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Neuronal Lysosomes

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Abstract

Lysosomes support diverse cellular functions by acting as sites of macromolecule degradation and nutrient recycling. The degradative abilities of lysosomes are conferred by a lumen that is characterized by an acidic pH and which contains numerous hydrolases that support the breakdown of major cellular macromolecules to yield cellular building blocks (amino acids, nucleic acids, sugars, lipids and metals) that are transported into the cytoplasm for their re-use. In addition to these important hydrolytic and recycling functions, lysosomes also serve as a signaling platform that integrates nutrient and metabolic cues to control signaling via the mTORC1 pathway. Due to their extreme longevity, polarity, demands of neurotransmission and metabolic activity, neurons are particularly sensitive to perturbations in lysosome function. The dependence of neurons on optimal lysosome function is highlighted by insights from human genetics that link lysosome dysfunction to a wide range of both rare and common neurological diseases. How then is lysosome function adapted to the unique demands of neurons? This review will focus on the roles played by lysosomes in distinct neuronal sub-compartments, the regulation of neuronal lysosome sub-cellular localization and the implications of such neuronal lysosome regulation for both physiology and disease.

Keywords

lysosome; autophagosome; endosome; axon; dendrite; Alzheimer’s Disease; Hereditary Spastic; Paraplegia; mTORC1

Lysosomes degrade a broad range of macromolecules including: DNA, RNA, proteins, lipid membranes and carbohydrates. This catabolic activity allows cells to both clear unwanted materials as well as to generate nutrients in times of stress. Central to supporting such functions, lysosomes serve as a final destination for the secretory, endocytic and autophagic pathways (Figure 1). Lysosome biogenesis and ongoing replenishment of lysosome proteins depends on the secretory pathway through the endoplasmic reticulum and Golgi for the delivery of newly synthesized ion channels, transporters and luminal proteins including the

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diverse array of acid hydrolases that support lysosome-mediated degradative activity. Endosomes are critical for the delivery of both lysosomal proteins and substrates. To this end, endosomes act as an intermediate between the secretory pathway and lysosomes wherein trans-Golgi network derived vesicles containing newly synthesized proteins destined for lysosomes fuse with endosomes to support their subsequent delivery to lysosomes. Endocytosis and endosomal sorting also brings extracellular macromolecules to lysosomes. Furthermore, the late endosomal sorting of integral membrane proteins into intraluminal vesicles via the endosomal sorting complex required for transport (ESCRT) pathway is critical for the eventual lysosomal degradation of integral membrane proteins including receptors, ion channels and cell adhesion molecules (1). In parallel with the endocytic pathway, autophagy is a major source of lysosomal substrates wherein the membrane engulfment of cargoes such as protein aggregates and damaged organelles yields autophagosomes that must fuse with lysosomes in order for their contents to be degraded by lysosomal hydrolases (2). Thus, lysosomes do not function in isolation from other organelles but require ongoing delivery of both cargos and hydrolases from the endocytic and autophagic pathways. Lysosomes additionally make contacts with other organelles including the endoplasmic reticulum (ER) (3) and potentially mitochondria (4) that are thought to allow the non-vesicular transfer of lipids and calcium (5, 6).

Spatial Distribution of Neuronal Lysosomes

The interconnected relationships between lysosomes and other organelles pose particular challenges within the highly compartmentalized and spatially extended neuronal environment. Furthermore, the localized nature of distinct neuronal functions that depend on lysosomes require a precise distribution of lysosomes to specific sites within neurons and a potential need to redistribute lysosomes in response to ongoing changes in neuronal physiology.

Lysosomes have long been characterized as having a polarized distribution in neurons wherein they are most abundant in neuronal cell bodies, moderately present in dendrites and relatively rare in axons (7–9). This distribution pattern of neuronal lysosomes (Figure 2) raises questions about both the underlying mechanisms that control their movement and the possibility that distinct sub-populations of lysosomes might serve compartment specific functions. As for other organelles, microtubule-based motors play important roles in determining the transport of lysosomes into axons and dendrites (10). Interestingly, new data is beginning to emerge that further suggests compartment specific functions of neuronal lysosomes and underscores the importance of ensuring that lysosome position is matched to ongoing changes in neuronal demand.

