



Review

Lysosome trafficking and signaling in health and neurodegenerative diseases

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ABSTRACT

Lysosomes, single-membrane organelles defined by a uniquely strong acidic luminal pH and high content of acid hydrolases, are the shared degradative compartments of the endocytic and autophagic pathways. These pathways, and especially lysosomes, are points of particular vulnerability in many neurodegenerative diseases. Beyond the role of lysosomes in substrate degradation, new findings have ascribed to lysosomes the leading role in sensing and responding to cellular nutrients, growth factors and cellular stress. This review aims to integrate recent concepts of basic lysosome biology and pathobiology as a basis for understanding neurodegenerative disease pathogenesis. Here, we discuss the newly recognized signaling functions of lysosomes and specific aspects of lysosome biology in neurons while re-visiting the classical defining criteria for lysosomes and the importance of preserving strict definitions. Our discussion emphasizes dynein-mediated axonal transport of maturing degradative organelles, with further consideration of their roles in synaptic function. We finally examine how distinctive underlying disturbances of lysosomes in various neurodegenerative diseases result in unique patterns of auto/endolysosomal mistrafficking. The rapidly emerging understanding of lysosomal trafficking and disruptions in lysosome signaling is providing valuable clues to new targets for disease-modifying therapies.

1. Introduction

Neuronal survival is critically dependent on efficient lysosome function. The many neurological disorders involving declines of fundamental lysosomal activities are typically associated with aggressive neurodegenerative phenotypes (Fraldi et al., 2016; Lloyd-Evans and Haslett, 2016) (Table 1). Depending on the dosage and the severity of a given gene mutation, neurodegeneration associated with lysosome dysfunction can manifest at different points across the age spectrum from congenital disorders to aging-related diseases, the latter involving aging as a major risk factor (Nixon et al., 2008). During aging, a wide range of insults (e.g., oxidative modification of lysosomal components and lipofuscin accumulation) detrimentally affect various aspects of lysosomal function, including lysosomal acidification, hydrolase activities and chaperone-mediated autophagy (extensively reviewed in (Colacurcio and Nixon, 2016; Cuervo and Wong, 2014; Nixon, 2016)). The already declining autophagy-lysosomal function in aging is exacerbated by the increased need for clearance of damaged proteins and organelles in aged cells. The mounting deficit in lysosomal function during aging can thus uncover previously subclinical genetic conditions, which surface as late-onset neurodegenerative diseases.

Lysosomes are the terminal compartment shared by the major autophagic and endocytic pathways of degradation (Nixon et al., 2008). In macroautophagy (referred to as autophagy hereafter), intracellular substrates are enclosed in double membrane-bound autophagosomes, which fuse with late endosomes to form amphisomes, or with lysosomes to form autolysosomes. In the endocytic pathway, endocytosed materials targeted for degradation are sorted sequentially into early and late endosomes. Stepwise maturation of autophagosomes and endosomes culminates in the degradation of sequestered substrates in lysosomes. Lysosomes are strictly defined as single membrane-bound organelles characterized by a highly acidic lumen of pH 4.5 to 5, strong enrichment in both acid hydrolases and lysosomal membrane proteins delivered by biosynthetic pathways, and a lack of mannose-6-phosphate receptors (M6PR) (Saftig and Klumperman, 2009). This longstanding strict definition of lysosomes, however, is infrequently followed rigorously in recent literature. Lysosomes are often identified based on the achievement of only partial acidification or degradative capability. Such compartments may encompass late endosomes, which are clearly functionally distinct and are differentially vulnerable to disease states, as we will further elaborate below. In addition, many studies visualize lysosomes with non-specific membrane markers that are present in a

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relatively broad range of vesicular compartments, including Golgi transport vesicles (Pols et al., 2013). Although the broadened definition of lysosomes may be adequate in certain contexts, the classical definition emphasizing full acidification is indispensable for two reasons. First, the neuronal cell body is clearly enriched in classically defined lysosomes as opposed to less mature compartments in axons, which have higher pH (Overly et al., 1995), and lower lysosomal hydrolase content and activity (Lee et al., 2011). Detailed characterization of their maturation, composition, and trafficking behavior calls for a more precise distinction among these organelles. Second, functional differences among endolysosomal and autophagic-lysosomal compartments have been increasingly recognized to confer varying vulnerabilities to each in disease states. Numerous disease-linked mutations affect endosomal or autophagic function upstream of lysosomes (Nixon, 2016) rather than directly impairing lysosomal function as in those listed in Table 1. One example is *CHMP2B*, a component of the endosomal sorting complex required for transport (ESCRT)-III. Mutations in *CHMP2B* induced enlargement of M6PR-positive late endosomes and impaired endosome-lysosome fusion, which are pathological changes specific to a subtype of frontotemporal dementia (FTD) not found in other neurodegenerative diseases such as Alzheimer's disease (AD) (Urwin et al., 2010). Thus, understanding disease-specific pathophysiology necessitates the rigorous identification of the primary defective compartment instead of generalizing endosomes and lysosomes into a broader “endolysosomal compartment”.

Beyond serving as the receiving end of maturing autophagosomes and endosomes, recent findings have placed lysosomes at the forefront of instructing cellular homeostasis in response to environmental cues. For instance, lysosomes serve as platforms for both anabolic and catabolic signaling (Napolitano and Ballabio, 2016; Zhang et al., 2014), the former being mediated via the mechanistic target of rapamycin complex 1 (mTORC1), which is the master regulator of cellular growth, and the latter being mediated via AMP-activated protein kinase (AMPK), the major sensor of energy stress. These advances, in addition to the increasingly appreciated vulnerabilities of autophagy-lysosomal function in neurodegenerative diseases, have provided great incentive to better understand the biology of lysosomes in general and in neurons. New lysosomal mechanisms identified in non-neuronal cells can serve as a framework for further investigation of potential neuron-specific features. In the first section of this review, “Lysosomes as signaling hubs for adaptation to environmental cues”, we will discuss recent findings in lysosomal signaling functions and how they affect cellular metabolism. In the second section “Lysosome biology in neurons under normal and pathological states”, we will introduce the neuron-specific spatial organization and trafficking of organelles in the lysosome system, as well as the disruption of lysosome maturation and trafficking under neurodegenerative conditions.

2. Lysosomes as signaling hubs for adaptation to environmental cues

Recent advances in our knowledge have placed lysosomes on the center stage of sensing and signaling environmental cues, including nutrient availability, growth signals and stress, thereby coordinating appropriate cellular responses. This section reviews the major known signaling modules on lysosomes and various downstream effects on gene expression, lysosome positioning and degradative function (Fig. 1). As we will soon discuss, these signaling pathways commonly converge on the regulation of transcription factor EB (TFEB), which activates the transcription of genes in the Coordinated Lysosomal Expression And Regulation (CLEAR) network (Napolitano and Ballabio, 2016). Under conditions favorable for cell growth, TFEB is sequestered away from the nucleus due to its phosphorylation by activated mTORC1 on lysosomes. Conversely, catabolism-inducing conditions stimulate TFEB nuclear translocation and gene expression required for lysosome biogenesis and autophagy induction.

