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Symposium

The Endolysosomal System and Proteostasis: From Development to Degeneration

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How do neurons adapt their endolysosomal system to address the particular challenge of membrane transport across their elaborate cellular landscape and to maintain proteostasis for the lifetime of the organism? Here we review recent findings that address this central question. We discuss the cellular and molecular mechanisms of endolysosomal trafficking and the autophagy pathway in neurons, as well as their role in neuronal development and degeneration. These studies highlight the importance of understanding the basic cell biology of endolysosomal trafficking and autophagy and their roles in the maintenance of proteostasis within the context of neurons, which will be critical for developing effective therapies for various neurodevelopmental and neurodegenerative disorders.

Key words: endosomes; membrane trafficking; polarity; neurons; autophagy; lysosome

Introduction

Neurons are extremely large cells with a long axon and multiple dendrites extending over centimeters or more. This large size creates significant challenges for regulating transport of membrane components, both from the biosynthetic pathway to deliver membrane proteins to their correct locations, as well as for removing membrane proteins from the surface and transporting them to new sites or to degrade them. In addition, neurons are extremely active, firing action potentials at rates up to ~50–100 impulses per second (Harris and Attwell, 2012), and they must sustain this activity for nearly a century! Consequently, the neuronal proteome is vulnerable to damage. The proteome susceptibility to damage is compounded by the longer half-life of neuronal proteins, in particular the synaptic proteome, compared with other tissues and cellular compartments (Price et al., 2010; Heo et al., 2018). To support their long-term viability and functionality, neurons require robust intracellular trafficking machinery and quality control mechanisms (Cajigas et al., 2010;

Yap and Winckler, 2015; Y. C. Wang et al., 2017), which need to be adapted specifically to accommodate their morphological complexity and longevity.

The endolysosomal system is comprised of a series of membranous organelles specialized for regulating both intracellular trafficking and proteostasis. While decades of research in non-neuronal cells have revealed important regulatory mechanisms for endolysosomal trafficking, recent studies have begun to unveil remarkably complex and spatially compartmentalized mechanisms regulating trafficking and proteostasis in neurons (Morgan et al., 2013; Terenzio et al., 2017; Jin et al., 2018a; Kiral et al., 2018). In the following sections, we will review recent advances in understanding such mechanisms, and their role in neuronal development and degeneration. In addition, we will discuss the regulation of neuronal proteostasis by the autophagy pathway, which intersects with the endolysosomal system to facilitate the elimination of damaged membrane and cytosolic proteins, protein aggregates, and membranous organelles. This review accompanies a minisymposium at the 2018 Society for Neuroscience Annual Meeting with the same title.

The endolysosomal system in neuronal development and homeostasis

The endolysosomal system has been well studied in non-neuronal cells and broadly classified into several subclasses, including the EE (early endosome), RE (recycling endosome), LE (late endosome), and lys (lysosome). The EE is the major sorting station for endocytosed receptors. Recycling cargos can return to the surface from the EE or from the RE. Degradative cargos fail to enter recycling pathways in the EE and are progressively sorted into intraluminal vesicles starting in the EE. The EE matures to a

