Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Neuronal autophagy and intercellular regulation of homeostasis in the brain

Aditi Kulkarni[1], Jessica Chen[1] and Sandra Maday

Neurons are particularly dependent on robust quality control pathways to maintain cellular homeostasis and functionality throughout their extended lifetime. Failure to regulate protein and organelle integrity is linked to devastating neurodegenerative diseases. Autophagy is a lysosomal degradation pathway that maintains homeostasis by recycling damaged or aged cellular components. Autophagy has important functions in development of the nervous system, as well as in neuronal function and survival. In fact, defects in autophagy underlie neurodegeneration in mice and humans. Here, we review the compartment-specific dynamics and functions for autophagy in neurons. Emerging evidence suggests novel pathways for the intercellular coordination of quality control pathways between neurons and glia to maintain homeostasis in the brain.

Address
Department of Neuroscience, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

Corresponding author: Maday, Sandra (smaday@pennmedicine.upenn.edu)
[1] These authors contributed equally.

Current Opinion in Neurobiology 2018, **51**:29–36

This review comes from a themed issue on **Cellular neuroscience**

Edited by **Juan Burrone** and **Erika Holzbaur**

https://doi.org/10.1016/j.conb.2018.02.008

Introduction

Maintaining the quality of the proteome and organelles is a point of vulnerability for neurons. In fact, the accumulation of misfolded protein is a defining hallmark for the progression of various neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Huntington's, Parkinson's, and Alzheimer's diseases [1]. A significant risk factor for all of these diseases is aging, which likely reflects the challenges neurons face to remain functional for so long. Neurons must perform specialized functions responsible for sensory perception, thought, and behavior. They communicate by firing electrical impulses at rates up to ~50 impulses per second [2], and must sustain this activity for a lifetime of ~80–90 years! As a consequence, neuronal proteins and organelles are vulnerable to overuse and damage [3,4]. Being post-mitotic, neurons cannot simply discard dysfunctional cellular components through the process of cell division. Thus, neurons require robust quality control mechanisms to maintain homeostasis and support their long-term viability and functionality.

Autophagy is a lysosomal degradation pathway that maintains cellular homeostasis by degrading and recycling cellular components [5–7]. In this process, autophagic substrates (e.g. proteins and organelles targeted for destruction) are sequestered within an autophagosome organelle and shuttled to lysosomes for degradation (Figure 1a). Degradation products are then exported from lysosomes to fuel new biosynthesis. Autophagy provides a constitutive mechanism to turnover and replenish cellular components, as well as a response to cellular stress such as nutrient deprivation, organelle damage, protein aggregation, and disease [8,9].

