Cellular and Molecular Life Sciences

REVIEW

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Endocytic membrane trafficking and neurodegenerative disease

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Abstract Neurodegenerative diseases are amongst the most devastating of human disorders. New technologies have led to a rapid increase in the identification of disease-related genes with an enhanced appreciation of the key roles played by genetics in the etiology of these disorders. Importantly, pinpointing the normal function of disease gene proteins leads to new understanding of the cellular machineries and pathways that are altered in the disease process. One such emerging pathway is membrane trafficking in the endosomal system. This key cellular process controls the localization and levels of a myriad of proteins and is thus critical for normal cell function. In this review we will focus on three neurodegenerative diseases; Parkinson disease, amyotrophic lateral sclerosis, and hereditary spastic paraplegias, for which a large number of newly discovered disease genes encode proteins that function in endosomal membrane trafficking. We will describe how alterations in these proteins affect endosomal function and speculate on the contributions of these disruptions to disease pathophysiology.

Keywords Alzheimer disease · ALS · Clathrin · Endocytosis · Endosome · HSP · Lysosomal storage disease · Multivesicular body · MVB · Neurodegeneration · PD · Trans-Golgi network · TGN

Abbreviations

ALS	Amyotrophic lateral sclerosis
AP-2/AP-5	Adaptor protein complex 2/5
CCPs	Clathrin-coated pits
CCVs	Clathrin-coated vesicles
CME	Clathrin-mediated endocytosis
CHC	Clathrin heavy chain
CLCs	Clathrin light chains
DENN	Differentially expressed in normal and neoplastic cells
EEA1	Early endosome antigen 1
EGFR	Epidermal growth factor receptor
ESCRT	Endosomal sorting complex required for transport
GAK	Cyclin G-associated kinase
GARP	Golgi-associated retrograde protein
GBA	Glucocerebrosidase
GEF	Guanine nucleotide exchange factor
HSP	Hereditary spastic paraplegia
ILVs	Intralumenal vesicles
KRS	Kufor-Rakeb syndrome
LRRK2	Leucine-rich repeat kinase 2
MDVs	Mitochondria-derived vesicles
MPR	Mannose-6-phosphate receptor
MVBs	Multivesicular bodies
OCRL	Oculocerebrorenal syndrome of Lowe
PD	Parkinson disease
PINK1	PTEN-induced kinase 1
PtdIns	Phosphatidylinositol
PtdIns(4,5)P2	Phosphatidylinositol 4,5-bisphosphate
PtdIns(3)P	Phosphatidylinositol 3-phosphate
PtdIns(4)P	Phosphatidylinositol 4-phosphate
SNARE	Soluble NSF attachment protein receptor
SNX	Sorting nexin
STAM	Signal transducing adaptor protein molecule

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TGN	Trans-Golgi network
UbBD	Ubiquitin-binding domain
V-ATPase	Vacuolar (H+)-ATPases proton pump
Vps	Vacuolar protein sorting

Introduction

Neurodegenerative diseases are among the most devastating and feared of human afflictions. The economic impact of these diseases is massive, and with a rapidly aging population, the challenges they pose will only increase. Hundreds of genetic loci form the basis of risk factors for the genetic architecture of neurodegenerative diseases [1]. Importantly, the protein products of these loci can often be placed into discrete cell biological machineries or pathways, leading to clues regarding the pathophysiological underpinnings of the disorders. One such pathway emerging from these genetic studies is membrane trafficking in the endosomal/lysosomal system. These trafficking pathways play critical roles in controlling the localization and levels of a myriad of proteins and it is now clear that alterations in these pathways contribute to numerous neurodegenerative disorders. In this review we will focus on three distinct but overlapping neurodegenerative diseases for which alterations in endo/lysosomal trafficking have been firmly established, namely Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and hereditary spastic paraplegias (HSPs).

PD is the second most common age-related progressive neurodegenerative disorder characterized by tremor and rigidity, resulting from death of dopaminergic neurons in the substantia nigra, with dementia and behavioral symptoms at later stages [2]. ALS, also known as Lou Gehrig's disease, is the most frequent adult-onset motor neuron disease characterized by very rapid and progressive weakness and muscle atrophy caused by cortical, bulbar, and spinal motor neuron degeneration [3]. HSPs are a class of clinically and genetically heterogeneous neurodegenerative disorders hallmarked by progressive lower limb spasticity arising from degeneration in the corticospinal tracts. Clinically, there are 'uncomplicated' and 'complicated' forms of HSPs, with the addition of seizures, dementia, cerebral or cerebellar atrophy among other symptoms for the complicated form only [4].

Although inherently different diseases, there are numerous commonalities that exist between the three disorders. For example, they all involve altered motor function, have age as a risk factor, have early onset progressive forms, and at the end stage their neuropathology have spread beyond the selective population and brain area of primary affected neurons [3–8]. Moreover, they share neuropathological hallmarks such as cytoplasmic inclusion bodies containing protein aggregates [5, 6, 8]. Finally, all three diseases have genetic forms. Interestingly, the affected genes never appear to be expressed exclusively in their respective vulnerable cellular populations, and in fact, these genes often have general cell biological functions, emphasizing the complexity of the underlying molecular mechanisms driving disease. To date it remains unknown why certain neuronal cellular populations are more vulnerable to death than others.