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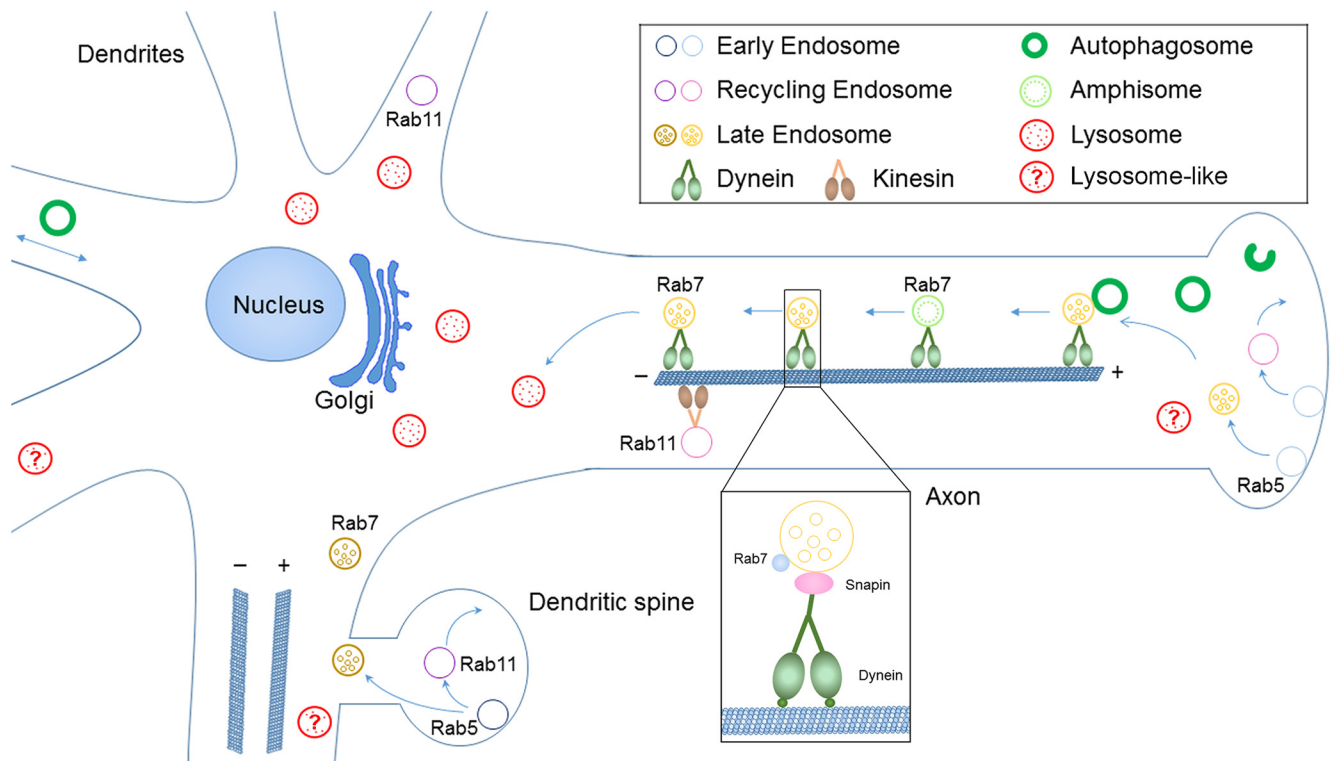


Figure 1. Schematic of endolysosomal trafficking and autophagy in neurons. Distinct endosomal subclasses are associated with particular sets of Rab GTPases. Early endosomes are Rab5-positive, late endosomes are Rab7-positive, and recycling endosomes are Rab11-positive. Endosomal trafficking is differentially regulated in dendrites versus axons of neurons. Mature lysosomes with high degradative capacity are located primarily in the soma or proximal neurites. Immature lysosome-like organelles are found in distal dendrites and axons. Axonal autophagosomes initiate largely in distal regions of the axon and gain retrograde motility through fusion with late endosomes to form amphisomes and coupling with dynein motors. In contrast, dendritic autophagosomes undergo bidirectional motility or oscillate within a confined region along the dendritic shaft.

LE by the timed exchange of specific effectors, proteins that associate with the cytosolic leaflet of the endosome membrane, such as Rab7. LEs contain many intraluminal vesicles and are often categorized by EM as “multivesicular bodies.” LEs undergo homotypic fusions with each other as well as fuse with lysosomes for cargo degradation; and in some cases, they fuse with the plasma membrane. From work done primarily in yeast and nonpolarized cells over many years, an impressive regulatory network of proteins is now known to participate in the sorting decision toward degradation. These include the Rab family of small GTPases. Distinct endosomal subclasses are associated with particular sets of Rabs, such as Rab5 for the EE and Rab7 for the LE. Indeed, one of the critical events for conversion of EEs to LEs is that Rab5 is replaced by Rab7. This allows the recruitment of a new set of effectors to the endosomal membrane, which will change the fate of the endosome (Naslavsky and Caplan, 2018).

Compared with endocytic organelles in fibroblasts and other nonpolarized cells, neuronal endolysosomes show a high level of spatial compartmentalization (Fig. 1). During brain development, neurons become highly polarized through extending dendrites and axons, and establishing synaptic connections with distant targets. This raises the intriguing question as to how neurons regulate the transport and degradation of proteins across these subdomains and microcompartments. Studies from different laboratories now support the idea that mature lysosomes with high degradative capacity are located primarily in the soma or proximal neurites (Cai et al., 2010; Lee et al., 2011; Gowrishankar et al., 2015; Maday and Holzbaaur, 2016; Tammineni et al., 2017b; Cheng et al., 2018; Yap et al., 2018). Remarkably, there is a strik-

ing spatial gradient of endosomal compartments in dendrites, with late endosomes (Rab7-positive/LAMP1-negative/cathepsinB-negative) found throughout dendrites, including distal portions, whereas degradative lysosomes (LAMP1-positive/cathepsinB-positive) are found in the soma and in the proximal portions of dendrites, but not distally. Surprisingly, the majority of dendritic Rab7-positive late endosomes do not contain LAMP1, unlike Rab7-positive late endosomes in fibroblasts (Yap et al., 2018). These results thus demonstrate that the “somatodendritic domain” is not homogeneous but contains distinct regions with functionally and molecularly distinct organelles. Most strikingly, degradative lysosomes are scarce in dendritic regions $>25 \mu\text{m}$ away from the soma. Finally, overexpression of a dominant-negative Rab7 demonstrates that Rab7 activity is required to mobilize distal predegradative dendritic late endosomes for transport to the soma and degradation (Yap et al., 2018). Because the vast majority of dendritic LAMP1-positive endosomes are not degradative lysosomes, bulk degradation of short-lived dendritic membrane cargos requires Rab7-dependent transport in late endosomes to somatic lysosomes.