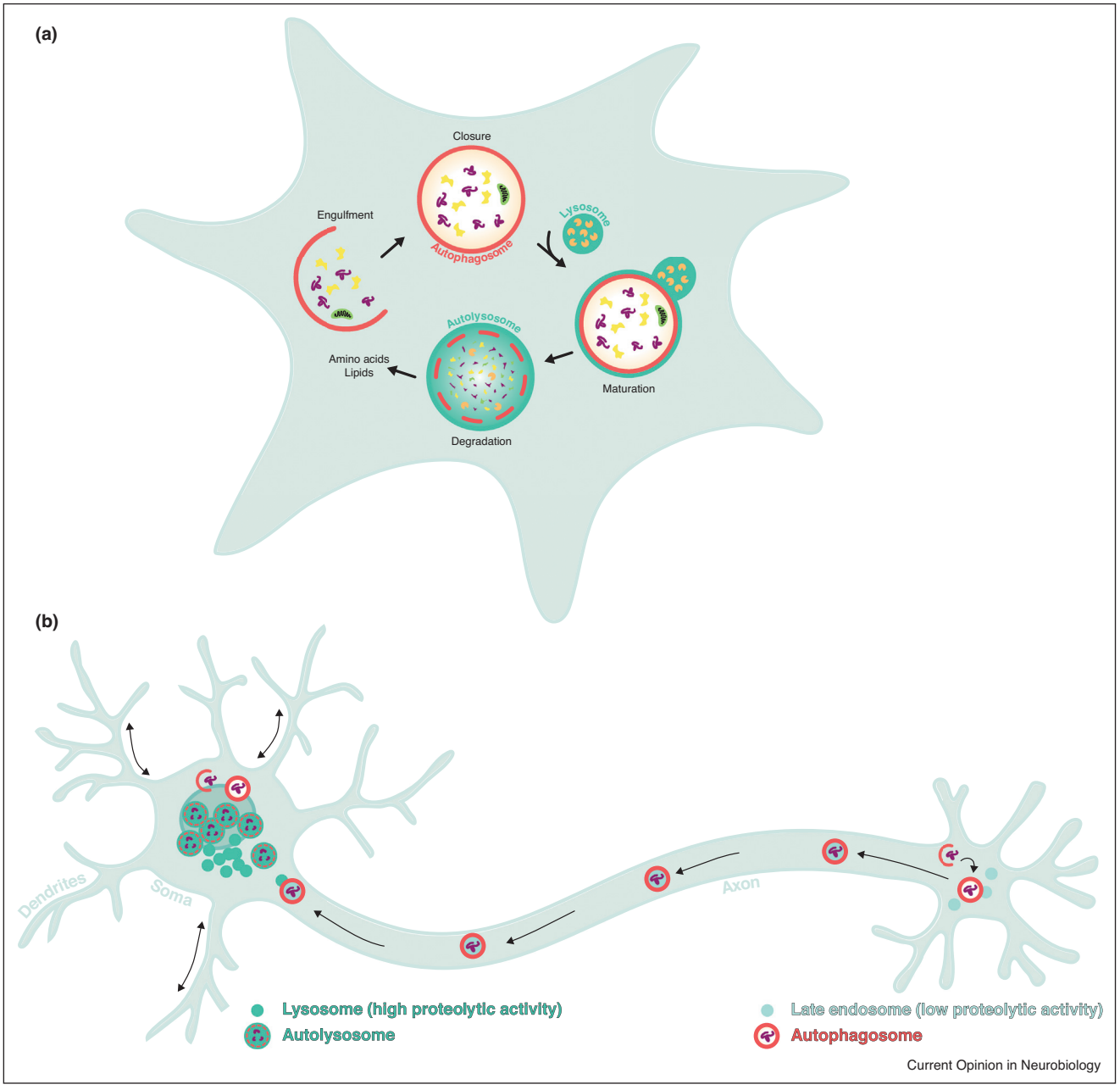
Autophagy is critical for neuronal homeostasis and survival [10–12]. Neural-specific depletion of genes required for autophagy is sufficient to cause axon degeneration and neuron death in mice [13,14]. Neuron loss is associated with an increase in ubiquitin-positive protein aggregates [15,16], indicating the importance of autophagy in the constitutive surveillance of proteome quality in neurons. Further, mutations in several key autophagy proteins have been linked to the progression of neurodegenerative disease in humans [17••,18,19], underscoring the essential role of autophagy in protecting neuronal health. Consequently, stimulating autophagy in neurons provides therapeutic value and has been shown to reduce neurotoxicity in models of ALS [20].

Here, we review the molecular basis for autophagy in each compartment of the neuron, comparing the axon, dendrites, and the soma. We focus on how compartment-specific dynamics of autophagosomes may facilitate their function. We then explore unconventional mechanisms for regulating neuronal autophagy, and the emerging contributions of non-canonical, intercellular pathways between neurons and glia in coordinating homeostasis in the brain.

Pathways for neuronal autophagy

Neurons have an elaborate morphology with highly branched dendritic arbors, and an axon that can reach up to a meter in length in humans. This complex architecture presents a logistical challenge for managing protein and organelle integrity at sites distant from the cell

Figure 1



Mechanisms of neuronal autophagy. **(a)** Schematic of autophagy. Autophagic substrates are packaged into autophagosomes which fuse with lysosomes to form a degradative autolysosome. **(b)** Pathway for autophagy in neurons. Axonal autophagosomes originate in the distal axon and travel to the soma. Following formation, autophagosomes fuse with late endosomes in the distal axon, and mature into degradative autolysosomes as they travel toward the proximal axon and soma where lysosomes are concentrated. Autophagosomes also form locally within the soma, and can migrate into dendrites to facilitate post-synaptic functions.

body where biosynthetic and degradative activities are concentrated. Insights into how autophagy is suited to each compartment of the neuron comes from tracking the spatiotemporal dynamics of a GFP-labeled autophagosome marker, LC3 [21,22].