2.1. Signaling modules on lysosomes

2.1.1. vATPase-SLC38A9-Ragulator-Rag GTPases

A lysosomal super molecular complex has been recognized to be able to sense multiple nutrients, including amino acids, cholesterol and glucose, and convey their availability to downstream anabolic or catabolic signaling. This complex is consisted of the vacuolar H⁺-ATPase (vATPase) complex, the multi-pass transmembrane protein SLC38A9, the pentameric Ragulator complex (LAMTOR 1–5) and the heterodimeric Rag GTPase complex (RagA/B and RagC/D). While vATPase is best known as the proton pump that carries out lysosomal acidification, its activity was also shown to be required for sensing intraluminal amino acid level (Zoncu et al., 2011). Likewise, SLC38A9 has dual functions as an amino acid transporter, as well as a sensor for arginine (Wang et al., 2015) and cholesterol (Castellano et al., 2017). These two sensors act in parallel and converge signals to the Ragulator complex. In the nutrient replete state, Ragulator's guanine nucleotide exchange factor (GEF) activity mediates GTP loading onto RagA/B (Bar-Peled et al., 2012); Rag GTPases in turn recruit mTOR to lysosomes, thereby facilitating the activation of mTOR kinase activity by the Rheb GTPase residing on lysosomes (Long et al., 2005). Loss of function of vATPase or SLC38A9 renders cells insensitive to stimulation by nutrients, repressing mTOR activation in the nutrient replete state (Castellano et al., 2017; Wang et al., 2015; Zoncu et al., 2011). In amino acid- or cholesterol-depleted states, interactions strengthen among Ragulator, Rags, and the sensors, while mTOR is inactivated and released from the lysosome surface (Castellano et al., 2017; Wang et al., 2015; Zoncu et al., 2011), favoring dephosphorylation of TFEB and its translocation into the nucleus. However, the mechanistic details regarding how the interaction of nutrients with vATPase or SLC38A9 influences the conformation/activity of each component in the complex remain to be elucidated.

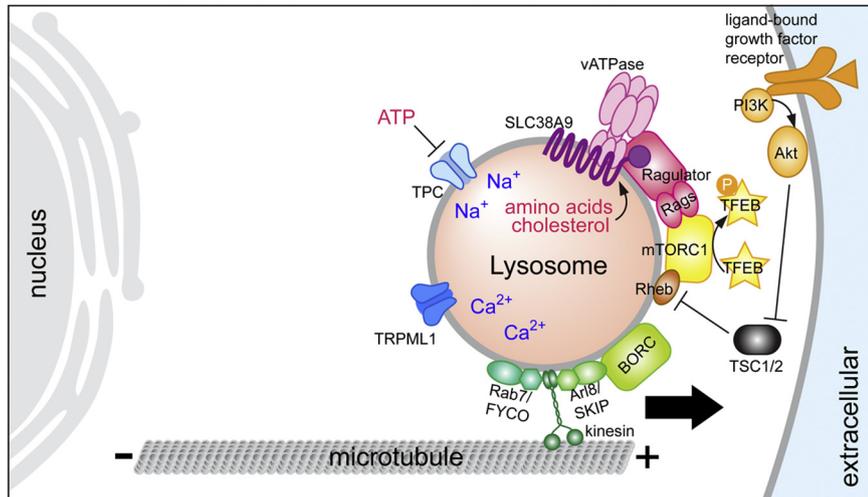
Interestingly, this Ragulator-based signaling platform was proposed to switch to catabolic signaling by activating AMPK during starvation and lysosomal stress induced by deacidification (Zhang et al., 2014). The authors showed that under glucose starvation or vATPase inhibition, vATPase and Ragulator on lysosomes formed an alternative complex with the scaffold protein AXIN, which facilitated AMPK activation by simultaneously binding AMPK and its activator LKB1. Concurrently, AXIN blocked Ragulator's GEF activity toward Rag and caused mTOR dissociation, thereby coupling mTOR inactivation to the recruitment of AMPK and its activation on lysosomes.

2.1.2. Lysosomal calcium and lysosomal cation channels

Free Ca²⁺ stored within lysosomes, a significant source of intracellular Ca²⁺ comparable to stores in the ER (Patel and Docampo, 2010), is emerging as an important signal that coordinates adaptive responses upon its release into the cytosol. Endolysosomal ion channels known to release Ca²⁺ include transient receptor potential cation channel mucopolipins (TRPMLs) and two-pore channels (TPCs). Many aspects remain controversial regarding the biophysical properties of these channels, including their ion permeability/selectivity and activation mechanisms. Nevertheless, the weight of evidence supports that these are both Ca²⁺-permeable channels activated by PI(3,5)P₂ (phosphatidylinositol 3,5-bisphosphate), and TPCs are also activated by NAADP (nicotinic acid adenine dinucleotide phosphate) (Morgan et al., 2011; Patel and Cai, 2015; Waller-Evans and Lloyd-Evans, 2015).

Lysosomal Ca²⁺ efflux via TRPML1 is activated in several stress conditions, including starvation (Li et al., 2016; Medina et al., 2015), lysosome deacidification (Lee et al., 2015; Raychowdhury et al., 2004) and oxidative stress (Zhang et al., 2016), as well as during physiological processes such as phagocytosis of large particles by macrophages (Samie et al., 2013). Notably, these stress conditions share the property of elevated lysosomal pH or vATPase dysfunction (Butterfield et al., 2014; Mundy et al., 2012; Ollinger and Brunk, 1995), suggesting that lysosome deacidification could be the common driving force for the

Anabolic signaling



Catabolic signaling

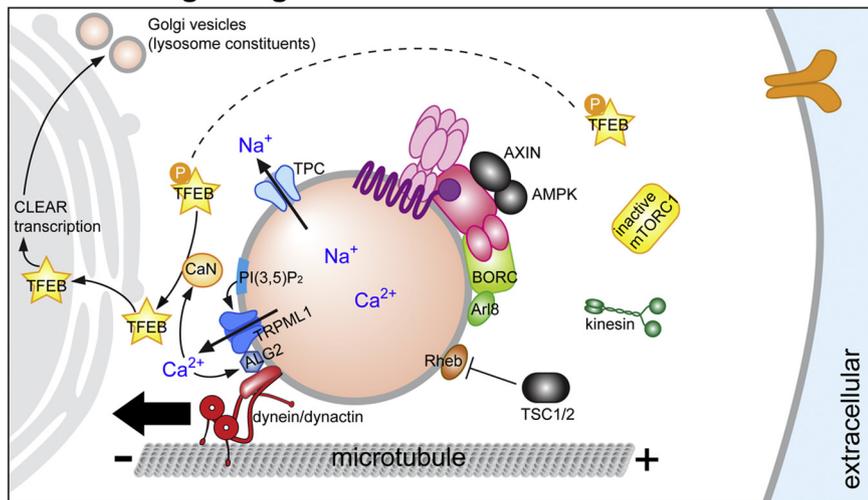


Fig. 1. Lysosome signaling in anabolic and catabolic states.

Anabolic signaling is favored by nutrient replete conditions (upper panel). mTORC1 is recruited to the lysosomal surface by the vATPase-SLC38A9-Ragulator-Rag GTPase complex, which senses amino acids and cholesterol levels within lysosomes. mTORC1, the master growth regulator, is activated by Rheb GTPase that is also present on the lysosomal surface and is activated by growth factor signals from the cell surface. mTORC1 phosphorylates TFEB, which is then sequestered in the cytoplasm. The interaction between Ragulator and BORG is weak, which facilitates kinesin recruitment by Arl8 and its effector SKIP. Kinesin is also recruited by Rab7 and its effector FYCO. Kinesin-mediated centrifugal transport of lysosomes to the cell periphery promotes mTORC1 activation by growth factor signaling on the cell surface. Both TRPML1-mediated Ca^{2+} release and the ATP-sensitive TPC-mediated Na^{+} release are inhibited under well fed conditions. Conversely, catabolic signaling is favored by nutrient depletion (lower panel). mTORC1 is released from vATPase-SLC38A9-Ragulator-Rag GTPase complex. The mTORC1 activator, Rheb GTPase, is inhibited in the absence of growth factor signaling. Inactivated mTORC1 is no longer able to phosphorylate TFEB. Ragulator instead interacts with AXIN and AMPK that promote catabolic signaling. Interaction strengthens between Ragulator and BORG, inhibiting kinesin recruitment. PI(3,5) P_2 -mediated activation of TRPML1 channel triggers lysosomal Ca^{2+} efflux, activating CaN, which in turn dephosphorylates TFEB and stimulates its nuclear translocation. Nuclear TFEB activates CLEAR gene transcription for lysosome biogenesis. TRPML1 activity also promotes dynein-mediated centripetal transport of lysosomes via the calcium-sensing protein ALG2. Perinuclear localization of lysosomes facilitates the delivery of nascent lysosomal constituent from the Golgi, thereby promoting lysosomal degradative function. Under low level of ATP, TPC-mediated Na^{+} release affects the lysosomal membrane potential in a manner that helps maintaining vATPase proton pumping activity during starvation.