A similar observation of LAMP1-containing organelles deficient in lysosomal proteases was made by Zu-Hang Sheng’s group in distal axons of mammalian DRG and cortical neurons (Cheng et al., 2018). These findings clearly suggest that distal and proximal compartments in both axons and dendrites are distinct. The current data favor a model by which compartments mature toward late endosomal and lysosomal fates in both axons and dendrites, as they are transported toward the soma, and that they progressively acidify and gain lysosomal hydrolases as they approach the soma (Ferguson, 2018). This has been shown nicely in

axons by several groups, including Ralph Nixon's group (Lee et al., 2011) and Shawn Ferguson's group (Gowrishankar et al., 2017). There are also intriguing data that transport and maturation of predegradative lysosomes in axons are impaired in Alzheimer's disease (AD) and could account for increased β -site APP cleaving enzyme 1 (BACE1)-dependent cleavage of amyloid precursor protein (APP) to the toxic β -amyloid ($A\beta$) (Gowrishankar et al., 2015). Finally, Juan Bonifacino's group reported differential acidity for LAMP1-containing organelles in proximal versus distal axons, which further supports the idea that LAMP1-containing organelles in distal axons do not have high degradative capacity (Farias et al., 2017), and might thus be more accurately categorized as "lysosome-like" or "predegradative" immature lysosomes, similarly to the distinction made by Gowrishankar et al. (2015) for axonal "lysosome-like organelles."

Interestingly, live imaging studies in the *Drosophila* brain reveal two parallel pathways for degrading membrane proteins locally in axonal terminals: a Rab7-dependent pathway for plasma membrane proteins, and a Rab7-independent pathway for degrading synaptic proteins (Jin et al., 2018b), suggesting that some degradative substrates can be degraded distally in axons in distinct organelles. In addition, a cathepsin was identified in distal axons in this study. Along the same lines, degradative lysosomes might also be found near synapses in dendrites, albeit infrequently, and could perform activity-dependent degradation near synapses (Goo et al., 2017). Whether these rare synapse-near lysosomes are specialized to degrade a subset of cargos (such as glutamate receptors) is not known but would be consistent with our recent finding that bulk degradation requires retrograde transport to the soma where degradative lysosomes are abundant (Yap et al., 2018). Another study reports activity-dependent exocytosis of CathepsinB from lysosomes in spines, a very intriguing novel mechanism of how spine growth is promoted by activity (Padamsey et al., 2017). These findings highlight the complexities in the composition of endolysosomal compartments, raise the possibility that dendritic and axonal endolysosomes differ, and suggest that the field needs to develop additional tools and clarify the nomenclature to distinguish related, but functionally distinct compartments.

In addition to its importance in regulating bulk degradation, Rab7 has also been shown to be important in regulating the levels of receptors important during development, such as N-cadherin during neuronal migration in corticogenesis (Kawauchi et al., 2010), TrkA trafficking during development of the peripheral nervous system (Ye et al., 2018), and synaptic function (Fernández-Monreal et al., 2012; T. Kim et al., 2017). Moreover, work in *Drosophila* shows a particular early sensitivity of neurons specifically to loss of Rab7 (Cherry et al., 2013). The regulated maturation of endosomal compartments is thus critical for regulating the levels of many membrane receptors critical to neuronal development, synaptogenesis and nervous system function.

Endolysosomal trafficking in neurodegeneration

Given the particular challenges neurons face in regulating intracellular trafficking and proteostasis, it is not surprising that defects in intracellular trafficking have been implicated in the pathogenesis of major neurodegenerative diseases. Below we discuss recent findings on the mechanisms of endolysosomal trafficking in neurodegeneration, using AD, Menkes disease, and Parkinson's diseases as examples.