Trafficking in the endo/lysosomal system has emerged as a common biological function affected in PD, ALS and HSPs. Endocytosis of protein and lipid cargo from the plasma membrane is critical for the normal function and survival of eukaryotic cells. Following endocytic entry, cargo is transported to early endosomes, the initial sorting station in the endocytic pathway, and a major sorting hub in the cell [9] (Fig. 1). From there, cargo can recycle back to the plasma membrane [10], either directly or via recycling endosomes [9]. Alternatively cargo molecules can be retained in early endosomes, which mature into late endosomes. Concomitant with this maturation process, cargoes undergo inward invagination into the lumen of the endosome leading to the formation of multivesicular bodies (MVBs). Eventually the late endosomes/MVBs fuse with lysosomes for degradation of the lipid and protein components. In parallel, proteins and other cargo are transported between endosomes and the trans-Golgi network (TGN). For example, newly synthesized lysosomal hydrolases are trafficked from the TGN to endosomes for eventual targeting to lysosomes, whereas the receptor that carries these enzymes is returned from endosomes to the TGN for additional rounds of hydrolase sorting. Essentially all steps in these pathways are altered by various mutations in PD, ALS and HSPs (Fig. 1). Alterations in these processes lead to dysfunctional lysosomes and accumulation of undegraded macromolecules, toxic to the cell [11]. In this review we discuss the genes involved in PD, ALS, and HSP that are functionally related to trafficking in the endo/lysosomal system (Table 1).

Step 1: clathrin-mediated endocytosis

Endocytic entry of protein and lipid cargo can be considered the first step in endosomal trafficking (Fig. 1). The most prominent form of endocytosis, known as clathrin-mediated endocytosis (CME), is driven by the formation of clathrin-coated pits (CCPs) and vesicles (CCVs). CME is the major entry route for nutrient and signaling receptors, cell adhesion molecules, ion channels and transporters, and numerous pathogens co-opt CME to access cells [12]. Additionally, specialized forms of CME drive the reformation of synaptic vesicles (SVs) following

Fig. 1 Various steps/organelles in endocytic membrane trafficking are diagrammed. Proteins that are encoded by genes altered in neurodegenerative diseases are indicated and are color-coded (*blue* PD, *red* ALS, *green* HSP)

neurotransmitter release [13, 14]. The first step in CME is the generation of a phosphatidylinositol 4,5-bisphosphate [PtdIns(4, 5)P$_2$]-rich patch on the plasma membrane. Once formed the PtdIns(4,5)P$_2$-rich zone recruits the adaptor protein-2 (AP-2), which binds PtdIns(4,5)P$_2$ and dynamically recruits clathrin heavy chain (CHC) associated with clathrin light chains (CLCs) in structures called triskelia, the assembly unit of clathrin coats [15–19]. Triskelia assembly into a CCP contributes to membrane curvature, further mediated by some thirty endocytic accessory proteins that interact with AP-2/clathrin [20]. As the CCP reaches a deeply invaginated stage, the GTPase dynamin is recruited to the neck of the pit where it self-polymerizes into rings, and drives membrane scission upon its GTP hydrolysis, pinching off the CCV from the plasma membrane [21–23]. However, before the cargo-laden cytosolic vesicles can fuse with endosomes the clathrin coat needs to be removed. CCV uncoating requires: (a) dephosphorylation of PtdIns(4,5)P$_2$ by a phosphatidylinositol 5-phosphatase, either synaptojanin or the oculocerebrorenal syndrome of Lowe (OCRL) protein, and (b) recruitment of auxilin or cyclin G-associated kinase (GAK), both

DNAJ domain-containing proteins that recruit the ATPase heat shock cognate 70, which facilitates disassembly of the clathrin cage using its ATPase activity [24–27].

Synaptojanin and auxilin are enriched in the nervous system and in particular at presynaptic nerve terminals, where they function in CCV-mediated recycling of SVs [28, 29]. Using homozygosity mapping and whole-exome sequencing, mutations in both these proteins have been recently discovered as causative of early onset familial forms of PD [30–32]. The PD mutations in synaptojanin reduce its phosphatase activity [31]. Interestingly, these mutations are not in the 5-phosphatase domain, but in the Sac1-like phosphatase domain, which primarily dephosphorylates PtdIns(3)P and PtdIns(4)P to PtdIns [33–35]. The inhibition of the Sac1 phosphatase activity is expected to impair SV endocytosis. Although the cellular effect of the PD mutation in auxilin remains undetermined, the mutation resides in a domain crucial for its recruitment to CCVs, and low levels of auxilin mRNA are detected in patients bearing this mutation [32]. These findings suggest that auxilin's function to regulate CCV uncoating may be strongly altered or non-existent due to the lack of auxilin or

Table 1 Membrane trafficking proteins causative of neurodegenerative disease. This table lists genes that are mutated in ALS, HSP, and PD that function in membrane trafficking

Gene	Protein name	Disease	Protein function	References
SYNJ1	Synaptojanin	Recessive early onset PD	Uncoating of CCVs	[30, 31]
DNAJC6	Auxilin	Recessive early onset PD	Uncoating of CCVs	[32]
PARK17	GAK	Associated via genome-wide association studies with PD	Uncoating of CCVs	[40, 41]
ALS2	Alsin	Recessive early onset ALS	GEF for Rab5 at early endosomes	[48–50]
ATP6AP2	ATP6AP2	X-linked parkinsonism with spasticity	Vital accessory protein of the V-ATPase complex	[62]
PARK8	LRRK2	Familial PD	Kinase at endosomes	[69, 70]
SPG53	Vps37A	Recessive complicated HSP	ESCRT-I subunit	[92]
SPG4	Spastin	Familial HSP	ATPase that interacts with the ESCRT-III machinery	[96]
SPG20	Spartin	Recessive complicated HSP	Potential function in sorting or trafficking of degradative cargo through MVBs	[100]
ATP13A2/ PARK9	ATP13A2	Recessive early onset parkinsonism	P-type ATPase transporter of unknown function at endosomes, lysosomes, and autophagosomes	[106, 152]
VPS35	Vps35	Familial late onset PD	Component of retromer complex	[115, 116]
DNAJC13	RME-8	Familial PD	DNAJ protein that interacts with retromer and the WASH complex	[124]
SPG8/ KIAA0196	Strumpellin	Early onset familial HSP	Component of the WASH complex	[129]
VPS54	Vps54	Resembles early onset ALS (wobbler mouse model)	Component of the GARP complex	[132, 133]
RAB7L1	Rab7L1	Variance in locus protective for PD	Unknown function in retrograde trafficking from endosome to TGN	[138]
C9ORF72	C9ORF72	Sporadic and familial ALS	Potential GEF implicated in endo/lysosomal trafficking	[145, 146]
SPG48	AP-5 ζ/KIAA0415	Recessive HSP	AP-5 subunit at late endosomes and/or lysosomes	[159, 160]
SPG11	Spatacsin	Recessive HSP	AP-5 binding accessory protein	[161]
SPG15	Spastizin/ ZFYVE26	Recessive complicated HSP	AP-5 binding accessory protein	[162]
GBA1	Glucocerebrosidase	Risk factor for PD	Lysosomal enzyme that converts glucosylceramide into glucose and ceramide	[166–168]
PARK6	PINK1	Recessive early onset PD	Mitochondrial kinase	[171]
PARK2	Parkin	Recessive early onset PD	E3 ubiquitin ligase	[172]
OPTN	Optineurin	Familial ALS	An autophagy receptor	[179]