Axonal Lysosome Biogenesis and Transport

Reports of the low steady state abundance of lysosomes in axons (7, 8) long resulted in limited research into functions of axonal lysosomes and the mechanisms controlling their abundance. However, more recent studies into autophagy in axons stimulated new interest on this topic. Time lapse imaging of autophagosome formation and transport revealed a tonically high rate of autophagy in distal regions of axons (11, 12) as well as the ability of

autophagosomes to form around acutely damaged axonal mitochondria (13). The formation of such autophagosomes likely represents an important step in preventing the accumulation of potentially deleterious old or damaged proteins and organelles in axons. However, autophagosomes must eventually fuse with lysosomes in order for their contents to be degraded. Rather than occurring in a single step by fusing with a nearby lysosome, the lysosome-mediated degradation of axonal autophagosome contents appears to happen via a maturation process whereby these axonal autophagosomes first fuse with endosomes and such fusion is a prerequisite for the initiation of dynein-mediated microtubule-dependent transport back towards the neuronal cell body (11, 14–16). These autophagosome-endosome hybrids (sometimes referred to as amphisomes) appear to mature into lysosomes as they make their retrograde journey (17). Indeed, they acquire proteins that typically define lysosomes such as LAMP1 and their retrograde transport is accompanied by their acidification (14, 16–18). However, these lysosomes may not mature to possess full degradative activity until they reach the neuronal cell body as they have only very low levels of multiple lysosomal proteases (19). Although mechanisms that limit luminal protease abundance and acidification in axonal lysosomes are not fully understood, some interesting clues have recently emerged. For example, neuronal lysosome acidification and function is dependent on presenilin 1 in a manner that may be independent from its γ-secretase proteolytic activity (20). Furthermore, it has been observed even in much smaller non-neuronal cells in culture that lysosomes at the cell periphery are less acidic and possess less degradative activity (21). These spatially distinct lysosome sub-populations were proposed to arise due the reduced efficiency of delivering newly synthesized proteins to lysosomes that are furthest from the trans-Golgi network that is concentrated in the perinuclear region. Such challenges in the delivery of newly synthesized lysosomal proteins are expected to be particularly relevant over the long distances encountered in neurons (22).

The connection between maturity state and retrograde axonal lysosome transport raises questions about how these organelles interact with molecular motors. Due to the polarized orientation of microtubules in axons where plus ends are pointed towards the axon tips, kinesins mediate outward/anterograde transport of axonal cargoes while the retrograde journey depends on dynein (23, 24). While there is not currently a complete understanding of how these maturing lysosomes are coupled to dynein for retrograde axonal transport, several proteins have been implicated in this process including: Rab7, RILP, JIP1, JIP3 and snapin (16, 17, 25–27). The degree to which these proteins function in sequential versus parallel pathways remains to be firmly established. However, the overall process of lysosome maturation in conjunction with retrograde transport implies the existence of distinct lysosome sub-populations and routes of delivery for integral membrane proteins such as LAMP1 versus luminal hydrolases as has been described in non-neuronal cells (21, 28). From a practical perspective, the maturation process whereby endosomes and autophagosomes acquire specific lysosome properties in a progressive manner raises challenges for the precise experimental distinction between these organelles. However, such concerns are largely mitigated by awareness that endosomes, autophagosomes and lysosomes are closely related components of a dynamic degradative pathway (Figure 1) and the use of multiple markers of these related organelles in experiments that investigate this pathway.

Evidence for the de novo assembly of axonal lysosomes via a maturation process furthermore comes from electron microscopy analysis of the consequences of local axonal transport blockade that revealed a much more robust enrichment for organelles with lysosome-like morphology on the distal compared to proximal side of the blockade (29). This selectively high abundance of lysosomes distal to the block implies that morphologically distinct lysosome precursors are shipped into axons, assembled distally into lysosomes and then robustly transported in the retrograde direction.