Endocytic trafficking, Menkes disease, and Parkinson's disease

Normal and disease mechanisms can be inferred from interactomes, comprehensive maps of the temporal, spatial, and/or genetic interactions established by wild-type and mutant versions of a gene or its products (Barabási and Oltvai, 2004; Vidal et al., 2011; Ghiassian et al., 2015). Here we discuss insights from the interactomes of the copper transporter ATP7A and the endosome localized Vacuolar Protein Sorting 35 (VPS35), a subunit of the retromer sorting complex. Mutations in these genes cause severe neurodegenerative disorders, Menkes disease and Parkinson's disease, respectively (OMIM 309400 and 300011 for ATP7A, OMIM 601501 and 614203 for VPS35). These diseases are conceptualized as distinct entities. However, commonalities in their interactomes suggest that their pathogeneses may have more in common than we currently suspect.

Loss-of-function mutations in ATP7A causes Menkes disease (OMIM 309400), a widespread neurodegeneration of forebrain neurons usually lethal in early life. (Menkes et al., 1962; Menkes, 1988, 1999; Lutsenko et al., 2007; Kaler, 2011; Zlatić et al., 2015). ATP7A mutations produce disease by preventing protein expression, impairing copper transport into the Golgi lumen, and/or by halting ATP7A at different subcellular compartments along the exocytic and endocytic route (Vulpe et al., 1993; Petris and Mercer, 1999; B. E. Kim et al., 2003; Tümer, 2013; Yi and Kaler, 2015). This later observation suggests that genetic defects in sorting complexes necessary for ATP7A traffic should in part phenocopy ATP7A genetic defects.

ATP7A localizes to the Golgi apparatus at steady state and cycles between the cell surface and the Golgi complex via endosomes (Lutsenko et al., 2007; Kaler, 2011). This trafficking cycle requires multiple cytosolic sorting complexes, among them the retromer complex (Setty et al., 2008; Ryder et al., 2013; Steinberg et al., 2013; Gokhale et al., 2015; Phillips-Krawczak et al., 2015; Yi and Kaler, 2015; Comstra et al., 2017). The retromer complex is of interest to neurodegeneration mechanisms because mutations in several of its subunits (VPS35, VPS29, and VPS26A) cause Parkinson's disease in humans (Kumar et al., 2012; McMillan et al., 2017). The mechanism by which retromer complex mutations cause Parkinson's disease is intimately tied to the membrane protein cargos whose subcellular localization depends on the activity of the retromer complex. These cargos include, but are not limited to, the mannose-6-phosphate receptor (IGFR2), ATG9A, LAMP2a (LAMP2), and synaptic neurotransmitter receptors (Seaman, 2004; Steinberg et al., 2013; McMillan et al., 2017). Retromer-dependent defects in the sorting of these cargos impair autophagy and chaperone-mediated-autophagy (Kaushik and Cuervo, 2012) and decrease the content of hydrolases in the lysosome lumen (Seaman, 2004; Kaushik and Cuervo, 2012; McMillan et al., 2017). These hydrolases are necessary for aggregate and damaged organelle disposal via autophagy pathways. Although ATP7A is a retromer cargo, ATP7A has not been considered as a contributor to Parkinson's pathogenesis (Ryder et al., 2013; Steinberg et al., 2013; Phillips-Krawczak et al., 2015; Small and Petsko, 2015; S. Wang and Bellen, 2015; Comstra et al., 2017; McMillan et al., 2017; Zhang et al., 2018).

Why should we care about the intersection between ATP7A, sorting complexes, and Parkinson's disease pathways? Alterations of copper content and copper buffering mechanisms are a common occurrence in sporadic cases of Parkinson's disease (Gaggelli et al., 2006; Davies et al., 2014; Lan et al., 2016). This is an important observation because copper induces α synuclein protein aggregation, protein and organelle oxidative damage, and

perturbs mitochondrial function (Paik et al., 1999; Rasia et al., 2005; Zischka et al., 2011; Aboud et al., 2015). Genetic evidence also supports a connection between copper and Parkinson's disease. ATP7A genetically interacts with the Parkinson's and spastic paraplegia associated gene UCHL1, which encodes a deubiquitinating enzyme (Leroy et al., 1998; Bilguvar et al., 2013; Zlatić et al., 2018). The mitochondrion could be an organelle where defective ATP7A and retromer function could converge to cause or modulate neurodegeneration. This idea is supported by the observation that retromer function is required to maintain mitochondria morphology and function (Tang et al., 2015; W. Wang et al., 2016). Mitochondrial fragmentation and depolarization mark organelles for autophagic destruction, a pathway controlled by the Parkinson's disease genes pink and parkin (PARK2) (Pickrell and Youle, 2015; Pickles et al., 2018). This pink-parkin (PARK2) pathway is likely involved in retromer-dependent mechanism as indicated by genetic interactions between *Drosophila* Vps35 and parkin (Malik et al., 2015). Thus, similar to VPS35, it is possible that parkin (PARK2)- and pink-dependent mitophagy mechanisms may also be part of the ATP7A interactome. This raises the interesting hypothesis that possible mechanistic links, at the level of mitochondrial function or mitochondrial quality control, between clinically dissimilar diseases, such as Parkinson's disease, Menkes disease, and AD, may be more widespread than we have so far envisioned (C. L. Wang et al., 2012; Ye et al., 2015).