calcium signaling via TRPML1. During starvation, TRPML1-mediated Ca^{2+} efflux has a twofold effect. First, local increase in Ca^{2+} surrounding lysosomes activates calcineurin (CaN), a calcium/calmodulin-dependent protein phosphatase, which in turn dephosphorylates TFEB to facilitate its nuclear translocation (Medina et al., 2015). As a result, activation of TFEB target gene transcription supports lysosome biogenesis, catabolism and cellular adaptation to starvation. Second, released lysosomal Ca^{2+} activates dynein-mediated transport of lysosomes to enhance their perinuclear localization, thereby facilitating autophagosome-lysosome fusion and substrate digestion during starvation-induced autophagy (Li et al., 2016). TRPML1 activity induced by starvation is dependent on PI(3,5) P_2 (Li et al., 2016), a low abundance endolysosome-specific phospholipid and the only known endogenous agonist of TRPML1 (Dong et al., 2010). PI(3,5) P_2 may serve as a permissive factor that allows TRPML1 activity specifically on endolysosomal membranes, but not on other membranes, or it can be transiently and locally upregulated, for instance during phagocytosis that requires focal exocytosis of lysosomes to form plasma membrane protrusions (Samie et al., 2013).

While channel opening is typically evoked by agonists, TRPML1's open probability has been shown to increase in response to insults, including lysosomal deacidification (Raychowdhury et al., 2004) and the presence of oxidants (Zhang et al., 2016). The effect of pH on TRPML1 channel activity was tested by reconstituting in vitro translated TRPML1 into a lipid bilayer in the absence of PI(3,5) P_2 . Basal

TRPML1 activity was detected at near neutral pH, but it was almost completely suppressed at an acidic pH similar to that of lysosomal lumen (Raychowdhury et al., 2004). This suggests that lysosome deacidification could induce agonist-independent Ca^{2+} efflux, consistent with observations of TRPML1 stimulation in cells with suppressed vATPase activity and elevated lysosomal pH (Christensen et al., 2002; Lee et al., 2015). Furthermore, sustained TRPML1 channel opening was triggered after exposure to oxidants (Zhang et al., 2016). Basal channel activity was also induced by reactive oxygen species (ROS) following mitochondrial damage. As a result, effluxed Ca^{2+} activated TFEB, thereby upregulating both autophagy and lysosomal clearance to remove damaged mitochondria and preventing further oxidative damage (Zhang et al., 2016). The authors proposed that ROS is an external stimulus possibly from damaged mitochondria in close contact with lysosomes, but considering linkages between oxidative stress and lysosomal pH disruption (Butterfield et al., 2014; Ollinger and Brunk, 1995), it will be interesting to examine whether lysosome pH contributes as a driving force in this mechanism.

Another class of Ca^{2+} release channels, TPCs, is proposed to be a primary target of NAADP signaling that mediates a wide range of physiological processes, including endolysosomal trafficking and regulation of plasma membrane excitability (Morgan et al., 2011). Recently, one facet of NAADP-TPC1 signaling was implicated in a role in tempering signals induced by epidermal growth factor (EGF). TPC1 activity was shown to be involved in the formation of late endosome-ER

contact sites, which facilitated dephosphorylation of endocytosed EGF receptor by an ER-resident phosphatase that prevented over-activation of downstream pathways (Kilpatrick et al., 2017). In addition to NAADP, sphingosine has been newly identified as an activator of TPC1, which triggers TFEB nuclear translocation upon Ca^{2+} efflux (Hoglinger et al., 2015), reminiscent of TRPML1 activity discussed above. Notably, it was proposed in a provocative study that TPCs act as endolysosomal Na^+ channels that are not activated by NAADP, but are instead ATP-sensitive with roles in adaptation to starvation (Cang et al., 2013). Confirmation of this finding and further evidence will be needed to resolve ongoing controversies regarding TPC activation and functional roles.

It is worth noting that the above regulatory signals are responsive not just to nutrient conditions but also cellular stress. Different organs or cell types are routinely exposed to different kinds of stimulations and stressors. For instance, neurons are vulnerable to oxidative stress (Uttara et al., 2009), but they are relatively protected from the substantial nutrient shifts faced by liver cells (Boland and Nixon, 2006). Thus, the versatility of lysosomal signaling is well-suited to function in diverse cellular contexts, including neurons.

2.2. Interplay between lysosome signaling, positioning and degradative function

Cellular nutrient status not only controls gene expression via TFEB, as we have discussed, but also dynamically regulates lysosome positioning in cells. In many cell types, lysosomes and late endosomes are concentrated in an immobile perinuclear cloud proposed to be sequestered by the ER, with a distinct subset of motile vesicles in the cell periphery (Jongsma et al., 2016). We will next discuss how nutrient status modulates the recruitment and activity of microtubule-based motors, dynein/dynactin and kinesins, on lysosomes. Resultant changes in the positioning of lysosomes in turn affect their degradative and signaling functions (Pu et al., 2016). It should be noted that these studies rely heavily on visualizing lysosomes with several markers that are not necessarily lysosome-specific. While late endosomes and lysosomes are generally not well distinguished by commonly used markers, LAMP-containing vesicles may even include weakly acidic precursor vesicles containing lysosomal constituents derived from Golgi and reformed autolysosomes (Pols et al., 2013; Yu et al., 2010), and other nondegradative compartments (Cheng et al., 2018). Caution should thus be used to interpret studies using different lysosomal markers, and future studies need to consider the critical defining property of full acidification to pH at or below 5.0 in the identification of authentic lysosomes.

Starvation induces dynein/dynactin-dependent perinuclear clustering of LAMP1 vesicles. It was shown that dynein activation following starvation-induced lysosomal Ca^{2+} efflux was dependent on the enhanced interaction between the TRPML1-associated calcium sensing protein, ALG-2, and the dynactin component, dynamitin (Li et al., 2016). Another study demonstrated that starvation-induced TFEB activation increased the transcription of TMEM55B, a lysosomal transmembrane protein that recruits JNK-interacting protein 4 (JIP4), which was proposed to serve as an adaptor for dynein/dynactin (Willett et al., 2017). Collectively, these results implicate two parallel mechanisms by which starvation can upregulate lysosome-associated dynein function, although the mechanistic details remain unclear. The former mechanism is rapidly activated in an on-demand manner, and the latter one is slower acting but supports the sustained up-regulation of dynein function through modified gene expression. Perinuclear clustering of lysosomes, and possibly LAMP-containing carriers of nascent lysosomal membrane proteins from Golgi, is expected to promote their encounter with endosomes and autophagic vacuoles (AVs) and thereby facilitate the clearance of autophagic substrates (Jongsma et al., 2016; Willett et al., 2017). Furthermore, movement of endolysosomes toward the perinuclear region of the cell is beneficial for their acidification and

maturation, which is likely due to a more efficient delivery of lysosome constituent proteins from the biosynthetic pathway (Johnson et al., 2016).