The physiological significance of spatially restricting lysosome maturation and the degradation of cargoes captured within axonal endosomes and autophagosomes to the somatodendritic region of neurons is not yet clear but could help to recycle key nutrients such as amino acids close to the major site of protein translation in the neuronal cell body. Alternatively, the extreme lengths of axons could pose a challenge for the delivery of active lysosomal proteases as such journeys could take hours to days during which time such enzymes might digest themselves as well as any cargoes with which they were co-packaged. Answering such questions will require a better understanding of the mechanisms that control axonal lysosome transport and a careful analysis of the consequences of mislocalizing lysosomes on neuronal physiology.

Recent studies have begun to shed light onto new mechanisms that support the transport of lysosomes by kinesin motors. Building on observations from non-neuronal cells that established a critical role for the small GTPase Arl8 in the kinesin-mediated delivery of lysosomes towards the plus ends of microtubules at the cell periphery (30), Arl8 and its upstream regulator known as BORC were recently shown to play an important role for regulating anterograde axonal transport of lysosomes (31). BORC is an octomeric protein complex that is essential for the recruitment of Arl8 to lysosomes (32), possibly by functioning as a guanine nucleotide exchange factor for Arl8 (33). In *C. elegans*, BORC-dependent regulation of Arl8 is also important for the axonal transport of synaptic vesicle precursors (33, 34). However, the precise relationship between transport of synaptic vesicle precursors and lysosomes as well as the evolutionary conservation of such mechanisms remains to be established.

Axonal Lysosomes and Alzheimer’s Disease

Questions concerning axonal lysosome biogenesis and transport have taken on new importance in light of data linking them to Alzheimer’s disease. From the earliest electron microscope observations of Alzheimer’s disease amyloid plaques, it was apparent that extracellular protein aggregates (later identified as amyloid fibrils) are surrounded by swollen neurites that are filled with organelles with lysosome-like morphology (35), a finding that has been solidified and elaborated on in a more recent study (36). Such lysosome filled neuritic swellings also arise at amyloid plaques in mouse models of Alzheimer’s disease where they have been shown to correspond predominantly to axons and the lysosomes within them are distinct from those found in neuronal cell bodies based on their relatively low content of multiple lysosomal hydrolases(19, 37, 38).

The altered distribution of axonal lysosomes that arises in Alzheimer's disease raise urgent questions about how axonal lysosome abundance is regulated. An important role for JIP3 (also known as MAPK8IP3) in regulating axonal lysosome abundance comes from the discovery of loss-of-function mutations in the JIP3 gene in multiple organisms that result in the ectopic axonal accumulation of lysosomes (39–41). While different models have been proposed to account for this JIP3 KO phenotype, studies in vertebrates have supported a model wherein JIP3 plays a critical role in promoting the efficient retrograde transport and maturation of lysosomes (39, 41, 42). Interestingly, in primary cultures of mouse JIP3 KO neurons, lysosomes are strikingly abundant in axonal swellings that are very similar to those that occur around amyloid plaques in Alzheimer's disease but which do not require amyloid plaques for their formation (41). In support of a disease relevance of axonal lysosomes, their accumulation in JIP3 KO neurons was accompanied by enhanced APP processing, elevated Aβ peptide levels and a worsening of amyloid plaque pathology when crossed to a mouse model of Alzheimer's disease (41). JIP3 is a large (>1000 amino acids) protein that interacts with both dynein and kinesin motors as well as with multiple small GTPases (43, 44). JIP3 may thus have a function that is similar to the RILP adaptor protein that supports dynein-mediated transport of lysosomes by acting as a bridge between Rab7 on the surface of endolysosomes and the dynein motor. The severe axonal lysosome defects in JIP3 KO neurons along with the Alzheimer's disease implications support the need for more studies to test this model and to define the specific mechanisms whereby JIP3 and other factors support lysosome transport in axons.