loss of recruitment to CCPs. It will be of interest to determine if the cellular effects of the PD-mutation in auxilin phenocopy auxilin knockout mice, which show accumulation of CCVs in presynaptic nerve terminals, impaired rates of SV endocytosis, and early postnatal morbidity [36]. Regardless, it is likely that patients with mutations in either synaptojanin or auxilin have impaired recycling of SVs with defects in neurotransmitter release. In general synaptic activity is required for neuronal survival such that even subtle defects in activity could lead, over time to loss of selective neuronal populations.

OCRL and GAK are homologous to and play similar functions as synaptojanin and auxilin, respectively, but have a ubiquitous tissue/cellular distribution [37–39]. GAK has been linked to PD in multiple genome-wide association studies [40, 41]. CME is the major mechanism for uptake of key nutrients and it regulates signalling of a plethora of receptors, such that alterations in GAK, which would lead to disruption of CCV uncoating, could cause a loss of key factors required for cell survival. Although this could influence the viability of many cell types, neurons, which are large and long-lived are likely to be particularly susceptible to such insults and this could contribute to pathophysiology of PD. Alternatively, dysfunction of CME in cells that are required to support neuronal survival could contribute to neuronal death.

Step 2: early endosomes

Following CME, CCVs uncoat and fuse with early endosomes, the initial sorting station in the endocytic pathway, and a major sorting hub in the cell for internalized ligand/ receptor complexes, proteins, and lipids [9] (Fig. 1). Cargo

that is delivered to early endosomes has three main destinations: recycling to the plasma membrane, degradation in lysosomes, and retrograde trafficking to the TGN.

Docking and fusion of uncoated endocytic vesicles with early endosomes occurs via a protein complex involving the small GTPase Rab5 [42]. Rab GTPases are master regulators of membrane trafficking and cycle between active, GTP-bound and inactive GDP-bound states. In their active state, mediated by guanine nucleotide exchange factors (GEFs), Rabs bind effector proteins that mediate downstream signalling pathways [43]. Early endosome antigen 1 (EEA1) on early endosomes provides an initial tethering site for incoming Rab5-positive vesicles [44, 45]. A second tethering factor is the Rab5 GEF alsin, which regulates Rab5 activity and interacts with EEA1 [46, 47]. ALS2, encoding alsin, is mutated in a recessive juvenile form of ALS leading to a truncated alsin protein that no longer associates with EEA1 [48–50]. The absence of mutated alsin from early endosomes is likely to decrease the levels of active Rab5, hampering not only cargo sorting but also endosomal maturation, hence deregulating membrane flow through the endosomal system. Additionally, alsin activates Rac1 at early endosomes, which helps regulate the actin cytoskeleton [46]. Thus, loss of alsin may also inhibit Rac1 activity and thus restrain cellular actin dynamics. In agreement, knockdown of alsin in rat embryonic spinal motor neurons triggers a motor neuron degeneration phenotype in a Rac1-dependent manner with axonal outgrowth defects in the surviving neurons [51]. To elucidate the general effect of alsin loss-of-function, both knockdown and knockout animal models have been generated. These models reveal numerous defects that can be related to endosomal dysfunction. Among them, a reduction in early endosome size accompanied by internal accumulation of surface receptors that fail to recycle, decreased endosomal fusion, altered distribution of surface proteins, age-dependent and slowly progressive loss of cerebellar neurons and enhanced spinal motor neuron death, as well as motor coordination deficits [50–57]. It is difficult to determine the precise mechanisms by which these numerous changes lead to neurodegeneration but it is likely that altered localization of specific proteins alter neuronal survival. For example, loss of alsin function leads to disrupted endosomal transport of the receptor for brain-derived neurotrophic factor, a key neuronal survival molecule [53]. This would lead to disruption of an important survival signal for neurons. Moreover, endosomal trafficking defects in alsin$^{-/-}$ spinal motor neurons cause a decrease in the surface levels of a calcium impermeable form of glutamate receptor, making the neurons more vulnerable to glutamate-induced excitotoxicity [54]. Together, these results indicate that alterations in cargo sorting at early endosomes, coupled with disruption

of early endosomal maturation contribute to ALS disease pathophysiology.

The lumen of the endosome is mildly acidic and endosomal acidification is required for endosome maturation and the eventual delivery of cargo to lysosomes. The vacuolar (H$^+$)-ATPases proton pump (V-ATPase) controls endosomal acidification maintaining an acidic lumenal pH ($\sim$6.0) that allows dissociation of ligand/receptor complexes in early endosomes [58, 59]. The receptors are then recycled back to the plasma membrane to undergo additional rounds of internalization, while their dissociated ligands continue to lysosomes for degradation. ATP6AP2/(pro)renin receptor is a vital accessory protein of the V-ATPase complex that regulates V-ATPase activity. If deleted, the V-ATPase driven acidification of intracellular endo/lysosomal vesicles is compromised resulting in vacuoles containing undigested contents [60, 61]. Recently, mutations in ATP6AP2 were discovered as causative of X-linked Parkinsonism with spasticity. The ATP6AP2 mutations cause altered splicing, giving rise to overexpression of a minor splice isoform with reduced ability to activate the V-ATPase [62]. It is plausible that a reduction of the active full-length ATP6AP2 may compromise endo/lysosomal acidification by V-ATPase and perturb endosomal/degradative trafficking in neurons, ultimately causing PD pathology, as seen with ATP6AP2 knockdown in a cell line [62]. Similar to mutations in alsin, changes in endosomal acidification resulting from altered ATP6AP2 function could disrupt trafficking of selective proteins that are required for neuronal survival. Disruption of lysosomal acidification will clearly lead to accumulation of undegraded macromolecules, which are toxic to the cell. Interestingly, ATP6AP2 is a ubiquitous protein, yet the effect of its mutation is confined to the nervous system [62]. This may be explained by the enhanced need of neurons for survival factor signalling or their sensitivity to accumulation of undegraded toxic macromolecules, given their long-lived nature. In conclusion, several early endosomal proteins have been found to be causative of neurodegenerative disorders when mutated, emphasizing the importance of a functional sorting station inside the cell that coordinates several crucial membrane trafficking pathways.