In contrast to starvation, the nutrient replete state enhances the kinesin-dependent dispersion of vesicles marked by LAMP1 or endocytosed dextran to the cell periphery. The BLOC-1-related complex (BORC) has been identified as the lysosomal scaffolding complex necessary for the recruitment of the GTPase Arl8, which promotes kinesin recruitment through the Arl8 effector, SKIP (Pu et al., 2015). At least three mechanisms have been proposed to regulate kinesin recruitment on lysosomes in response to nutrient status. First, it was shown that BORC/Arl8/kinesin interaction was disrupted by depletion of amino acids or growth factor, in part due to a strengthened interaction between BORC and Ragulator nutrient sensing complex on lysosomes (Filipek et al., 2017; Pu et al., 2017). Second, the amino acid replete state promotes the formation of ER-lysosome contacts, which facilitate the transfer of ER-associated kinesin to the lysosomal surface through the interaction between FYCO1 and protrudin (Hong et al., 2017). Third, kinesin recruitment to lysosomes is favored by the normal cytosolic pH, and is disrupted by starvation-induced alkalinization of the cytosol (Korolchuk et al., 2011). In this scenario, the implications of cytosolic pH change on lysosomal pH remain to be determined. Consequent to kinesin activity, peripheral translocation of lysosomes facilitates the interaction of lysosome-associated mTOR with an upstream activator protein kinase B (PKB/Akt) on the cell surface, thereby promoting growth factor signaling (Hong et al., 2017; Korolchuk et al., 2011). In contrast, neither Akt inhibition nor its overexpression affects lysosome positioning (Korolchuk et al., 2011). These findings suggest that growth factor signaling is primed by the presence of abundant nutrients within cells.

3. Lysosome biology in neurons under normal and pathological states

The newly recognized lysosome signaling functions discussed above have remained largely unexplored in neurons, and their significance in neuronal physiology has only begun to be addressed. While the neuronal lysosome system shares many similar features with that in other cell types, proper lysosome function in neurons is uniquely challenging due to the exceptionally long distance between the cell body and distal ends of neurites, especially axons, which can extend up to 1 m in human. For this reason, an efficient transport system must be in place to ensure rapid collection and degradation of lysosomal substrates throughout the vast cytoplasmic volume of many neurons. Early studies have established that mature lysosomes are mostly concentrated in the cell body (Overly et al., 1995), with a decreasing pH gradient of endocytically-derived vesicles from the distal to the proximal axon (Overly and Hollenbeck, 1996), suggesting that maturation of endolysosomes is coupled to their retrograde axonal transport. Indeed, disrupted lysosome function, trafficking, and maturation go hand in hand under several neurodegenerative conditions, as we will soon discuss. In the following sections, we will review the neuronal spatial organization and transport mechanisms of organelles in the endo- and auto-lysosomal network (Fig. 2), as well as the relevance of the lysosome system to synaptic function. Finally, we will cover pathological states relevant to lysosome dysfunction and mistrafficking in neurons (Fig. 2).

3.1. Overview of neuronal lysosome system and trafficking of compartments

Neuronal lysosomes receive their substrates from autophagic and endocytic pathways as in non-neuronal cells. Autophagy in neurons is thought to be a housekeeping process mainly functioning in the clearance of damaged organelles and cellular waste to prevent buildup of toxic materials (Komatsu et al., 2007). In this housekeeping role, neurons are especially efficient in clearing AVs and amphisomes reaching

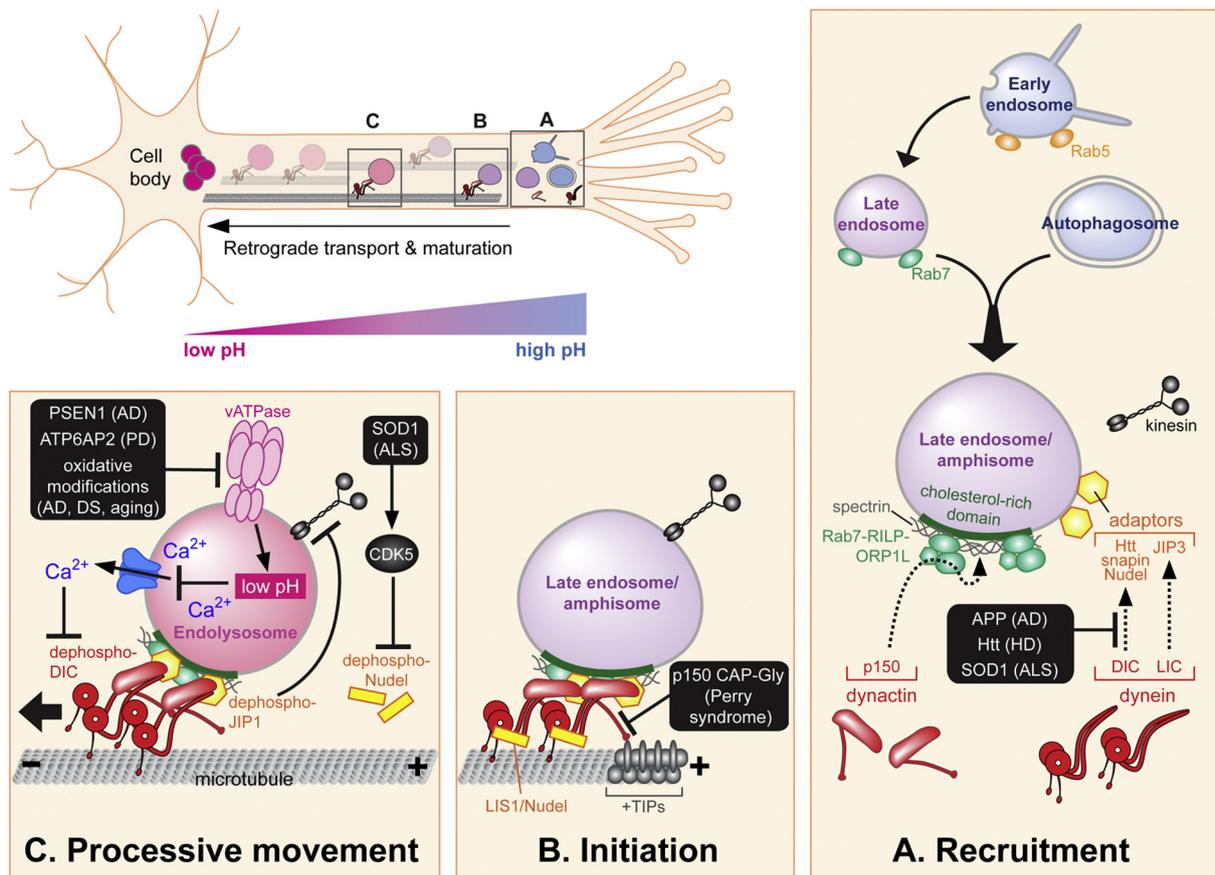


Fig. 2. Neurodegenerative diseases disrupt retrograde axonal transport of maturing degradative organelles in lysosomal pathways.

This schematic highlights disease-linked gene mutations or pathogenic factors implicated in the impairment of motor-cargo association or motor activity. Mutations of many additional genes alter organelle function and structure, including abnormal enlargement in vesicle size (refer to (Nixon, 2016)), contributing to transport deficits or to other deficits of endosomal-lysosomal function or autophagy. Upper left panel shows the progressive acidification of degradative organelles as they are transported retrogradely from the distal to the proximal axon, becoming fully acidified in the cell body. Boxed areas are enlarged in bottom and right panels. (A) Early endosomes mature into late endosomes in a process that involves the conversion of Rab5 into Rab7 associated on endosomal membranes. Late endosomes fuse with double-membraned autophagosomes to form amphisomes. Dynein and dynactin are recruited to late endosomes or amphisomes. Dynein is recruited via interaction of dynein subunits DIC or LIC with various adaptors, which is competitively inhibited by aberrant interactions between dynein subunits and pathogenic peptides or proteins associated with AD, HD and ALS. Dynactin is recruited by Rab7 effectors to cholesterol-rich membrane domains and transferred to spectrin. (B) Retrograde transport is initiated in a process that requires the ordered recruitment of microtubule plus-end binding proteins (+TIPs) and the dynactin p150 CAP-Gly domain, as well as dynein interaction with LIS1/Nudel. p150 mutation within the CAP-Gly domain is associated with Perry syndrome. (C) Processive movement is promoted by (i) clustering of multiple dynein motors within cholesterol-rich membrane domain, (ii) inhibition of kinesin by maintaining the dephosphorylated status of the adaptor JIP1, (iii) Nudel dephosphorylation, which is inhibited in ALS and (iv) maintenance of dephosphorylated status of DIC. Lysosomal deacidification results from loss of PSEN1 function in AD or other disease mechanisms, hyper-activating Ca^{2+} efflux and leading to aberrant DIC phosphorylation, which detrimentally impacts dynein activity.