The importance of retrograde axonal transport of lysosomes in limiting opportunities for amyloidogenic APP processing in Alzheimer's disease is also supported by studies of the snapin gene (45). Snapin has been proposed to directly connect late endosomes/lysosomes to dynein and thus support their retrograde movement along axonal microtubules (25). Studies of mouse snapin KO neurons strongly support a broad role for snapin in supporting neuronal lysosome homeostasis (25). However, subsequent to its characterization as a regulator of retrograde axonal endolysosome transport, snapin was identified as a component of BORC (32), the complex that is required for Arl8-mediated transport of lysosomes into axons (31). As snapin is now implicated in both anterograde and retrograde transport of axonal lysosomes, future studies are required to revisit the functions of snapin and to further define the specific contributions of each of these pathways to the phenotypes arising from snapin mutations.

Insights Into Neuronal Lysosomes From Human Genetics

A major factor that is likely to predispose neurons to be sensitive to perturbations in the transport of lysosomes is the exceptional distance over which neuronal lysosomes must be transported. The challenges of transporting organelles over great distances are particularly striking in the extremely long axons of upper and lower motor neurons and may contribute to risk for diseases that preferentially affect these neurons such as hereditary spastic paraplegia (HSP). HSPs represent a collection of human diseases that arise from mutations in more than 50 genes (referred to as SPG genes for their role in spastic paraplegia) that overwhelming affect the motor neurons that innervate distal extremities (46). Within the large constellation of SPG gene mutations that affect diverse aspects of cytoskeleton

organization and axonal transport of organelles are multiple genes that more narrowly highlight the importance of neuronal lysosome subcellular localization and function. These include SPG11 and SPG15 (also known as spatacsin and ZFYVE26/spastizin respectively) genes that encode clathrin coat-like proteins that interact with the lysosome-localized AP-5 complex and are implicated in membrane tubule formation from lysosomes and the recovery of membrane proteins following autophagosome-lysosome fusion (47, 48). More recent studies further document a reduction in the abundance of neuronal lysosomes and autophagic defects in SPG11 mutant mice (49, 50). In addition to representing the most common cause of autosomal recessive HSP, SPG11 mutations can also cause amyotrophic lateral sclerosis (ALS, another motor neuron disease) as well as a form of Charcot-Marie-Tooth disease (51, 52), a peripheral neuropathy that affects sensory neurons that also have very long axons.

In addition to SPG11 and SPG15, protrudin (SPG33) has connections to both HSP and lysosomes. Protrudin is an endoplasmic reticulum localized integral membrane protein that reaches out to make contact with late endosomes/lysosomes by binding to the PI3P lipid within their membranes via its FYVE domain (53). At such points of membrane contact between the endoplasmic reticulum and lysosomes, protrudin facilitates the formation of a protein complex between Rab7 (a small GTPase), FYCO1 (a Rab7 effector) and kinesin 1 that supports the plus-end directed movement of lysosomes on microtubules and their delivery to the cell periphery (53). Although insights into the role for protrudin at ER-lysosome contacts have largely been derived from studies of non-neuronal cells, high resolution reconstruction of axonal organelles and their contacts have recently documented contacts between late endosomes/lysosomes with the ER in neurons (54). The general importance of ER-endolysosome contacts in HSP is more broadly supported by the recent characterization of 3 additional SPG genes that include spastin (SPG4, a microtubule severing protein), strumpellin (SPG8, involved in recycling of proteins from endosomes) and REEP1 (SPG31, a protein that shapes ER tubules) to have roles at contacts between late endsosomes and the ER (3). In addition to promoting transport of late endosomes and lysosomes, such sites might also serve as sites of lipid transfer to and from the ER (6). Consistent with the importance of such functions, lysosomal lipid accumulation occurs in SPG11 mutant mice (55).

Distinct lysosome functions and regulation have been reported for other specific types of neurons. These include a role for lysosome exocytosis in the axon outgrowth of sympathetic neurons (56) that might be dependent on the protudin-dependent control of kinesin-mediated lysosome transport (53). Meanwhile, a role for axonal lysosomes as sites of TRPVA1-mediated calcium release in dorsal root ganglia (DRG) neurons defines a novel function for axonal lysosomes in sensory neurons in the regulation of Ca2+ signaling (57). Collectively, all of the abovementioned insights into known mechanisms that control the transport, abundance and function of axonal lysosomes as well as the clues coming from hereditary spastic paraplegia genetics emphasize the importance of axonal lysosomes to neuronal health and physiology. This data furthermore points to complex interactions between lysosomes, cytoskeletal motors and the endoplasmic reticulum that requires further elucidation.