Endolysosomal trafficking of APP and BACE1 and AD

AD is an age-dependent neurodegenerative disease that is the most common cause of dementia among the elderly. More than 90% of AD cases are of the late-onset and sporadic form, LOAD, the causes of which remain unclear. One key pathological feature of the AD brain is extracellular plaques containing A β , which is produced intracellularly through sequential cleavage of the APP by BACE1 and γ -secretase. The rate-limiting step for A β generation is the physical convergence between APP and BACE1 in endosomes (Koo and Squazzo, 1994; Zou et al., 2007; Cirrito et al., 2008; Sannerud et al., 2011; U. Das et al., 2013; Sun and Roy, 2018). Because both APP and BACE1 are membrane proteins that traffic through the endolysosomal system, understanding their trafficking patterns within the endosomal pathways is critical for elucidating the mechanisms of AD pathogenesis.

Remarkably, a number of LOAD risk variants identified through genetic screens are of genes encoding regulators of endocytic trafficking (Bertram et al., 2007; Rogaeva et al., 2007; Harold et al., 2009; Hollingworth et al., 2011; Naj et al., 2011), including *Bin1* and *CD2AP* (Guimas Almeida et al., 2018). Using a loss-of-function approach in primary mouse cortical neurons, it was recently reported that the regulation of trafficking of APP and BACE1 through early endosomes in axons is different from dendrites. APP endosomal sorting is dependent on CD2AP but only at dendritic endosomes, whereas BACE1 recycling is dependent on Bin1 predominantly in axonal endosomes. Bin1 and CD2AP localization was polarized, while CD2AP was enriched in dendritic endosomes, and Bin1 was in axonal endosomes (Ubelmann et al., 2017). This polarization translated into a preferential accumulation of A β 42 in dendrites when CD2AP was knocked down and in axons when Bin1 was knocked down. This differential regulation of APP processing in axons and dendrites had not been observed before. These studies shine a mechanistic spotlight on how neuronal cellular machinery could be causing AD cellular phenotypes.

Previous studies indicated that APP and BACE1 localize to both axons and dendrites with APP enriched in axons (Brunholz et al., 2012). APP and BACE1 endocytosis can occur from the axonal and dendritic plasma membrane (Simons et al., 1995; Yamazaki et al., 1996; Schneider et al., 2008; Sullivan et al., 2014; Niederst et al., 2015). APP proteolytic processing by BACE1 and γ -secretase can occur both in axons and in dendrites, being more prominent presynaptically (Buxbaum et al., 1998; Lyckman et al., 1998; Lazarov et al., 2002; Buggia-Prévoit et al., 2013; DeBoer et al., 2014; Niederst et al., 2015). The secretion of newly formed A β likely occurs more presynaptically, although it can also occur postsynaptically (Lazarov et al., 2002; Wei et al., 2010; DeBoer et al., 2014). Axonally secreted A β contributes locally to presynaptic dysfunction and to extracellular amyloid deposition, but can also trigger spine loss and postsynaptic glutamate receptors endocytosis (Wei et al., 2010). Thus, a polarized increase of A β production may eventually lead to an initial presynaptic or postsynaptic dysfunction preceding a more generalized neuronal dysfunction.

The polarized production and secretion of A β raise the intriguing possibility that proteins regulating cellular polarity are involved in this process. Indeed, recent studies have highlighted a role for the cell polarity regulator partitioning-defective 3 (Par3) in A β production through modulating both APP and BACE1 trafficking. Interestingly, the effects of Par3 on APP and BACE1 trafficking are through two distinct mechanisms. Par3 regulates APP trafficking through the endocytic adaptor protein Numb (Sun et al., 2016). By contrast, Par3 and its binding partner atypical PKC (aPKC) regulate BACE1 retrograde endosome-to-TGN trafficking through PACS1 (Sun and Zhang, 2017). In the absence of Par3, both APP and BACE1 are enriched in the late endocytic compartments, leading to increased intracellular A β accumulation (Sun et al., 2016; Sun and Zhang, 2017).