Step 3: the ESCRT machinery and formation of MVBs

Another important organizer of early endosomes is clathrin, which forms a bilayered clathrin coat on the early endosome membrane through interactions with multiple endosomal membrane proteins [63–67]. As described below, this clathrin coat is important for sorting specific cargo for degradation. Intriguingly, we recently discovered

that the major PD gene LRRK2, which is a kinase, interacts with CLCs, which are components of clathrin triskelia [15, 16, 68–70]. Using CRISPR/Cas9 technology we introduced a HA-tag under the endogenous promoter of LRRK2, revealing that endogenous LRRK2 co-localizes with CLC and EEA1, reflecting bilayered clathrin coats on early endosomes [68, 71]. Consistent with our localization of LRRK2 to the endosomal system, it was recently demonstrated that expression of LRRK2 G2019S, the most common mutation in familial PD, delays epidermal growth factor receptor (EGFR) degradation by decreasing Rab7 activity [72]. Transition from Rab5-positive early endosomes to Rab7-positive late endosomes is mediated by active Rab5, which recruits effectors that activate Rab7, causing late endosome maturation [73]. Remarkably, LRRK2 phosphorylates Rab5, accelerating its GTPase activity [74]. Thus, expression of LRRK2 G2019S, which is a mutation that enhances the kinase activity, would lead to decreased levels of active Rab5 (due to increased GTPase activity) with decreased transition of early endosomes to late endocomes. Consistent with this hypothesis, expression of LRRK2 G2019S in astrocytes diminishes the lysosomal capacity of the cells [75]. This would lead to the accumulation of undegraded macromolecules, such as misfolded α-synuclein, which are toxic to the cell. Alterations in LRRK2 regulation of Rab5 activity on early endosomes would also alter endosomal cargo sorting, as already described for EGFR [72]. This could disrupt receptor signalling pathways required for cell survival.

The transition from early to late endosomes occurs on multiple levels and includes changes in organelle structure, protein, and lipid composition. The maturation process is initiated with the inward budding of membrane to form intralumenal vesicles (ILVs) containing cargo destined for degradation (Fig. 1). The selection and concentration of these cargoes into the ILVs depends on their ubiquitination. Ubiquitinated surface receptors and other proteins are thus "marked" to travel to lysosomes, whereas non-ubiquitinated cargo will generally recycle back to the plasma membrane [76]. Packaging of the ubiquitinated cargo into ILVs and the formation of the vesicles themselves is mediated by the endosomal sorting complex required for transport (ESCRT)-0, -I, -II, and -III complexes, all of which consist of multiple soluble subunits that have to be recruited from the cytosol to the endosome, and are collectively termed E class vacuolar protein sorting (Vps) proteins [77, 78]. The generation of the ILVs drives the formation of a MVB, which in essence is a late endosome [79]. The size of the ILV depends on the cargo and formation process [80].

Recognition of endocytosed ubiquitinated receptors starts with Hrs and its interacting partner signal transducing adaptor protein molecule (STAM), which together comprise ESCRT-0 [81]. Hrs and STAM are recruited to endosomes via interactions with the bilayered clathrin coat [64, 67, 82, 83]. Additionally, Hrs interacts directly with the ESCRT-I complex facilitating ESCRT-I recruitment to endosomes [84, 85]. Both ESCRT-I and ESCRT-II are heterotetrameric protein complexes [86]. Subunits from ESCRT-0, -I, and -II all recognize ubiquitinated cargo [87–89] and function as adaptors to recruit ESCRT-III, which then facilitates vesicle formation via recruitment of curvature-bending proteins [77, 79, 90, 91]. Mutations in several genes causative of HSPs have been linked to failure of the ESCRT machinery, revealing a role of altered endo/lysosomal trafficking in these motor neuron pathologies. For instance, a homozygous missense mutation in *SPG53*, encoding Vps37A, an ESCRT-I subunit correlates causally to HSP [92]. Although mRNA and protein levels of Vps37A did not show significant differences between unaffected and affected individuals, reduced motility in Zebrafish was observed upon Vps37A knockdown [92].

For MVB formation the dissociation of the ESCRT machinery and the bilayered clathrin coat is crucial and is mediated by the ATPase Vps4A/B [93, 94]. While ESCRT-III assembly stabilizes the membrane neck of a growing ILV, Vps4 binding to ESCRT-III subunits constricts the neck and facilitates its release from the membrane [95]. Interestingly, the most commonly mutated autosomal dominant HSP gene *SPG4*, encoding spastin, is linked to the ESCRT-III machinery [96]. Mutations in *SPG4* causative of HSP appear to lead to spastin loss-of-function, suggesting a haploinsufficiency rather than gain-of-function phenotype [97]. Spastin is an ATPase and interacts with the ESCRT-III accessory protein CHMP1B. Both spastin and CHMP1B share a microtubule binding domain and their co-expression results in a localization pattern reminiscent of microtubules [98]. Additionally, spastin also interacts with another ESCRT-III accessory protein, increased sodium tolerance 1 (Ist1). Interestingly, knockdown of spastin in human cells and Zebrafish spinal motor axons leads to extensive early endosomal tubulation due to defective fission of ILVs, and re-direction of recycling cargo towards late endosomes/lysosomes. Both cellular phenotypes are dependent on the lack of spastin interacting with the ESCRT-III machinery proteins CHMP1B and Ist1. These findings imply that altered early endosomal tubulation and/or disrupted early endosomal sorting of selective signalling receptors via the ESCRT machinery may, at least in part, be causative of axonal degeneration [99]. Finally, *SPG20*, which encodes spartin, is another HSP gene [100]. An interaction with Ist1 appears to localize spartin to early and late endosomes, whereas the ATPase activity of Vps4 is required to remove spartin from endosomes [101–103]. The HSP mutation of spartin results in a truncated form of the protein, possibly indicating a loss-of-