In addition to contacts between lysosomes and the ER, emerging evidence from non-neuronal cells has identified lysosome-mitochondria contacts containing the yeast Vps13 protein (4, 58) that are also likely to be important for the maintenance of lysosome homeostasis in neurons. Indeed, neurodegeneration and protein degradation defects in were observed in a *Drosophila* Vps13 mutant (59). Furthermore, future discoveries of neuronal functions for contacts between lysosomes, mitochondria and potentially other organelles can be predicted based on human genetics studies that have linked human Vps13 homologues (of which there are 4) to neurological diseases. More specifically, Vps13a mutations cause a neurodegenerative disease known as acanthocytotic chorea (60). Vps13b mutations have been identified in Cohen syndrome, a disease with complex phenotypes affecting multiple organs and which also includes a cognitive component (61). Finally, Vps13c mutations cause a Parkinson's-like disease (62) and further support the likely importance of membrane contact sites between lysosomes and other organelles in neurons. Elucidation of the specific functions conferred by Vps13 isoforms and their relevance to neuronal cell biology represents an exciting new field that is expected drive further research into contacts between lysosomes and other organelles. These specific examples of rare mutations in lysosome-related genes that cause human neurodegenerative disease are part of a much larger spectrum of mutations and genetic variants that either cause, or increase risk for, a wide range of neurodegenerative diseases that include Alzheimer's disease, Parkinson's disease, frontotemporal dementia and amyotrophic lateral sclerosis (63–66). Such insights from human genetics strongly support the need for a better understanding of how lysosome function is adapted to meet the unique demands of the specific neuron subtypes that are affected by these diseases.

Presynaptic activity regulates axonal flux of cargos to lysosomes

As outlined above, axonal lysosomes are dynamically controlled and intimately connected to other organelles. These lysosomes must also adapt to meet axonal demands that are triggered by neuronal activity such as the ESCRT-dependent turnover of presynaptic proteins in response to neuronal stimulation (67, 68). This Rab35-dependent pathway helps to ensure the clearance of old or damaged synaptic vesicle proteins. The potential importance of such regulated turnover of synaptic vesicle proteins is illustrated by the neurological consequences of human mutations in TBC1D24, the Rab35 GAP (69, 70). In addition to endosomal sorting mechanisms for the selective clearance of synaptic vesicle proteins, presynaptic autophagy also promotes the clearance of synaptic vesicles in a manner that is depends on local dynamic interactions between synaptic vesicle proteins and autophagy regulators (71–73). The critical relationship between presynaptic protein turnover and lysosome function is further supported by the discovery that presynaptic defects arising in lysosome storage diseases are a major contributor to neurodegeneration (74). Likewise, mutations in Rab7, a GTPase with major roles in late endosome maturation and transport, cause Charcot-Marie-Tooth disease Type 2B, an axonal peripheral neuropathy (75). Important neuronal Rab7 functions are linked to synaptic activity by observations that neurodegeneration in *Drosophila* Rab7 mutants was suppressed by limiting neuronal activity (76). The accumulation of axonal lysosomes in response to epileptic activity in mice further suggests the existence of mechanisms to redistribute neuronal lysosomes in a stimulus-

dependent manner that potentially matches their function to ongoing changes in demand (77).

Dendritic Lysosomes and Synaptic Plasticity

In contrast to axonal lysosomes, where much of the research has focused on mechanisms that support transport over long distances, much of our understanding for specialized functions of lysosomes in dendrites comes from studies of receptor down-regulation in support of synaptic plasticity but also converges on questions related to local delivery of lysosomes to sites of demand.