The endolysosomal trafficking of BACE1 is also differentially regulated in dendrites versus axons. Dendritic BACE1 undergoes unidirectional retrograde transport, which is regulated by the Eps-15-homology-domain-containing family proteins (Buggia-Prévoit et al., 2013). By contrast, axonal BACE1 undergoes bidirectional transport in dynamic tubulo-vesicular carriers (Buggia-Prévoit et al., 2014). Sorting of BACE1 to the axons is Rab11-dependent (Buggia-Prévoit et al., 2014), and axonal BACE1 is retrogradely transported by the dynein adaptor Snapin in Rab7-positive late endosomes to the cell body for degradation in mature lysosomes (Ye and Cai, 2014; Ye et al., 2017). Finally, visualization of APP and BACE1 convergence through fluorescence complementation also confirms that APP and BACE1 trafficking are differentially regulated in dendrites and axons (U. Das et al., 2016).

The autophagy-lysosome system in neuronal homeostasis and neurodegeneration

Protein and organelle homeostasis requires cooperation between the endolysosomal system and autophagy. Autophagy is a cellular quality control pathway that is essential for neuronal function and viability (Yamamoto and Yue, 2014; Ariosa and Klionsky, 2016; Kulkarni and Maday, 2018). In this process, proteins and organelles targeted for destruction are engulfed and sequestered by autophagosomes, and delivered to lysosomes for breakdown by resident proteases (Mizushima and Komatsu, 2011; Weidberg et al., 2011; Feng et al., 2014). Degradation products can then be recycled to fuel new biosynthetic reactions. Autophagic cargos in neurons can include synaptic proteins and vesicles (Rowland et al., 2006; Hernandez et al., 2012; Shehata et al., 2012; Binotti et al., 2015; Lüningschrör et al., 2017; Nikolettou et al., 2017; Ok-

erlund et al., 2017; Nikolettou and Tavernarakis, 2018), mitochondria (Cai et al., 2012; Maday et al., 2012; Ashrafi et al., 2014; Rangaraju et al., 2014; Wong and Holzbaur, 2014b; Xie et al., 2015; Ebrahimi-Fakhari et al., 2016), and pathogenic protein aggregates, such as cytoplasmic α -synuclein aggregates (Tanik et al., 2013), mutant huntingtin aggregates (Wong and Holzbaur, 2014a), and amyloid β peptides (Yu et al., 2005; Feng et al., 2017; Tammineni et al., 2017a). Thus, autophagy provides a constitutive mechanism to replenish cellular components, and also a dynamic response to cellular stress, such as nutrient deprivation, organelle damage, protein aggregation, and disease (Schneider and Cuervo, 2014).

Alterations in autophagy are associated with neurodevelopmental abnormalities and neurodegeneration (Tang et al., 2014; Dragich et al., 2016; Stavoe et al., 2016; Kulkarni and Maday, 2018; Li et al., 2018; Lieberman et al., 2018; Schöffner et al., 2018). Neuron-specific loss of autophagy is sufficient to induce neurodegeneration in mice (Hara et al., 2006; Komatsu et al., 2006; Komatsu et al., 2007; Nishiyama et al., 2007), and mutations in key autophagy genes lead to neurodegenerative disease in humans (Frake et al., 2015; M. Kim et al., 2016; Maday, 2016). Thus, evidence supports a neuroprotective role for autophagy in the nervous system. Our understanding of the mechanisms that regulate autophagy, particularly within each compartment of the neuron (e.g., axons vs dendrites vs the soma), however, are only beginning to be elucidated.

Autophagy in the axon follows a vectorial trajectory that delivers cargo from the distal axon to the soma. Axonal autophagosomes initiate largely in distal regions of the axon (Fig. 1) (Hollenbeck, 1993; Maday et al., 2012; Maday and Holzbaur, 2014; Cheng et al., 2015a; T. C. Wang et al., 2015; Soukup et al., 2016). Following formation, autophagosomes then undergo retrograde trafficking toward the soma, and this transport is coupled to their maturation into degradative compartments (Hollenbeck, 1993; Yue, 2007; Lee et al., 2011; Maday et al., 2012; Maday and Holzbaur, 2014; Cheng et al., 2015a; T. Wang et al., 2015; Tammineni et al., 2017a). Once in the soma, autophagosomes are confined within the somatodendritic domain (Maday and Holzbaur, 2016), which likely facilitates cargo degradation by promoting fusion with proteolytically active lysosomes that are enriched in this region (Lee et al., 2011; Gowrishankar et al., 2015; Xie et al., 2015; Tammineni et al., 2017b; Cheng et al., 2018; Yap et al., 2018). Thus, the soma contains multiple populations of autophagosomes at different maturation states, including axonally derived autophagosomes combined with those generated locally (Maday and Holzbaur, 2016). Inhibition of lysosome function results in accumulation of autophagosomes specifically within the soma and not in the axon (Maday and Holzbaur, 2016), indicating that the soma is the primary site of autophagosome deposition and cargo degradation. In contrast to the unidirectional motility exhibited by axonal autophagosomes, dendritic autophagosomes undergo bidirectional motility, or oscillate within a confined region along the dendritic shaft (Fig. 1) (Maday and Holzbaur, 2014). In total, emerging evidence reveals compartment-specific mechanisms for autophagosome trafficking that may facilitate a range of functions within the neuron, particularly at sites far from the soma (Maday, 2016; Kulkarni and Maday, 2018).