function phenotype [100]. Interestingly, cellular depletion of spartin slows down the rate of EGFR degradation implying a function in sorting or trafficking of degradative cargo through MVBs [101, 102].

Of the many candidate signalling pathways that could be disrupted by mutations in spastin or spartin is that stimulated by bone morphogenic protein. Both HSP disease genes are inhibitors of bone morphogenic protein signalling, and upregulation of this pathway causes axonal abnormalities in multiple model systems [99]. Thus, an emerging theme of this review is that disease genes that regulate endosomal trafficking can lead to altered localization or levels of specific signalling receptors when mutated. These changes will disrupt signalling cascades that are required for neuronal survival. In this way changes in a general cellular processes, endosomal trafficking can lead to dysfunction of selective neuronal populations based on specific receptor systems that are disrupted.

Step 4: exosome secretion

While MVBs for the most part fuse with lysosomes for cargo degradation, they can also fuse with the plasma membrane to release the ILVs to the extracellular space (Fig. 1). In such a scenario the MVBs are termed exosomes and the release of the ILVs is referred to as exosome secretion [104]. Exosomes contain a unique and diverse array of contents including lipids, cell adhesion proteins, intercellular signalling molecules, RNAs, antigens, viruses, prions, and β-amyloid peptides, amongst many others (a detailed description of multiple proteomic and RNA analyses of exosomes is provided by the ExoCarta protein database [105]). Although precise mechanisms remain poorly understood, a diverse range of functions have been ascribed to exosomes, among which are immune-regulatory processes, spreading of viruses and prions, facilitation of communication between tumorigenic cells and their environment, and the pathogenesis of neurodegenerative disorders [104].

Recent studies highlight the importance of exosomes in neurodegenerative disease. *ATP13A/PARK9* harbors multiple loss-of-function mutations causative of Kufor–Rakeb syndrome (KRS), which is characterized by juvenile-onset Parkinsonism with pyramidal degeneration and dementia [106]. The product of the *ATP13A2/PARK9* gene is ATP13A2, a P-type ATPase transporter that transports inorganic cations. ATP13A2 is found at MVBs and promotes the secretion of ILVs containing α-synuclein [107]. Tsunemi et al. [108] demonstrated that KRS patient fibroblasts with loss of ATP13A2 function have less ILVs in MVBs, emphasizing a role for ATP13A2 at MVBs. Interestingly, these fibroblasts also have reduced levels of

ILVs released into the culture media, while ATP13A2 overexpression in both a human cell line and primary mouse cortical neurons increased levels of exosome fusion and ILV release. Furthermore, the amount of α-synuclein secreted by exosomes was dependent on ATP13A2 protein levels [108]. Together, these findings suggest that KRS pathology, in part, may depend on augmented intracellular accumulation of α-synuclein, believed to be toxic for the cell, due to the lack of functional ATP13A2 resulting in diminished exosomal secretion from MVBs [108]. However, ATP13A2 also localizes to lysosomes and autophagosomes, which will be discussed in Step 6 where its dysfunction has been described to contribute to lysosomal deficiency causative of PD.

Step 5: retrograde trafficking to the TGN

While many proteins that reach endosomes are targeted for recycling to the plasma membrane or for degradation in lysosomes, others are transported from early endosomes to the TGN, a process termed retrograde trafficking (Fig. 1). This type of trafficking from endosomes to the biosynthetic/secretory system is mediated by a membrane sculpting/protein-sorting complex called retromer [109]. The retromer is a heteropentameric coat-like protein complex, comprised of a sorting nexin (SNX) dimer that binds to PtdIns(3)P patches on the endosomal membrane and drives membrane curvature, and a cargo-recognition Vps26/Vps29/Vps35 trimer, which sorts cargo into membrane tubules for delivery to the TGN [110]. One well-studied cargo for retromer-derived carriers is the mannose-6-phosphate receptor (MPR). Newly synthesized lysosomal hydrolases are tagged in the lumen of the Golgi with a mannose-6-phosphate tag. This allows the hydrolases to interact with the MPR, which then packages them into CCVs at the TGN for delivery to endosomes [110]. Once at endosomes, the acidic luminal pH causes the hydrolases to dissociate and to mature into lysosomes, while the MPR returns to the TGN via retromer-mediated retrograde trafficking for additional rounds of hydrolase sorting [111]. In addition to recognizing cargo, the retromer also recruits a multi-protein complex termed the WASH complex to endosomal membranes. The WASH complex activates Arp2/3 leading to actin nucleation and the formation of branched actin filaments, which facilitates endosomal membrane dynamics required for budding and fission of retromer vesicles [112, 113]. Recruitment of the WASH complex is facilitated by its association with the Vps35 subunit of the retromer [114]. Intriguingly, mutations in Vps35 have been discovered as causative of autosomal-dominant, late-onset PD [115, 116]. The best-characterized mutation, Vps35D620N still interacts with Vps26 and

Vps29 to form the cargo-sorting sub-complex of retromer, but the mutation disturbs the recruitment of the WASH complex, and there is dysfunctional retrograde trafficking, accumulation of α-synuclein in endosomes, and impaired lysosomal and autophagy function [117–121]. Moreover, in vivo expression of Vps35D620N in rodent substantia nigra neurons or *Drosophila* dopaminergic neurons induces dopaminergic degeneration accompanied by motor defects resembling the pathophysiology of PD [117, 122, 123]. A similar array of defects is observed upon abolishment of retromer/WASH complexes, hence it is conceivable that all of the Vps35D620N-induced defects can be contributed at least partially to loss of the retromer/WASH complex.