In a stimulus dependent manner, AMPA and kainate type glutamate receptors are endocytosed, ubiquitinated and subjected to endosomal sorting processes that either direct the internalized receptors towards recycling endosomes for plasma membrane reinsertion or to lysosomes for degradation (78–82). This endosomal trafficking leading to lysosomal destruction of AMPA receptors is physiologically important for AMPA receptor down regulation in the contexts of plasticity and pathology (83–85). In parallel, evidence has also been presented in support of a role for autophagy in the down-regulation of AMPA receptors in long term depression (86).

A central role for lysosomes in the degradation of integral membrane proteins such as glutamate receptors is not surprising due to the major role played by lysosomes in the turnover of signaling receptors and other integral membrane proteins that occurs across cell types. However, it has long been a mystery about where in neurons dendritic endosomal cargoes such as AMPA receptors eventually end up in lysosomes for degradation. Do they have to travel long distances back to the cell body? Or are lysosomes targeted to the dendritic sites where their activities are required. Interestingly, it was recently shown that stimulation of NMDA and AMPA receptors increases the abundance of lysosomes within dendritic spines and further evidence was presented that supports a role for local degradation of internalized AMPA receptors at such sites (87). In addition to supporting the local turnover of glutamate receptors, lysosome exocytosis and subsequent cathepsin B-dependent remodeling of the extracellular matrix was recently shown to regulate the plasticity of dendritic spine morphology (88). Collectively, these studies raise important new questions about the signal transduction and membrane trafficking mechanisms that link synaptic activity to the delivery and/or retention of lysosomes in dendritic spines.

In addition to the emerging ideas concerning spatial control of lysosomes responsible for ionotropic glutamate receptor down-regulation, the abundance of ionotropic receptors for other neurotransmitters such as GABA are also likely to be controlled by lysosome-mediated degradation (89). Likewise, it is well established from work in non-neuronal systems that lysosomes play an important role in controlling the abundance of receptors that are of great relevance to neurons such as G-protein coupled receptors (90). Beyond the acute topic of neurotransmission, lysosomes contribute to the overall architecture of dendrites as revealed by abnormal dendritic arborization in *Drosophila* mutants for an endolysosomal transporter (91). Dendritic lysosome abundance also undergoes striking changes during the development of specific mammalian neuron subtypes [for example during the second postnatal week in

rat Purkinje cells (92)]. Based on these intriguing observations, more investigation is required for the comprehensive understanding of the underlying mechanisms and physiological significance of the compartmentalization and regulation of lysosome functions in dendrites.

Neuronal Lysosomes and mTORC1 Signaling

Multiple studies in non-neuronal cells have identified the surface of lysosomes as the intracellular site where diverse signals converge to activate the kinase activity of mTORC1 (93, 94). This activation critically depends on the nutrient-sensitive Rag GTPases that recruit mTORC1 to lysosomes (95). The mTORC1-Rag interaction is thought to bring mTOR into proximity of the Rheb GTPase that activates mTOR in response to growth factor and energy-dependent signals (96). In non-neuronal cells, these coordinated actions of Rag and Rheb GTPases ensure that mTORC1 is selectively activated under conditions that are favorable for cell growth and proliferation. However, this mechanism also renders mTORC1 signaling dependent on local lysosome availability and raises questions about the regulation of mTORC1 in mature neurons where major growth is not a priority but where mTORC1 signaling instead controls multiple aspect of neuronal physiology.

This leads to questions about whether neuron-specific signals converge on the Rag and Rheb proteins to control mTORC1 activation under physiological contexts where neuronal mTORC1 signaling is important, such as in the regulation of synaptic plasticity or axon growth (97–105)? If so, does such signaling require the local availability of the lysosomes on which such GTPases reside? These questions are important because even though mTORC1 signaling affects multiple compartments within neurons including both axons and dendrites (97–105), neuronal lysosomes are not uniformly distributed (Figure 2). In fact, as described above, lysosomes are most prominently found in neuronal cell bodies and proximal dendrites (Figure 2). This pattern has also been long documented in the intact brain (7–9). Thus, a role for lysosomes as platforms for the activation of mTORC1 raises lysosome subcellular localization challenges within the highly compartmentalized intracellular environment of neurons. This contrast between the restricted distribution of lysosomes and the many sites of mTORC1 signaling suggests that either distinct pools of lysosomes are dynamically targeted to sites of neuronal mTORC1 action or that alternative mechanisms to support localized mTORC1 activation might occur in neurons.