the perikaryon. However, autophagy can also be induced by prolonged starvation in cultured primary neurons (Boland et al., 2008; Rubinsztein and Nixon, 2010), in vivo in brain (Kaushik et al., 2011), and by an assortment of other stimuli (Rosic et al., 2011; Tsvetkov et al., 2010). Several investigators have suggested that neurons are relatively less sensitive to starvation than other cell types (Maday and Holzbaaur, 2016), which is consistent with the general concept that the brain is endowed with several defense mechanisms designed to resist negative effects of peripheral nutrient fluctuation (Boland and Nixon, 2006).

Unlike autophagosome formation in random cytoplasmic locations in some cell types, neurons show spatially restricted autophagosome biogenesis, which is mostly enriched at distal ends of axons in both growing and synaptically connected neurons (Maday and Holzbaaur, 2014; Maday et al., 2012), while less frequent autophagosome formation has also been observed in mid-axons, cell bodies and dendrites (Maday and Holzbaaur, 2014). Despite being constitutively formed, autophagosomes are efficiently transported and cleared and are rarely found in neurites or cell bodies unless lysosome function is disrupted

(Boland et al., 2008). Nascent autophagosomes in distal axon rapidly acquire endolysosomal markers, LAMP1 and Rab7 (Lee et al., 2011), via syntaxin 17-dependent fusion (Cheng et al., 2015), thereby gaining access to late endosome-associated motor proteins required for long-range transport (Cheng et al., 2015). Likewise, endocytic substrates acquire long-range motility only after transiting through early endosomes and maturing into late endosomes (Deinhardt et al., 2006), a process that involves the conversion of the membrane-associated Rab GTPase from Rab5 to Rab7 (Deinhardt et al., 2006) and recruitment of compartment-specific phosphoinositides (Liu et al., 2017). Unlike the bidirectional transport of AVs in some non-neural cell types, axonal amphisomes and late endosomes predominantly undergo long-range retrograde transport while simultaneously acidifying and maturing into lysosomes, and ultimately fusing with mature lysosomes enriched in the cell body (Cheng et al., 2015; Lee et al., 2011; Maday et al., 2012). In addition to carrying cellular wastes targeted for lysosomal degradation, a subset of axonal late endosomes and amphisomes also carry retrograde signals *en route* to the cell body such as ligand-bound growth factor receptors (Kononenko et al., 2017; Zhou et al., 2012). Once

axonal AVs enter the cell body, they are restricted from re-entry into the axon (Maday and Holzbaur, 2016). In contrast to the extensively studied axonal transport, less is known about lysosomal trafficking in dendrites, although LysoTracker-, LAMP1- or Rab7-labeled vesicles have been shown to move bidirectionally in dendrites (Farias et al., 2017; Goo et al., 2017; Gowrishankar et al., 2017; Schwenk et al., 2014). Upon complete substrate degradation in the cell body, it is likely that fully matured lysosomes undergo reformation to recycle lysosomal membrane proteins and hydrolases for new rounds of lysosomal formation, as in non-neuronal cells (Bright et al., 2016; Yu et al., 2010).

Collective evidence in the literature is most consistent with a strongly biased retrograde axonal transport of acidifying AVs and late endosomes and fully mature lysosomes toward the cell body. First, cell bodies, but not axons, are abundantly enriched in fully acidified lysosomes of ~pH 5 (Overly et al., 1995) with high level of active lysosomal proteases (Lee et al., 2011). Second, local block of axonal transport causes the selective accumulation of organelles with typical endolysosomal ultrastructure on the distal side of the blockade (Tsukita and Ishikawa, 1980). Third, it has been noted that LysoTracker vesicles that are at least partially acidified undergo predominant retrograde transport (Gowrishankar et al., 2017). Moreover, we observed exclusive retrograde motility in acidic LAMP1 vesicles co-labeled with LysoTracker, as well as fully mature LAMP1 vesicles containing active cathepsin D (Lie & Nixon, submitted manuscript). On the contrary, another recent study claimed that axonal lysosomes are transported bidirectionally (Farias et al., 2017). The latter study visualized acidic LAMP1 vesicles with a LAMP1 construct dually labeled with an acid-insensitive fluorescent protein and a supercliptic pHluorin probe, which is quenched at or below pH 6 (Tanida et al., 2014). The insufficient selectivity of this probe for highly acidic organelles likely accounts for the seemingly contradictory observation. We speculate that anterogradely transported LAMP1 vesicles are weakly acidified, non-endolysosomal structures, such as LAMP carriers from Golgi (Pols et al., 2013) or immature structures derived from autolysosome reformation (Yu et al., 2010). This issue will require further investigations to fully resolve, such as labeling of multiple active lysosomal hydrolases and ratiometric pH measurements, but it again highlights the value of cautious interpretation of results from using different organelle markers without detailed consideration of intraluminal pH.

3.2. Axonal transport mechanisms of endolysosomes and amphisomes

Axonal microtubules are arranged unipolarly such that minus ends are oriented toward the cell body (Baas et al., 1988). Retrograde axonal transport of endolysosomes and amphisomes is thus driven by the microtubule minus end-directed motor, dynein, a multi-subunit complex with its motor activity residing in dynein heavy chains. Processive dynein activity requires its simultaneous binding to an appropriate cargo adaptor and its multi-subunit activator, dynactin (McKenney et al., 2014). Studies in neurons and non-neuronal cells have complementarily provided mechanistic insights on how dynein and dynactin are recruited to these organelles, demonstrating various linkages between endolysosomal adaptors and dynein/dynactin subunits. Our discussion below provides examples of these linkages to illustrate later described disease-related disruptions but is not meant to be comprehensive.

3.2.1. Recruitment of dynein and dynactin

Direct binding of dynein intermediate chain (DIC) to snapin mediates dynein recruitment to late endosomes and amphisomes in neurons (Cai et al., 2010; Cheng et al., 2015). Snapin deficiency reduced the association of DIC with LAMP- and TrkB- containing endosomes, impairing retrograde motility of these organelles, which was rescued by expressing wild-type snapin but not its mutant variant defective in DIC binding (Cai et al., 2010; Zhou et al., 2012). In addition, NudE/NudE-like (Nudel) (Lam et al., 2010) and huntingtin (Htt) (Caviston et al.,

2007) have also been implicated in DIC recruitment to membranous organelles. Another dynein subunit, dynein light intermediate chain (LIC), interacts with the scaffold protein JIP3 (Arimoto et al., 2011). Loss of JIP3 function resulted in the accumulation of late endosomes or lysosomes marked by LAMP1 or LysoTracker in large axonal terminal swellings (Drerup and Nechiporuk, 2013), as well as focal swellings in dystrophic axons (Gowrishankar et al., 2017). Interestingly, phosphorylation status of both DIC and LIC has been shown to affect dynein association with endolysosomes (Mitchell et al., 2012; Scherer et al., 2014). For instance, DIC isoform 1B phosphorylation at S80 facilitated dynein recruitment on signaling endosomes after growth factor stimulation (Mitchell et al., 2012). Whether and how these different mechanisms work in concert to promote dynein recruitment remain to be investigated.