Retrograde transport of LEs/amphisomes is mediated by dynein motors. A number of studies proposed that the RILP-Rab7-ORP1L complex regulates dynein-driven retrograde transport of autophagosomes and endolysosomes (Johansson et al., 2007; Progida et al., 2007; Rocha et al., 2009; van der Kant et al., 2013;

Wijdeven et al., 2016). In particular, Rab7 interacts with RILP and ORP1L to form a RILP-Rab7-ORP1L complex, which mediates dynein motor recruitment through RILP interaction with p150Glued, a component of dynactin complex. While this model has been well tested in non-neuronal cells, such as HeLa and MelJuSo cells, the evidence of its involvement in retrograde axonal transport in neurons is still lacking. Snapin was proposed to serve as an adaptor of dynein motors, which directly interacts with the dynein intermediate chain. Snapin localizes on the late endosomal membrane through a hydrophobic region at its amino terminal and direct interaction with dynein motors mediates the recruitment of dynein motors to LEs, enabling long-distance transport of LEs from distal axons toward the soma (Cai et al., 2010; Cai and Sheng, 2011). Furthermore, through fusion with LEs to form amphisomes, newly generated autophagosomes in axons and presynaptic terminals gain retrograde transport motility by recruiting LE-loaded dynein-Snapin motor-adaptor complex (Cheng et al., 2015a). Such a mechanism facilitates the efficient clearance of autophagic cargos within lysosomes in the soma, thereby reducing autophagic stress in distal axons (Cheng et al., 2015a, b). Intriguingly, *snapin* deficiency did not impact the association of p150Glued (dynactin complex) with these organelles (Cai et al., 2010; Cheng et al., 2015a; Ye et al., 2017). This suggests that dynein-Snapin-mediated retrograde transport is independent of the dynactin complex, which is different from the mechanism mediated by the RILP-Rab7-ORP1L complex. Moreover, JIP3 has been shown to be involved in the regulation of lysosome transport through various mechanisms (Drerup and Nechiporuk, 2013; Edwards et al., 2013; Edwards et al., 2015; Gowrishankar et al., 2017). There is no evidence showing the direct involvement of JIP3 in dynein-mediated retrograde transport of LEs/amphisomes. Studies in zebrafish excluded the possibility that JIP3 regulates retrograde transport of LEs and autophagosomes (Drerup and Nechiporuk, 2013). Therefore, Rab7 or Snapin-mediated mechanisms are different from JIP3-associated pathways and likely act in parallel.

The accumulation of misfolded protein is associated with the pathogenesis of various neurodegenerative diseases (Cushman et al., 2010), which underscores the importance of proteostasis pathways in maintaining neuronal function and survival. In particular, autophagy-lysosomal dysfunction has been implicated as one of the main cellular defects contributing to the onset and progression of AD (Nixon, 2013). In AD brains, autophagic vacuoles accumulate massively within dystrophic neurites (Nixon et al., 2005). This raises a fundamental question as to whether defects in autophagic clearance contribute to AD-associated autophagic stress. Recent studies revealed that retrograde transport of amphisomes is impaired, leading to aberrant accumulation of amphisomes in axons and presynaptic terminals in the brains of AD-related mutant human APP (hAPP) transgenic (Tg) mice and AD patients (Tammineni et al., 2017a). Soluble β oligomers are found to be enriched in axons and interact with dynein motors. This interaction interferes with the coupling of the dynein motor with its adaptor Snapin, interrupting the recruitment of dynein motors to amphisomes. Such a defect disrupts dynein-driven retrograde transport of amphisomes, trapping them in distal axons and thus impairing their degradation within lysosomes in the soma (Tammineni et al., 2017a). Accordingly, deletion of *snapin* in mice causes AD-like axonal autophagic stress, whereas overexpressing Snapin in hAPP neurons reduces autophagic accumulation at presynaptic terminals by enhancing amphisome retrograde transport (Tammineni and Cai, 2017; Tammineni et al., 2017a).