Further evidence of the relationship between retromer/WASH-mediated retrograde trafficking and PD comes with the observation that an autosomal-dominant mutation in RME-8 is causative of PD [124]. RME-8 is a DNAJ domain-containing protein, shown to interact with both SNX of the retromer complex and FAM21 of the WASH complex and to regulate retromer/WASH complex function in the formation of retromer-derived vesicles [125–128]. RME-8 interacts with heat shock cognate 70, which drives uncoating of CCVs and RME-8 regulates clathrin-coats on endosomes [126]. Although to date the physiological effect of the RME-8 PD mutation remains unclear, dysfunctional retromer clearly contributes to PD pathology.

Intriguingly, retromer malfunction has also been linked to HSPs as mutations in a highly conserved region of *SPG8*, encoding strumpellin, have been found to be causative of HSP [129]. Strumpellin is a component of the WASH complex but the effect of the HSP-mutants in strumpellin remain elusive since the mutant protein still incorporates into the WASH complex at endosomes and there does not appear to be any influence on endosomal tubulation [130]. Future research will be needed to examine the functional influence of the mutations in strumpellin and to explain why the exceptionally long axonal nature of corticospinal neurons, which depend on proper membrane trafficking, render them susceptible to degeneration resulting in HSP pathology.

Once retromer-derived vesicles arrive at the TGN they need to dock and fuse to deliver their cargo. This process is facilitated by a heterotetrameric tethering complex termed the Golgi-associated retrograde protein (GARP) complex [131]. The physiological requirement of the GARP complex became clear when a spontaneous mutation in one of its subunits, Vps54, was shown to be causative of progressive motor neurodegeneration in the wobbler mouse. The mutation reduces Vps54 levels and thereby the stability and levels of the GARP complex. Of interest is that the wobbler mouse phenotypes closely resemble early-onset ALS, providing an animal model for sporadic ALS [132, 133]. Loss of Vps54 was further shown to inhibit

MPR retrograde trafficking leading to trapping of MPR in endosomes, with endosome swelling [134, 135]. While relatively recent genome studies find that alteration of *Vps54* does not appear to be a common cause of ALS, the wobbler mouse model may still provide insight into the importance of retrograde trafficking and selective vulnerability of motor neuron axons that rely heavily on membrane trafficking to innervate their distal skeletal muscle partners and to respond to survival signals that come from the muscle and undergo retrograde transport [131, 136, 137].

Another gene that functions in membrane trafficking in the endosomal system/TGN and has been linked to PD is *Rab7L1* [138]. The protein product of the gene, Rab7L1 (also called Rab29) localizes to the TGN where it appears crucial for TGN integrity and retrograde trafficking from endosomes to the TGN [139, 140]. Interestingly, using protein–protein interaction arrays, Rab7L1 was found to associate with LRRK2 [140]. In primary neurons, depletion of Rab7L1 mimics phenotypes of lysosomal dysfunction seen with expression of LRRK2-G2019S, while Rab7L1 overexpression rescued the LRRK2-G2019S-induced phenotypes [140, 141]. It is likely that these phenotypes involve the retromer, in particular, expression of the PD-associated retromer protein Vps35 abolishes alterations in MPR trafficking seen with Rab7L1 depletion/LRRK2-G2019S overexpression, thus placing LRRK2/Rab7L1/Vps35 in a common (retrograde) endosomal/TGN/lysosomal trafficking pathway. Malfunction of this network causes lysosomal storage diseases that exhibit severe and progressive neurological dysfunction [11, 142]. The fact that Rab7L1 function is linked to two other PD genes in the endo/lysosomal system, stresses once again the crucial role of this pathway in neurodegeneration.

All of the studies described in this section clearly indicate that alteration in retromer function is a common cell biological locus in neurodegenerative diseases. While the reasons for this are not entirely clear it is likely related to altered lysosomal function. Disruption of retomer-mediated trafficking will leave the MPR stranded in endosomes and thus it will be unavailable to bind to newly synthesized lysosomal hydrolases in the lumen of the TGN. Therefore, lysosomes will fail to acquire their full complement of hydrolases and to properly degrade proteins, lipids and other macromolecules. This can have several consequences relevant to neurodegenerative disease. First, it can lead to the accumulation of misfolded/toxic forms of specific proteins. For example, the accumulation of misfolded α-synuclein following lysosomal dysfunction is toxic for neurons. Second, lysosomal degradation of macromolecules generates cellular nutrients that are critical for cell growth and function, and a lack of these products could hamper cell survival. Third, lysosomes signal their nutrient

state using a lumen-to-cytoplasm signalling pathway and alterations in this pathway can trigger apoptosis. Fourth, functional lysosomes are required for the degradation of autophagsomes and thus altered lysosomal function will disrupt autophagy. Autophagy (see step 7 below) is critical for turnover of misfolded proteins and non-functional organelles such as mitochondria, which would thus accumulate. It is likely that neurons, given their large size, long lives and high metabolic demands will be especially sensitive to lysosomal disruption.

Finally, a pathogenic G_4C_2 hexanucleotide repeat expansion in *C9ORF72*, suggested to reduce C9ORF72 protein levels, was recently identified as the major genetic abnormality in both sporadic and familial ALS [143–146]. A bioinformatics study found that C9ORF72 contains a differentially expressed in normal and neoplastic cells (DENN) domain [147]. The DENN domain is an enzymatic module that functions as a GEF for Rab GTPases and thus DENN domain-containing proteins have emerged as a large and diverse family of Rab regulators in membrane trafficking [148, 149]. Interestingly, in motor neurons C9ORF72 co-localizes with Rab7 and Rab11 at endosomes and C9ORF72 depletion inhibits the transport of endocytosed Shiga toxin through the endosomal system [150]. It is thus likely that C9ORF72 functions as an activator for a specific Rab in endosomal trafficking. Alterations in this pathway could lead to altered proteostasis or disruption in localization of specific cargo molecules important for motor neuron survival.