Dynactin was proposed to be recruited via a stepwise process initiated by the interaction between the dynactin p150 subunit and the Rab7 effector, Rab-interacting lysosomal protein (RILP) (Johansson et al., 2007). Deletion of the dynactin-interaction domain in RILP resulted in a loss of endolysosomal association with dynactin, but not dynein, suggesting that these two complexes are independently recruited (Tan et al., 2011). Following p150-RILP binding, another Rab7 effector known as oxysterol-binding protein-related protein 1L (ORP1L) participates in a chain of events that result in the attachment of dynactin to β III spectrin on late endosomes (Johansson et al., 2007). Notably, ORP1L was shown to sense membrane cholesterol level, and to inhibit dynactin recruitment and autophagosome-endolysosomal fusion under low cholesterol conditions by forming inter-organelle membrane contact sites with the ER (Wijdeven et al., 2016). Although the exact physiological consequence is unclear, this phenomenon further illustrates the previously discussed sensory and self-regulatory capabilities of degradative organelles.

3.2.2. Retrograde transport initiation and processivity

In axon terminals, efficient transport initiation at microtubule plus-ends is especially dependent on the ordered recruitment of microtubule plus-end binding proteins, which in turn recruit dynactin via the CAP-Gly domain of p150 (Moughamian et al., 2013). This mechanism is thought to help engage dynactin-bound cargoes, including LAMP1 vesicles, to the dynamic microtubule plus-ends in axon terminals, but it appears to be less important in non-polarized cells. In addition, the dynein cofactor Lissencephaly 1 (LIS1) was shown to function in endosome transport initiation in fungal hyphae, possibly by promoting dynein engagement to microtubules and cargo loading (Egan et al., 2012). Once transport has been initiated, neither p150 CAP-Gly domain nor LIS1 is required for processive dynein activity under the conditions of these studies (Egan et al., 2012; Moughamian and Holzbaur, 2012). Consistent with the roles of p150 and LIS1 as axonal transport initiation factors, the local translation of these proteins in distal axons was triggered by growth factor stimulation or withdrawal, thereby supporting the induced retrograde transport of signaling endosomes (Villarin et al., 2016).

Although AVs undergo long-range retrograde transport, they were copurified with both dynein and kinesin components (Maday et al., 2012), suggesting the presence of mechanisms that strongly bias dynein-mediated motility. Directionality of transported vesicles is regulated, in part, by the phosphorylation status of scaffold proteins. Phosphorylated JIP1 at S421 was shown to promote anterograde motility by binding and activating kinesin heavy chain (Fu and Holzbaur, 2013). In AVs, this effect was inhibited by maintaining the dephosphorylated status of JIP1 and by JIP1-LC3 binding, thus promoting retrograde motility (Fu et al., 2014). In addition, Htt phosphorylation at S421 promoted kinesin recruitment and anterograde transport of vesicles containing brain-derived neurotrophic factor (Colin et al., 2008). It is possible that Htt is similarly dephosphorylated in retrograde transported organelles. In addition to kinesin suppression, dynein clustering also contributes to the bias in retrograde transport in

degradative organelles. Late phagosomes were shown to develop cholesterol-rich microdomains that provided a platform for the clustering of multiple dynein motors, allowing the generation of cooperative force for efficient retrograde transport (Rai et al., 2016). Late endosomes, also known to be cholesterol-rich, are likely to employ a similar mechanism to promote retrograde motility.

3.3. Relevance of the lysosome system to synaptic function

Proper function of the lysosomal system is increasingly implicated in the maintenance and plasticity of synapses. It is not known whether fully mature lysosomes exist at pre- or post-synaptic terminals due to the lack of formal pH measurements. However, in growth cones, endocytic organelles have a mean pH of 6.29, which is typical of early endosomes (Overly and Hollenbeck, 1996). Based on the handling of autophagy-lysosomal substrates in general, presynaptic lysosomal substrates are likely targeted for retrograde axonal transport and are remotely degraded in the cell body. Several proteins enriched at presynaptic terminals have been identified as regulators of autophagic or endocytic pathways. For instance, Endophilin A and Synaptojanin 1 promote autophagy induction (Vijayan and Verstreken, 2017) while Bassoon suppresses autophagy induction (Okerlund et al., 2017), whereas snapin promotes vesicle sorting to the endolysosomal pathway (Di Giovanni and Sheng, 2015). Concerted regulation by these factors directs a subset of synaptic vesicles toward lysosomal degradation in the cell body, ultimately modulating the pool size of synaptic vesicles. Lysosomal function also maintains presynaptic protein homeostasis. In lysosomal storage disease (LSD) models, lysosome dysfunction induced the proteasomal degradation of cysteine string protein α , a presynaptic protein, consequently reducing its availability at synapses and disrupting synaptic function (Sambri et al., 2017). Furthermore, two proteins directly involved in lysosome acidification by promoting the delivery of vATPase V0a1 subunit to lysosomes, presenilin-1 (PSEN1) (Lee et al., 2010) and palmitoyl-protein thioesterase 1 (Bagh et al., 2017), are also implicated in presynaptic function (Kim et al., 2008; Zhang et al., 2009). It will be interesting to test whether their roles in lysosome acidification and presynaptic function are interrelated.

In addition to roles in presynaptic function, the lysosomal system has recently been demonstrated to influence the maintenance and structure of dendritic spines. Synaptic activity was shown to selectively induce the mobilization of LAMP1 vesicles to activated dendritic spines (Goo et al., 2017). The authors postulated that localized induction of lysosomal degradation is important for synaptic protein turnover and maintenance of synaptic structure, which is consistent with the loss of spines triggered by lysosomal proteolysis inhibition (Goo et al., 2017). Structural plasticity of spines was also shown to be regulated in an activity-dependent mechanism. Back-propagated action potential was shown to evoke lysosomal Ca^{2+} release that triggered lysosome exocytosis (Padamsey et al., 2017). As a result, the local release of lysosomal cathepsin B activated matrix metalloproteinase 9, which remodeled the extracellular matrix to facilitate spine growth (Padamsey et al., 2017). It is noted that although the organelles of interest in these two studies are at least partially acidified with some degradative capacity, it is unclear whether fully mature lysosomes are implicated. Collectively, these results indicate that beyond the maintenance of cellular homeostasis in individual neurons, the lysosome system has profound impact on neuronal connectivity and is also responsive to synaptic activity, again highlighting the dynamic sensory and adaptive capabilities of lysosomes. Along this line, deep brain stimulation, which results in synaptic activation among its possible effects, was found to promote the autophagic clearance of Tau oligomers, alleviating Tau pathology in disease models (Akwa et al., 2017).

3.4. Relevance of lysosome dysfunction and mistrafficking to neurodegenerative diseases

Lysosome dysfunction induced by a growing number of gene mutations has been linked to the pathogenesis of neurodegenerative disease across the age spectrum, including LSDs, AD, FTD and Parkinson's disease (PD) (Gotzl et al., 2016; Lloyd-Evans and Haslett, 2016; Nixon, 2013; Nixon et al., 2008) (Table 1). The products of these genes have a wide range of functions in lysosomes, including lysosomal hydrolases and their targeting, lysosomal acidification, lysosomal ion channels and transporters, vesicular trafficking, signaling, as well as lysosomal substrates (Table 1). Notably, lysosome acidification deficit has been identified as a common theme in aging and several neurodegenerative conditions (Colacurcio and Nixon, 2016). Consistent with lysosomal dysfunction, AD brains are characterized by grossly swollen dystrophic neurites containing massive yet selective accumulation of AVs with incompletely degraded substrates (Nixon et al., 2005). Similar accumulations of AVs and multivesicular bodies in swollen axons have also been found in various LSD models (Koike et al., 2005; Lloyd-Evans and Haslett, 2016). Besides a block in substrate degradation demonstrated in all of these disorders, the focal accumulations of degradative organelles in axons also implies an impairment in their retrograde axonal transport, suggesting that their motility may be influenced from “inside-out” via abnormalities originating within the lumen. Given the growing interest in lysosome trafficking and positioning as discussed in the previous section, we will focus on lysosome axonal transport deficits in neurodegenerative conditions. For in-depth discussion of disease-related lysosome dysfunction in general, please refer to recent extensive reviews (Colacurcio and Nixon, 2016; Lloyd-Evans and Haslett, 2016; Nixon, 2016). Here, we will first elaborate on the neuropathology of AD, and in that context, we will further discuss emerging evidence that ties impaired endolysosomal axonal transport deficits to pathogenic factors of AD and other neurodegenerative diseases.

