Molecular and Cellular Neuroscience xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

The endosomal pathway in Parkinson's disease

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ARTICLE INFO

Article history:
Received 6 January 2015
Revised 16 February 2015
Accepted 17 February 2015
Available online xxxx

Keywords:
Endosome
Lysosome
Alpha-synuclein
Ubiquitin
Parkinson's disease

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.

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 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

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http://dx.doi.org/10.1016/j.mcn.2015.02.009
1044-7431/

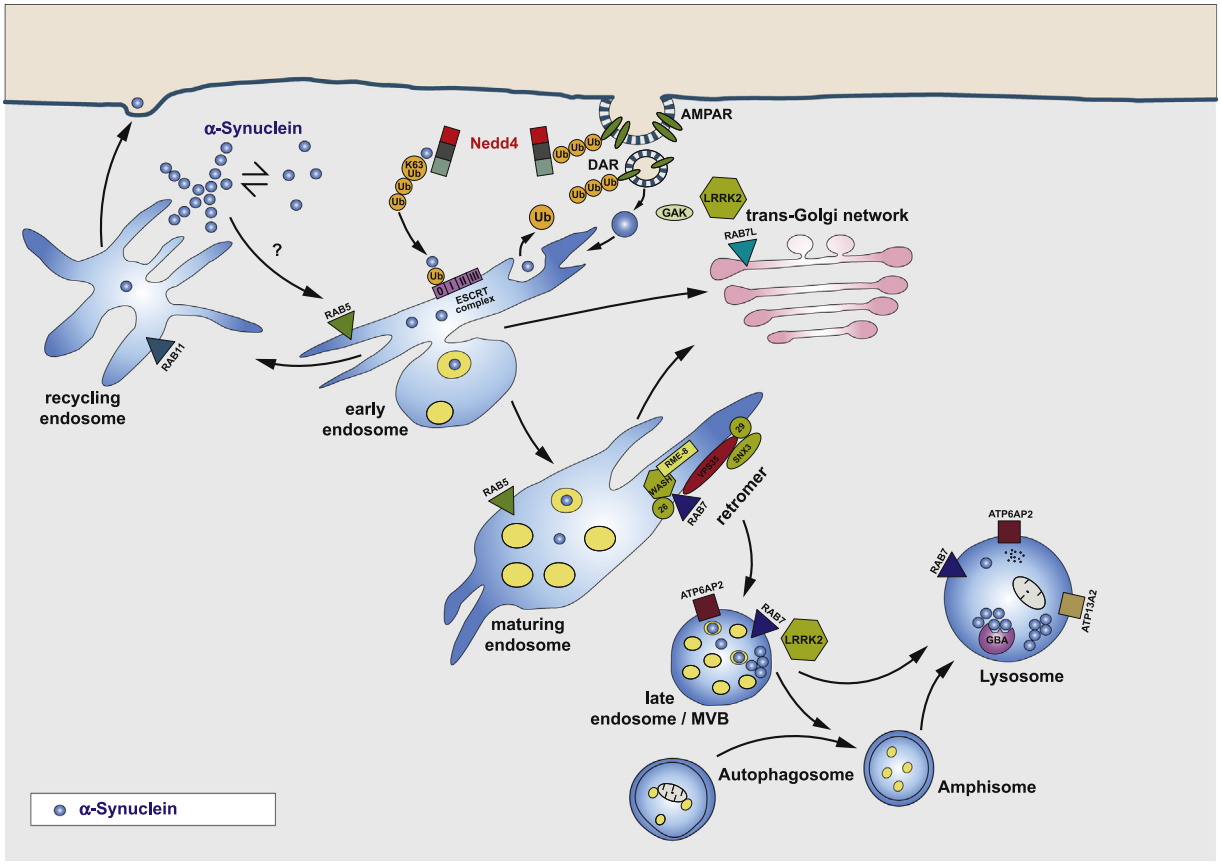

Fig. 1. The endosomal pathway and molecular mechanisms by which it could be disrupted in PD. Conjugation of a Lys-63 linked ubiquitin (Ub) chain to intracellular α-synuclein or transmembrane receptors, e.g. dopamine (DAR) or AMPA receptor (AMPAR), by E3 Nedd4, serves as a trafficking-signal to the endosome 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.

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.

Please cite this article as: Perrett, R.M., et al., The endosomal pathway in Parkinson's disease, Mol. Cell. Neurosci. (2015), http://dx.doi.org/10.1016/j.mcn.2015.02.009