Step 6: lysosomes

Even as cargo is transported out of the early endosome, the endosomal membrane is maturing into MVBs/late endosomes [73]. Eventually late endosomes fuse with lysosomes for degradation of their lipid and protein content (Fig. 1). ATP13A2 localizes to late endosomes and lysosomes, where its loss-of-function has been linked to lysosomal deficiency causative of PD [151–154]. Moreover, expression of PD-causing LRRK2 mutations, which lead to a decrease in lysosomal capacity, alter the levels of ATP13A2 [75]. A range of lysosomal defects associated with cell death have been reported for ATP13A2 deficiency in patient-derived fibroblasts and cell lines; instability of the lysosomal membrane, hampered lysosomal acidification, and a reduction in lysosomal enzyme proteolytic processing leading to an accumulation of non-degraded macromolecules in the lysosome (including α-synuclein) [153–155]. The substrates of the ATP13A2 transporter remain uncertain but it has been speculated that lysosomal dysfunction upon ATP13A2 deficiency or mutation could result from alterations in the transport of metal ions leading

to an imbalance between the lumen of the lysosome and the cytosol [107, 156]. It has also been hypothesized that ATP13A2 functions as a late endosomal/lysosomal lipid flippase [157]. As such, ATP13A2 flippase loss-of-function could account for all of the phenotypes observed in ATP13A2 deficient cells through control of membrane curvature and its stability, lipid dynamics to organize microdomains required for interaction with coat and accessory proteins that regulate vesicular processes like exosome formation from MVBs, and fusion of late endosomes with lysosomes [157].

Recently, a novel adaptor protein complex (AP-5) was identified that localizes to late endosomes/lysosomes [158]. Relatively little is known about AP-5 function, but it is assumed to play a role in cargo sorting and vesicular membrane trafficking by forming a coat structure independent of clathrin. Interestingly, the AP-5 ζ subunit (aka KIAA0415) is encoded by *SPG48*, mutations in which have been causally linked to autosomal recessive HSP [158, 159]. Originally, KIAA0415/AP-5 ζ was identified by Slabicki et al. [159] in a screen for DNA repair genes and thought to be a putative helicase. However, the DNA repair phenotype could be indirect as it lacks the required helicase enzymatic motifs but instead has high homology to AP large subunits [158]. Hirst et al. [158] subsequently demonstrated that AP-5 depletion leads to the accumulation of swollen MVBs with MPR clustering in early endosomes. Importantly, KIAA0415/AP-5 ζ interacts with two more HSP proteins, spatacsin and spastizin/ZFYVE26, encoded by *SPG11* and *SPG15*, respectively, which are suggested to be AP-5 binding accessory proteins [158–162]. All three proteins co-localize to late endosomes/lysosomes, and depletion of spatacsin or spastizin phenocopies AP-5 knockdown. Interestingly spatacsin and spastizin have predicted secondary structures containing α-solenoids and a β-propeller domain (spatacsin) similar to that of CHC, suggesting that AP-5/spastizin/spatacsin form a coat complex with spastizin facilitating docking to PtdIns(3)P membrane patches, spatacsin forming a clathrin-like scaffold, and AP-5 regulating protein sorting [160]. In agreement with endo/lysosomal trafficking defects contributing to HSP pathophysiology, spastizin knockout mice show age-dependent accumulation of non-degraded lysosomal material, increased levels of lysosomal enzymes in the brain, and progressive motor neuron loss resulting in late-onset spastic paraplegia [163]. Moreover, *SPG11* and *SPG15* patient fibroblasts show enlarged lysosomes with abnormal lysosomal storage in the SPG15 patient cells [164]. Thus, future research should focus on AP-5 function to identify further players in endo/lysosomal malfunction contributing to HSP pathophysiology.

Glucocerebrosidase (GBA) is a lysosomal enzyme responsible for the conversion of the glycolipid glucosyl-ceramide into glucose and ceramide. *GBA* loss-of-function mutations are causative of Gaucher disease with parkinsonism, the most common lysosomal storage disease [165]. Moreover, *GBA* mutations have since been ascribed as a risk factor for PD [166–168]. In dopaminergic neurons, derived from GBA-mutant patient human induced pluripotent stem cells, α-synuclein degradation is hampered leading to augmented intracellular accumulation and aggregation of α-synuclein with corresponding neurotoxicity [169]. Furthermore, aggregated α-synuclein inhibits the lysosomal activity of GBA in both neurons and idiopathic PD brains in turn implying that reduction of functional GBA may contribute to the pathogenesis of sporadic synucleinopaties also observed in PD. In contrast, it is also reported that GBA-mutants overexpressed in cultured cell lines show no change in GBA activity but still generated α-synuclein accumulation that are cleared upon induction of autophagy, or enhanced GBA translocation into lysosomes [170]. Hence, lysosomal disruption both by GBA gain-of-function and loss-of-function drives pathogenic α-synuclein accumulation, which may contribute to PD pathology.

As described in step 5, alterations in lysosomal function are clearly linked to neuronal death. Neuronal death can result from a range of problems including accumulation of misfolded proteins that are toxic to cells, loss of critical metabolic nutrients and altered survival signalling. But why are neurons, and even selective populations of neurons vulnerable when these basic cellular insults are occurring in all cells? The answer to this question remains speculative but there are clearly specific aspects of neuronal cell biology, namely their large size and the fact they are postmitotic and as old as the organism they inhabit, that makes them vulnerable. This phenomena is exemplified by lysosomal storage diseases, which are rare inborn errors of metabolism. There are as many as 50 distinct lysosomal storage diseases resulting from problems ranging from gross abnormalities in generalized sorting of lysosomal hydrolases to lysosomes to loss of enzymatic activity of a specific lysosomal hydrolase. As such, each lysosomal storage disease displays a range of symptoms and affected cells and tissues, but essentially all such diseases feature sever and progressive neurological disorders [142]. Clearly neurons are particularly sensitive to lysosomal dysfunction.

