) and alter receptor recycling and/or α-synuclein degradation. In turn, α-synuclein accumulation in cell and animal models further exacerbates defective endosomal processing by impairing the machinery involved in the sorting or fusion of endosomes.

We propose that such a vicious circle could be sufficient to explain the selective vulnerability of dopaminergic neurons to neurodegeneration in PD: throughout lifespan dopaminergic neurons slowly accumulate neuromelanin, causing the easily identified histological appearance of the 'substantia nigra' (Fedorow et al., 2005). Early studies suggested that neuromelanin accumulation predisposes dopaminergic neurons to degeneration (Hirsch et al., 1988) and identified endolysosomal markers and lipid vesicles in association with or enclosing these pigmented granules (Duffy and Tennyson, 1965; Tribl et al., 2005). Thus, neuromelanin accumulates within endosomal compartments with increasing age and could impair endosomal function selectively in the dopaminergic neurons. In this respect PD could be considered a regional 'storage-type' disease process, predisposing the nigral dopaminergic neurons to neurodegeneration with LB in accordance with the recent realization that widespread neuronal lipofuscin deposition in storage diseases such as Gaucher's (Wong et al., 2004), Niemann–Pick type C1 (Saito et al., 2004) and the lipidoses (Suzuki et al., 2007) increases the risk of dementia with diffuse deposition of α-synuclein inclusions. Why is it then that only some individuals develop sporadic Parkinson's disease? It is possible that if humans were to live long enough, they would all invariably develop LB pathology or Parkinson's disease. It is certainly true that the incidence of LB in post-mortem brains is higher than clinical parkinsonism (Gibb et al., 1989). However, a more plausible explanation is that an age-related pathological depletion of functional endosomes may increase the susceptibility to stochastic molecular defects in this same pathway, which in some individuals may trigger the aforementioned vicious circle that culminates in PD. It is our view that these molecular defects are not restricted only to candidates identified in genetic or genome-wide studies but that such hits provide only some pieces of the puzzle as discussed in earlier sections of this review. It is very likely, as evidenced by functional and screening studies in cell and animal models, that the druggable targets form distinct nodes within such interconnected protein networks. In this respect, pharmacological chaperones that stabilize the retromer or improve GBA trafficking or compounds that promote Nedd4 function are especially promising, whereas further studies of ubiquitin signaling, could provide the missing link between genetic and acquired defects in endosomal trafficking.

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