The genetics of several human neurological diseases strongly supports the importance of neuronal mTORC1 regulation. The Nprl2, Nprl3 and DEPDC5 proteins form the GATOR1 complex which has GTPase activating protein (GAP) activity towards the lysosome-localized RagA/B proteins and which thereby suppresses mTORC1 activity when amino acid levels are low (106). Human loss-of-function mutations in the genes encoding these GATOR1 subunits result in mTORC1 hyperactivation and cause familial focal epilepsies accompanied by brain malformations (107–109). Additional human mutations causing epilepsy and/or neurodevelopmental defects have been identified in SZT2, a gene that was originally identified in mice due to mutations that lowered seizure susceptibility, and which is now known to encode a component of the KICSTOR complex that plays a critical role in recruiting GATOR1 to lysosomes (110–114). While impaired developmental processes

likely contribute to the neurological consequences of GATOR1 and KICSTOR mutations, SZT2 is most highly expressed in the mature mouse brain and spinal cord, suggesting the existence of important neuronal functions that extend beyond a developmental context (110). Indeed, Rag GTPases are also robustly localized to lysosomes in neurons of the mature mouse brain (19).

Mutations in the human TSC1 and TSC2 genes result in mTORC1 hyperactivation and cause tuberous sclerosis, a disease that is characterized by a variable constellation of symptoms that commonly includes neurological problems including epilepsy, intellectual disabilities and autism (115–117). TSC1 and TSC2 proteins along with a third protein, TBC1D7, form a lysosome-localized protein complex that inhibits mTORC1 signaling by acting as a GTPase activating protein (GAP) for the Rheb GTPase (118–122). While considerable evidence supports neurodevelopmental roles for these proteins in the development of tuberous sclerosis (123), it is also well established that TSC-dependent control of mTORC1 signaling is an important regulator of protein translation in mature neurons and is involved in the ongoing regulation of post-synaptic density composition and dendritic spine dynamics (124, 125). These critical neurological functions for TSC proteins in the regulation of mTORC1 signaling coupled with the central role played by lysosomes as the subcellular site for scaffolding this signaling pathway emphasize the importance of elucidating how lysosome abundance and distribution is controlled within neurons.

Conclusions

Observations from both model organisms and humans have focused attention on neuronal lysosomes and the underlying molecular mechanisms that match their functions to the unique demands of neurons. Of particular interest is the accumulating evidence that lysosomes are dynamically distributed throughout neuronal sub-compartments and perform a broad range of hydrolytic and signaling functions that are of relevance to neuronal physiology and pathophysiology. Beyond questions related to specific genetic diseases, lysosome related genes have also recently been implicated in healthy aging of the brain (126). Moving forward, there is clearly an urgent need for efforts to discover and define new aspects of lysosome cell biology and to elucidate how the varied functions of lysosomes are dynamically adapted to meet neuronal demand.

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Highlights

- Lysosomes contribute to diverse aspects of neuronal physiology through both degradative and signaling functions.
- Due to their large size and highly polarized morphology, neurons are highly dependent on mechanisms that transport lysosomes to sites of demand.
- A wide range of human neurological diseases arise due to defects in lysosome function.