In the axon, autophagosomes undergo a very striking processive and primarily unidirectional motility toward the soma (Figure 1b) [23–27]. Retrograde autophagosomes originate predominantly in the distal end of the axon [23,24] by recruitment of core autophagy

proteins (e.g. Atg5 and Atg13) to specific sites of the endoplasmic reticulum [25]. While the fundamental process of autophagosome formation utilizes core machinery conserved from yeast, neuron-specific proteins regulate rates of autophagosome biogenesis in pre-synaptic terminals [28–31]. Following formation, distal autophagosomes fuse with late endosomes [24,26], an event which may stimulate their journey toward the soma (Figure 1b) [32,33]. As autophagosomes travel from the distal axon to the soma, they mature into degradative autolysosomes (Figure 1b) [24,26]. Upon entry into the soma, autophagosomes are confined to the somatodendritic region and prevented from re-entering the axon [34••], potentially involving sorting mechanisms at the pre-axonal exclusion zone [35], the axon initial segment [36], or both. This compartmentalization likely facilitates their maturation into autolysosomes by promoting fusion with resident degradative lysosomes concentrated in the soma [26,34••,37••], and may ensure efficient recycling of biosynthetic building blocks to primary sites of protein synthesis.

This retrograde pathway for axonal autophagy provides a mechanism to deliver cargo from distal sites in the axon to the soma for degradation. Thus, the neuron has evolved mechanisms to override the spatial challenges of coordinating autophagy over the large distance of the axon. Whether this pathway represents constitutive, non-selective turnover of cellular components, or selective degradation of targeted substrates, or both, is unclear. Retrograde axonal autophagosomes contain cytosolic and organelle cargoes [24] that may balance the degradation of aging axonal components with the synthesis of new material supplied from the soma. Distal autophagy also likely plays a key role in quality control at the synapse, a site where cellular components are overused and prone to damage [3,4]. In fact, loss of autophagy impacts various aspects of synaptic development, maintenance, and function [38••,39–42]. Further, synaptic activity induces autophagy in pre-synaptic compartments [29,30,43], and pre-synaptic autophagy may in turn regulate neurotransmission by controlling synaptic vesicle number [31,42].

Recent work has shown that the axon may have unique and specialized machinery that functions in the selective autophagy of ubiquitinated substrates, which are important for axon guidance during development of the nervous system [44••]. Further, loss of autophagy has been linked to defects in axonal outgrowth [38••,45,46]. Together, these findings point toward a putative role for autophagy in the migrating growth cone essential for establishing proper connectivity of the brain.

Retrograde pathways for axonal autophagy may also perform non-canonical functions in the delivery of neurotrophin-mediated signaling information from the distal axon to the soma [47]. In contrast, autophagy can also be executed locally within the axon in response to induced organelle damage [48]. Future work will need to clarify the spatiotemporal pathways for axonal autophagy in constitutive surveillance versus responses elicited during stress.