Interestingly, the β -secretase BACE1 is concentrated in amphisomes, accumulating in the distal axons of AD neurons. In AD neurons, impaired retrograde transport of amphisomes augments autophagic retention of BACE1 in axons, exacerbating β -cleavage of APP and thus A β -induced synaptotoxicity by A β overproduction (Feng et al., 2017). This phenotype can be reversed by Snapin-enhanced retrograde transport through facilitating BACE1 trafficking to somatic lysosomes for degradation (Feng et al., 2017). Moreover, elevated Snapin expression via stereotactic hippocampal injections of adeno-associated virus particles in mutant hAPP Tg mouse brains decreases synaptic A β levels and ameliorates synapse loss, mitigating cognitive impairments associated with hAPP mice (Ye et al., 2017). Together, these studies provide new mechanistic insights into AD-linked autophagic pathology, and autophagy-mediated regulation of BACE1 turnover and APP processing through Snapin-mediated dynein-driven retrograde axonal transport. In addition, these findings build a foundation for future development of potential AD therapeutic strategies by restoring retrograde transport of amphisomes, and suggest a potential approach of modulating A β levels and attenuating synaptic deficits associated with AD.

Conclusions and future outlook

The endolysosomal system plays a key role in regulating neuronal proteostasis, and defects within the trafficking pathways have been implicated a number of neurodevelopmental and neurodegenerative disorders. While endolysosomal trafficking has been studied extensively in non-neuronal cells, recent studies in neurons have highlighted the importance of understanding the basic cell biology of intracellular trafficking within the context of neurons. Clearly, neurons have adapted their endolysosomal trafficking system to accommodate their morphological complexity, their high levels of activity, and longevity, and trafficking mechanisms are differentially regulated in dendrites, axons, and microcompartments, such as dendritic spines.

While great progress has been made in recent years, a number of important questions remain. For example, although mature lysosomes with high degradative capacity are found primarily in cell bodies, local degradation of cargos in axons and dendrites can occur (Jin et al., 2018b). Yet, it remains unclear which cargos are sorted locally in distal axons and dendrites to be degraded and recycled locally, and which cargos are transported toward the soma for degradation. The functional implications of local versus central degradation of different cargos are also unknown. Similarly, while recent studies have revealed differential regulation of dendritic versus axonal transport, how neurons establish and maintain these distinct regulatory mechanisms in different neuronal compartments remains largely unknown. In addition, recent studies have described contact sites between endosomes and ER as well as mitochondria (Rowland et al., 2014; Raiborg et al., 2015a, b; A. Das et al., 2016; Luarte et al., 2018), but there is a dearth of knowledge regarding the functional role of these contact sites in endosomal dynamics, lipid composition, signal transduction, and possibly calcium buffering.

Moreover, how is directional transport organized in dendrites? While axonal transport is relatively well studied, much less is known about the regulation of dendritic trafficking. Dendrites are also very long and require organized transport to ensure proper localization of receptors and regulated turnover. This holds for synaptic receptors whose surface density at postsynaptic sites sets synaptic strength, but also for receptors that signal during development. One critical aspect of both axonal and dendritic transport is directionality because the receptors need to be deliv-

ered either in an anterograde direction toward the axon terminals or distal dendritic segments, or be returned back toward the soma for degradation or signaling. The problem of how directional transport is organized has been solved on a conceptual level in the axon: microtubules are uniformly oriented with their plus ends toward the axon tip. Therefore, kinesin motors are responsible for anterograde axonal transport and dynein motors drive retrograde transport. In dendrites, such a simple solution to the problem of directionality did not present itself: microtubules are of mixed polarity, and either kinesin or dynein could in principle be responsible for retrograde transport of degradative cargos from distal dendrites to somatic lysosomes. Interestingly, a recent study shows that, in dendrites, stable and acetylated microtubules are oriented minus-end out, whereas dynamic, tyrosinated microtubules are of the opposite direction (Tas et al., 2017). Thus, preferential binding of acetylated versus tyrosinated microtubules by motor proteins can lead to directional transport within dendrites. In addition, dendritic microtubules organize into bundles of uniform polarity, which can locally bias the directionality of transport (Tas et al., 2017). However, how neurons regulate retrograde transport in dendrites still remains unclear. The hunt for understanding the machinery for directional dendritic transport thus continues!

Finally, the extent to which interactions between neurons and surrounding glia impact proteostasis networks in the brain is largely unknown (Kulkarni et al., 2018). Preliminary studies support a potential role for glia in regulating neuronal autophagy (Alirezaei et al., 2008; Gan et al., 2012; Madill et al., 2017). Further, glial autophagy may have profound effects on neuronal function, connectivity, and response to stress induced by injury (Gomez-Sanchez et al., 2015; Jang et al., 2016; H. J. Kim et al., 2017). Because many neurodegenerative diseases may propagate through a prion-like cell-to-cell transfer of disease-associated proteins (Cushman et al., 2010; Luk et al., 2012), it remains critical to define the precise role of endolysosomal trafficking and autophagy in both neurons and glia, particularly in response to neurotoxic stress (Davis et al., 2014; Melentijevic et al., 2017; Spiller et al., 2018).

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