Mutations in *PARK6* and *PARK2*, encoding the mitochondrial kinase PINK1 and cytosolic ubiquitin ligase parkin, respectively, have been shown to be causative of recessive juvenile PD [171, 172]. Recently, a novel PINK1/parkin-dependent pathway between mitochondria and lysosomal degradation has been discovered [173]. In a parkin- and PINK1-dependent manner, small mitochondria-derived vesicles (MDVs) bud off mitochondria upon oxidative damage to carry selected mitochondrial cargo to the lysosome for degradation [174]. Of interest is that compared to wild type, overexpression of various known parkin PD-mutants impedes the formation of MDVs [174]. Hence, the authors hypothesize that this mitophagy-independent pathway of MDVs regulates mitochondrial quality control, and if impaired, accumulation of non-degraded, oxidized proteins damages mitochondria, which eventually contribute to PD pathophysiology.

Step 7: autophagy

Cytoplasm containing aggregated or misfolded proteins and entire organelles can be engulfed by a double membrane structure, termed the phagophore, which expands and then closes upon itself to form an organelle called the autophagosome (Fig. 1). Consequently, the autophagosome fuses with the lysosome where its cytosolic contents are degraded by lysosomal hydrolases, after which nutrients are released back to the cytosol to be recycled. This process is termed macroautophagy, and will hereafter be referred to as autophagy. Additionally, autophagosomes can fuse with endosomes that will mature into lysosomes to degrade their content. Several cellular structures are engulfed and selectively degraded via autophagy; pathogens (termed xenophagy), ubiquitinated damaged mitochondria (mitophagy), and misfolded aggregated proteins (aggrephagy) [175]. Cellular stresses such as starvation, damaged organelles or pathogens induce autophagy to provide the cell with nutrients to survive the stress emergency [176, 177].

Atg (autophagy related) proteins that are recruited to the phagophore membrane control autophagosome formation. Selective degradation of ubiquitinated cargo is facilitated by autophagy receptors/adaptors that interact both with Atg proteins on the phagopore and cytosolic ubiquitinated cargo, thereby fulfilling a bridging function and enabling cargo to incorporate into autophagosomes. A crucial autophagy receptor is p62, which simultaneously binds ubiquitinated cargo and the microtubule-associated protein LC3 on autophagosomes allowing for cargo incorporation into the autophagosome [178].

Similar in function to p62 is optineurin, encoded by the *OPTN* gene and functioning as a receptor in autophagy. Several *OPTN* mutations are causative of familial ALS as well as a neurodegenerative eye disorder called primary open angle glaucoma [179, 180]. Optineurin operates in various cellular processes including membrane trafficking, maintenance of the Golgi apparatus, and autophagy [175]. Optineurin has numerous interacting partners including LC3 and the myosin VI motor protein, required for actin-based motility of autophagosomes towards lysosomes

[181], and autophagy is inhibited upon depletion of optineurin [182]. Recently, it was demonstrated that myosin VI binding is abolished in two *OPTN* mutations (within the myosin VI binding domain) causative of ALS [183]. Furthermore, different ALS-linked mutations in the ubiquitin-binding domain (UbBD) of *OPTN* cause reduced binding to myosin VI [184]. Overexpression of the optineurin UbBD mutants sequestered wild type optineurin into cytoplasmic inclusions, hence hampering the maturation of autophagosomes and clearance of these inclusions [184]. Additionally, expression of ALS-mutant optineurin blocked autophagosome fusion with lysosomes and triggered an endoplasmic reticulum stress response accompanied by fragmentation of the Golgi [183]. Mutant otineurin protein is found in ubiquitin-rich intracytoplasmic inclusions in the lumbar spinal cord from patients with ALS resulting from optineurin mutations, while wild-type optineurin is found in motor neuron ubiquitin-positive inclusions of patients with sporadic ALS [179, 185]. Moreover, optineurin-rich inclusions, loss of its binding to myosin VI, and reduced optineurin-positive vesicles were observed in lumbar spinal cord motor neurons of sporadic ALS patients [183]. Together these results suggest that optineurin/myosin VI function is crucial for autophagy, at least in motor neurons affected in ALS, and that their dysregulation presents pathological phenotypes in both familial and sporadic ALS. Intriguingly, optineurin has also been connected to PD, since it was found to be recruited to mitochondria by PINK1 as the primary autophagy receptor for mitophagy [186]. Future research will have to focus on PINK1 PD-mutants and optineurin recruitment to mitochondria for the induction of mitophagy in order to examine the extent of PD-related autophagy phenotypes that may contribute to PD pathology.

Conclusions

Extensive research has shown that neurodegenerative disorders alter functional and structural connectivity in the brain [187]. The underlying molecular mechanisms remain poorly understood, yet dysfunction in endocytic membrane trafficking is a recurrent theme, which may explain the neurodegenerative process. The unique morphology of neurons, consisting of long processes extending far beyond the cell soma, exerts high demands on accurate and coordinated delivery of proteins and lipids to their final destination. More specialized domains, such as proximal and distal dendrites, axonal growth cones, and synapses all rely heavily on tightly controlled membrane trafficking from the biosynthetic and endosomal compartments. As described in this review, functional alterations in many membrane trafficking proteins perturbs precise endosomal

trafficking, which may extend to dysfunctions in downstream membrane trafficking, and an accumulation of dysfunctional proteins and organelles, followed by neuronal vulnerability and eventual cell death. Similarly, accumulation of damaged mitochondria due to failed mitophagy may cause cellular energy imbalance and thereby contribute to neuronal vulnerability and potential cell demise. Unraveling the physiological functions of endosomal proteins may further help understand the pathophysiological changes occurring in neurodegeneration and assist in designing targeted novel therapeutics.

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