Despite its reasonable theoretical basis, direct evidence for axonal transport deficits in AD has been scarce and early studies were mostly limited to anterograde motility disruptions. There has been a long-standing belief that axonal transport is disrupted in AD based on structural evidence for declines of microtubules in AD brain (Vicario-Orri et al., 2015) and microtubule instability due to tau hyperphosphorylation and dissociation from microtubules (Iqbal et al., 2010). The consequences of MT loss would be expected to include a global deficit of microtubule-based axonal transport. When modeled in animals, this is a catastrophic event leading to axonal accumulations of the full range of transported constituents and to axonal degeneration (Griffin and Watson, 1988). By contrast, the most prevalent pattern of axonopathy in AD is a characteristic neuritic dystrophy in which a select population of axonal cargoes accumulate (Nixon et al., 2005). In mouse models, AD-related dystrophic axons have shown enduring preservation of axon integrity, with at least partially intact axonal transport (Coleman, 2011). The focal swellings contain near exclusive accumulation of AVs and endosomes, which are almost exclusively retrograde cargoes, with fewer numbers of mitochondria that are bidirectionally transported (Nixon et al., 2005; Suzuki and Terry, 1967). Notably, collections of ER, Golgi-derived vesicles, neurofilaments, and other forms of predominantly anterograde cargo are rarely abundant in affected AD axons except in extreme cases of degenerative change associated with loss of axon integrity. Consonant with these established features of AD neuropathology, experimental modeling of AD-related endolysosomal dysfunction (Lee et al., 2011) further supports the disrupted retrograde motility of a select population of degradative organelles and their accumulation in axons. In a familial AD mouse model, endolysosomes with low protease content were found to accumulate at focal axonal swellings closely associated with extracellular amyloid deposits, suggesting a local block in the trafficking and maturation of these organelles into lysosomes (Gowrishankar et al., 2015). The properties of these organelles closely resemble those of amphisomes

Table 1
 Genes with roles in lysosomal function that are mutated in neurodegenerative diseases across the age spectrum. Abbreviations: NCL, neuronal ceroid lipofuscinosis; INCL, infantile neuronal ceroid lipofuscinosis; AD, Alzheimer's disease; PD, Parkinson's disease (including various forms of Parkinsonism); ALS, amyotrophic lateral sclerosis; FTD, frontal temporal dementia; CMA, chaperone-mediated autophagy.

Gene	Protein	Known/proposed role in lysosomal function	Associated disease(s)	References
Lysosomal hydrolases and their delivery				
<i>CTSD</i>	Cathepsin D	Proteolysis	NCL, INCL, AD	(Vidoni et al., 2016)
<i>CTSA</i>	Protective protein-cathepsin A	Proteolysis	Galactosialidosis	(Caciotti et al., 2013)
<i>IDUA</i>	α -L-iduronidase	Glycosaminoglycan metabolism	Mucopolysaccharidosis type I	(Campos and Monaga, 2012)
<i>IDS</i>	Iduronate 2-sulfatase	Glycosaminoglycan metabolism	Mucopolysaccharidosis type II	(Kosuga et al., 2016)
<i>NAGLU</i>	N- α -acetylglucosaminidase	Glycosaminoglycan metabolism	Mucopolysaccharidosis type III, PD	(Ohmi et al., 2009; Winder-Rhodes et al., 2012)
<i>SMPD1</i>	Sphingomyelin phosphodiesterase 1	Spingolipid metabolism	Niemann-Pick disease type A, PD	(Gan-Or et al., 2015)
<i>GBA</i>	Glucosylceramidase β	Glycolipid metabolism	PD, Gaucher's disease	(Westbroek et al., 2011)
<i>GLB1</i>	β -Galactosidase	Ganglioside metabolism	GMI-gangliosidosis	(Sandhoff and Harzer, 2013)
<i>HEXB</i>	β -Hexosaminidase	Ganglioside metabolism	GM2-gangliosidosis	(Sandhoff and Harzer, 2013)
<i>VPS35</i>	VPS35	Hydrolase receptor sorting	PD	(Vilarino-Guell et al., 2011)
<i>SCARB2</i>	LIMP2	Receptor for GBA	Diffuse Lewy body disease, PD	(Bras et al., 2014; Michelakakis et al., 2012)
Lysosomal acidification				
<i>ATP6V1B1</i>	ATPase H+ transporting V1 subunit B1 (V1B1)	vATPase subunit	Renal tubular acidosis	(Karet et al., 1999)
<i>ATP6V1B2</i>	ATPase H+ transporting V1 subunit B2 (V1B2)	vATPase subunit	Dominant deafness-onycho dystrophy syndrome, Zimmermann-Laband syndrome	(Kortum et al., 2015; Yuan et al., 2014)
<i>ATP6V0A2</i>	ATPase H+ transporting V0 subunit A2 (V0a2)	vATPase subunit	Autosomal recessive cutis laxa type II	(Kornak et al., 2008)
<i>TC1R1G1</i>	ATPase H+ transporting V0 subunit A3 (V0a3)	vATPase subunit	Autosomal recessive osteopetrosis with neurodegeneration	(Kornak et al., 2000)
<i>ATP6V0A4</i>	ATPase H+ transporting V0 subunit A4 (V0a4)	vATPase subunit	Renal tubular acidosis	(Stover et al., 2002)
<i>ATP6AP2</i>	ATPase H+ transporting accessory protein 2	Coordination of vATPase assembly	PD	(Korvatska et al., 2013)
<i>ATP13A2</i>	ATPase 13A2	Heavy metal transport; lipid flippase	PD, NCL	(Bras et al., 2012; Ramirez et al., 2006)
<i>PSEN1</i>	Presenilin 1	Chaperone for delivery of vATPase V0a1 subunit to lysosomes	AD	(Lee et al., 2010)
<i>PPT1</i>	Palmitoyl-protein thioesterase 1 (CLN1)	Palmitoylation of vATPase V0a1 subunit for delivery to lysosomes	INCL	(Bagh et al., 2017)
<i>WFS1</i>	Wolframin ER transmembrane glycoprotein	Stabilization of vATPase V1A subunit	Wolfram syndrome	(Gharanei et al., 2013)
Lysosomal ion channels or transporters				
<i>MCOLN1</i>	Mucopolipin 1 (TRPML1)	Lysosomal Ca ⁺ channel	Mucopolipidosis type IV	(Bargal et al., 2000)
<i>TMEM175</i>	Transmembrane protein 175	Lysosomal K ⁺ channel	PD	(Jinn et al., 2017)
<i>CLCN7</i>	Chloride voltage-gated channel 7 (CLC7)	Lysosomal Cl ⁻ channel	Osteopetrosis	(Kasper et al., 2005)
<i>NPC1</i>	Niemann-Pick C1	Cholesterol export	Niemann-Pick disease type C	(Vanier, 2010)
<i>NPC2</i>	Niemann-Pick type C2 protein	Cholesterol export	Niemann-Pick disease type C	(Vanier, 2010)
Other functions				
<i>LYST</i>	Lysosomal trafficking regulator	Lysosomal fission; secretory lysosome exocytosis	Chediak-Higashi syndrome, PD	(Durchfort et al., 2012; Sepulveda et al., 2015; Weisfeld-Adams et al., 2013)
<i>ZFYVE26</i>	Spastizin (SPG15)	Autophagic lysosome reformation	Hereditary spastic paraplegia	(Chang et al., 2014)
<i>SPG11</i>	Spatacsin	Autophagic lysosome reformation	Hereditary spastic paraplegia	(Chang et al., 2014)
<i>TARDBP</i>	TAR DNA binding protein (TDP-43)	Regulation of TFEB translocation and dynactin expression	ALS, FTD	(Xia et al., 2016)
<i>CSORF72</i>	CSORF72	Regulation of mTORC1 signaling	ALS, FTD	(Amick et al., 2016)
<i>FIG 4</i>	FIG 4	Regulation of phosphoinositide signaling	ALS, Charcot-Marie-Tooth disease type 4J	(Chow et al., 2009; Chow et al., 2007)
<i>GRN</i>	Progranulin	Unclear; enhances lysosome acidification	FTD, NCL	(Tanaka et al., 2017)
<i>STT11</i>	Synaptotagmin 11	Unclear; required for proper lysosomal acidification	PD	(Bento et al., 2016)
<i>TMEM106B</i>	Transmembrane protein 106B	Unclear; upregulation induces lysosome enlargement	FTD	(Brady et al., 2013; Van Deerlin et al., 2010)