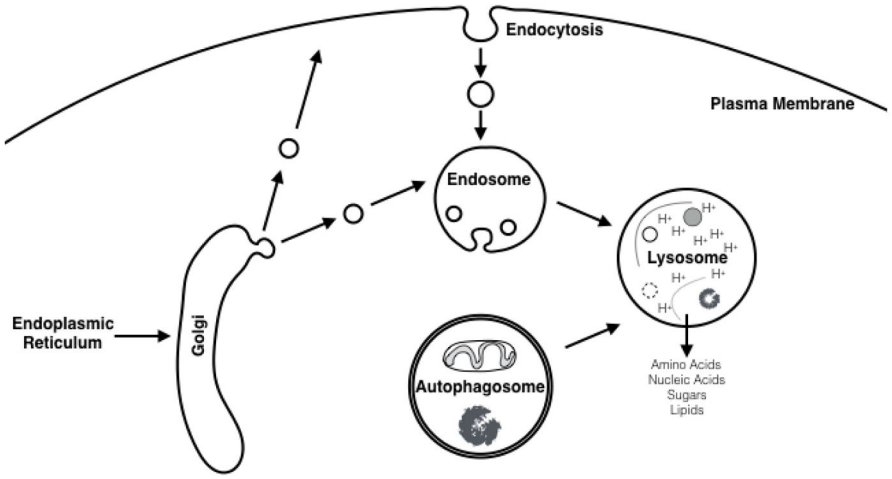

Figure 1.

Schematic representation of the dependence of lysosomes on membrane traffic from the secretory pathway (ER and Golgi) to endosomes for the delivery of proteins supporting lysosome biogenesis and maintenance. Meanwhile, the endocytic and autophagy pathways both deliver substrates for lysosomes to degrade. Although all of these organelles can be found in close proximity in neuronal cell bodies, the Golgi is not found in axons. Meanwhile autophagosomes form robustly in distal parts of neurons that can be separated from the cell body by more than a meter in the longest human neurons. This raises challenges for the ability of lysosomes to receive newly synthesized enzymes from the secretory pathway in order to mediate degradative functions at the most distal sites within neurons.

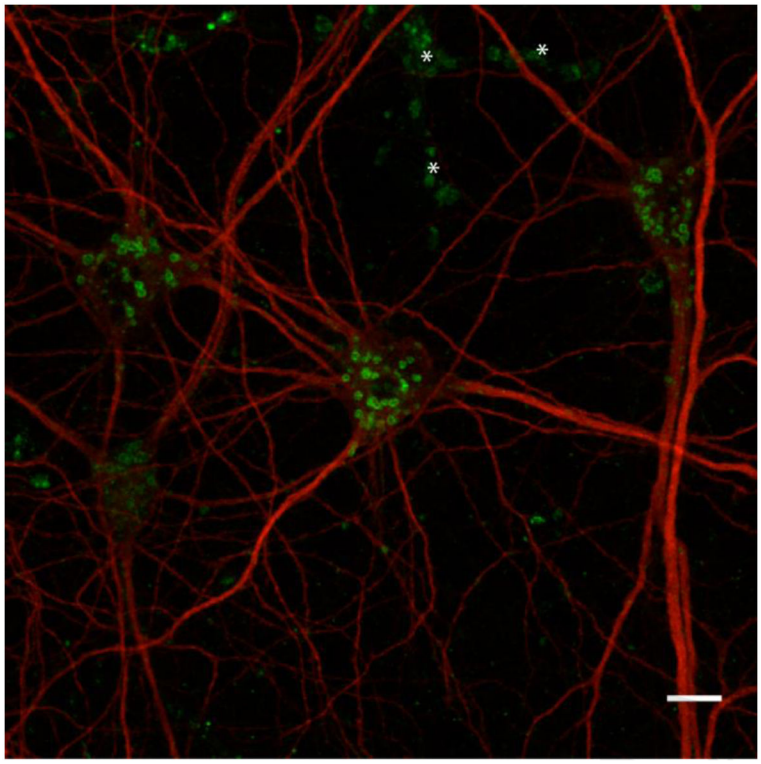

Figure 2.

Confocal image of lysosomes (LAMP1 signal, green) in mouse cortical neurons in culture along with MAP2B staining (red) which labels microtubules of neuronal dendrites. The asterisks indicate the position of non-neuronal lysosome signals arising from underlying glial cells. Although LAMP1 staining is commonly used to define lysosome distribution, due to the close relationship between lysosomes and other organelles of the secretory and endocytic pathways (Figure 1), the use of antibodies against multiple lysosomal proteins, including luminal hydrolases, is advisable for the definitive lysosome identification (Scale bar = 10 μm).