(continued on next page)

Table 1 (continued)

Gene	Protein	Known/proposed role in lysosomal function	Associated disease(s)	References
Lysosomal substrates				
<i>MAPT</i>	Microtubule associated protein tau	CMA substrate; mutants block CMA	PD, FTD	(Wang et al., 2009)
<i>SNCA</i>	α -Synuclein	CMA substrate; mutants block CMA	PD, FTD	(Bougea et al., 2017; Cuervo et al., 2004)
<i>LRRK2</i>	Leucine rich repeat kinase 2	CMA substrate; mutants block CMA	PD, FTD	(Dachsel et al., 2007; Orenstein et al., 2013)
<i>UCHL1</i>	Ubiquitin C-terminal hydrolase L1	CMA substrate; mutants block CMA	PD	(Kabuta et al., 2008)

and immature autolysosomes previously seen to accumulate in dystrophic swellings in AD (Nixon et al., 2005) and in vitro modeling of AD transport and protease deficits (Lee et al., 2011). It appears that AV accumulations and neuritic dystrophy develop much more frequently in axons than dendrites. Thus, it is interesting to speculate that the restricted entry of fully mature lysosomes into axons but not dendrites may enable the latter to more efficiently clear AVs and other cargoes locally without requiring their transport to the perikaryon.

Several lines of genetic evidence have linked pathogenic factors of familial AD to impaired dynein-mediated retrograde transport of AVs and endolysosomes. First, one study showed that intracellular A β oligomers were associated with the surface of late AVs in the neurites of mutant amyloid precursor protein (APP) transgenic mouse neurons (Tammineni et al., 2017). Based on the direct binding of dynein subunit DIC to A β 1–42 peptides and oligomers, it was proposed that excess intracellular A β competitively inhibited snapin-mediated dynein recruitment on amphisomes and caused their accumulation in distal axons (Tammineni et al., 2017). Retention of amphisomes and late endosomes, in turn, delayed the lysosomal degradation of β -site amyloid precursor protein cleaving enzyme 1 (BACE1), increasing APP processing by BACE1 (Ye et al., 2017). It is conceivable that these events together create a vicious cycle that snowballs endolysosomal transport disruption, production of toxic APP metabolites, and their local extracellular release as seeds for plaque formation. In the second line of evidence, consistent with transport impairment induced by excess APP processing, gene duplication of APP in Down's syndrome (DS) mice was found to disrupt retrograde axonal transport of nerve growth factor-containing endosomes, which was restored by deleting one copy of APP gene (Salehi et al., 2006). Endosome slowing was correlated to their abnormal enlargement caused by Rab5 overactivation in the presence of excess APP β -C-terminal fragments (Kim et al., 2016). This raises the possibility that structural alterations of cargoes, particularly the enlarged size, may dramatically increase the force required for their transport, contributing to transport deficits. Another possibility is that excess Rab5 on endosomes slows the replacement with Rab7 that is required for the recruitment of retrograde motility apparatus. In a third line of evidence, using PSEN1 knockout mouse neurons, we found that retrograde motility of deacidified lysosomes was impaired (Lie and Nixon, submitted manuscript). High lysosomal pH induced aberrant Ca²⁺ efflux from lysosomal TRPML1 channels, which caused hyperphosphorylation of the dynein subunit DIC. These results revealed a mechanism relevant to AD, PD and other diseases involving lysosomal acidification deficit.

Impaired dynein-mediated retrograde transport and clearance of AVs have also been found in familial amyotrophic lateral sclerosis (fALS) (Xie et al., 2015) and Huntington's disease (HD) models (Wong and Holzbaur, 2014). In these models, dynein components were sequestered by disease-linked mutant proteins, including pathogenic Htt containing polyglutamine expansions (Gunawardena et al., 2003), as well as fALS-linked SOD1^{G93A} mutant (Xie et al., 2015). In addition, Nudel dephosphorylation required for processive dynein movement is prevented by the hyperactivation of cyclin-dependent kinase 5 (CDK5) in fALS (Klinman and Holzbaur, 2015). Further challenging the compromised dynein function in disease conditions, dynein activity is required for autophagic clearance of aggregate-prone proteins such as mutant Htt and synuclein (Ravikumar et al., 2005). Loss-of-function mutation of dynein heavy chain accelerated the onset and enhanced the severity of tremors in heterozygous HD mice (Ravikumar et al., 2005). Thus, the clearance of aggregate-prone proteins and lysosomal substrates in general, is increasingly vulnerable to the normal decline in dynein-dynactin interaction associated with aging (Kimura et al., 2007), and is further impacted by the interference of dynein function by disease-linked proteins. A more detailed consideration of the neuropathology of these diseases, however, prompts caution in generalizing the concept of impaired dynein-dynactin function, *exclusive of additional disease factors*, to the development of neuritic dystrophy or axonopathy

involving accumulations of the same cargoes. For example, unlike the pattern of dystrophy in AD which involves enormous AV-containing swellings, the pattern in HD and ALS is characterized by much less frequent axonal swellings, which contain predominantly large Htt aggregates in HD (Waelter et al., 2001) or aggregated forms of neurofilaments in ALS (Xiao et al., 2006). Thus, although dynein impairments may contribute significantly to pathogenesis in all cases, other aspects of the dysfunction of the pathogenic proteins or their associated organelles may be more critical. Collective results of different disease models suggest that combined effects of dynein dysfunction, decreased lysosomal efficiency and increased autophagic burden induced by both aging and various pathogenic factors, together contribute to the different patterns of endolysosomal failure found in AD, PD, HD and ALS.

4. Conclusions and perspectives

The lysosome system is a site of special vulnerability in aging and multiple neurodegenerative diseases across the age spectrum. Rapidly growing evidence for ameliorative effects of lysosome enhancement in animal models of these diseases not only establishes the therapeutic promise of targeting the lysosomal system, but also firmly establishes its crucial, and in many cases primary, contribution to the pathogenesis of these diseases. For instance, boosting autophagy-lysosomal function by mTOR inhibition or TFEB overexpression has shown varying degree of success in AD, PD and LSD models (Decressac et al., 2013; Majumder et al., 2011; Spampinato et al., 2013). Other promising strategies include increasing lysosomal hydrolase activity (Sun et al., 2008), enhancing lysosome acidification by acidic nanoparticles (Bourdenx et al., 2016; Lee et al., 2015) or cAMP (Coffey et al., 2014), as well as boosting retrograde axonal transport of endolysosomes (Xie et al., 2015). Taking advantage of our expanding knowledge of newly recognized lysosomal signaling functions, the neurodegenerative disease field is now better equipped to identify viable lysosomal targets for the development of disease modifying interventions.

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Competing interests

The authors declare no competing interests.

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