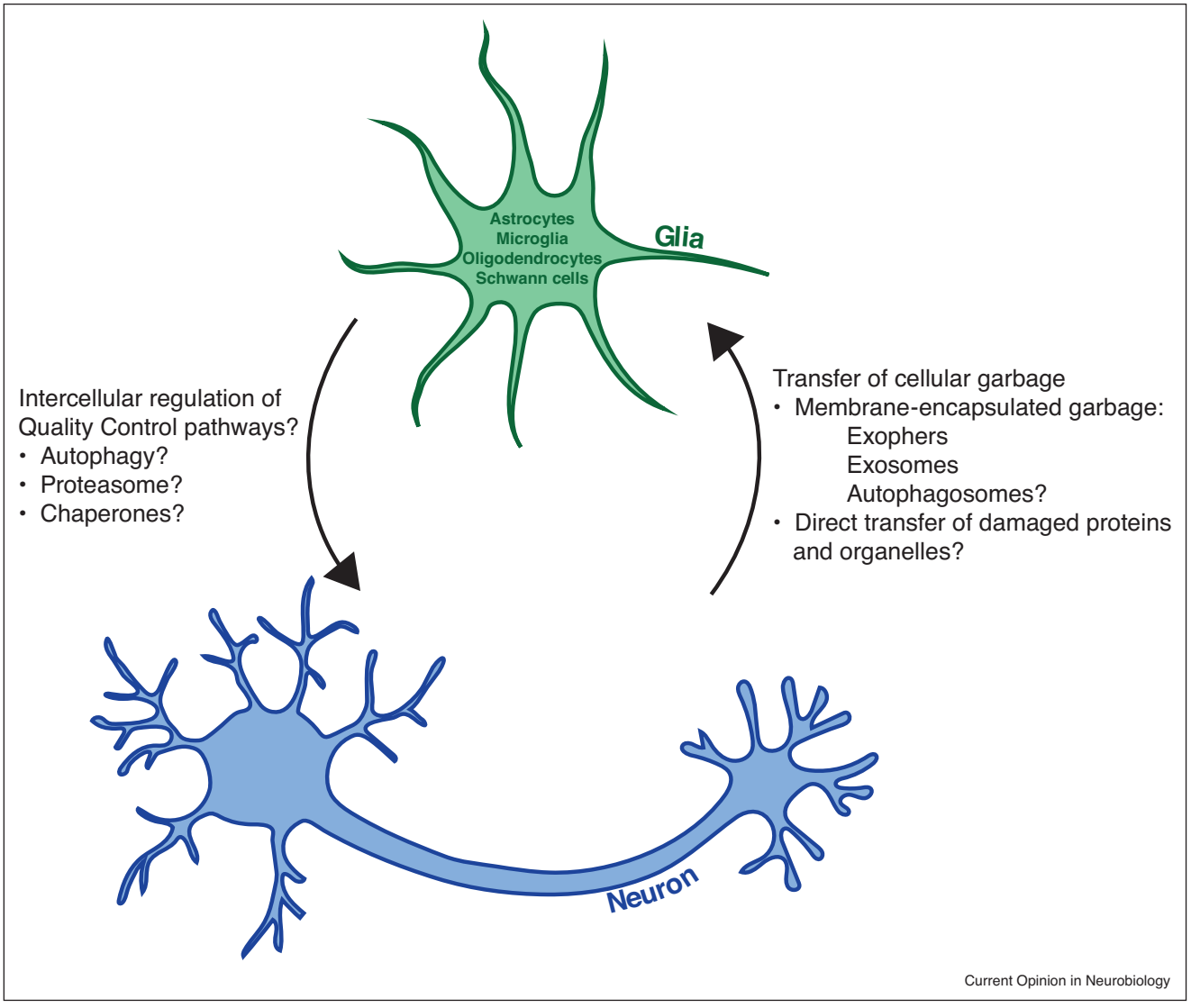
In the soma, autophagosomes are sourced from the axon, as well as generated locally [34••]. Autophagosome biogenesis in dendrites is limited under basal conditions of growth *in vitro* [25]. In response to enhanced synaptic activity, however, autophagosome density in dendrites increases either by local biogenesis or recruitment from the soma [49]. Unlike the vectorial movements exhibited by autophagosomes in the axon, autophagosomes in dendrites undergo bidirectional motility, or oscillate within a confined region along the dendritic shaft [25]. These fundamental differences in autophagosome motility likely reflect compartment-specific distinctions in microtubule orientation, that is, uniform polarity in axons and mixed polarity in dendrites [50,51]. Further, these differences in autophagosome motility may enable key functions uniquely tailored to the demands of each neurite compartment. In contrast to pre-synaptic autophagy, less is known about the function of autophagy in post-synaptic compartments. Post-synaptic autophagy may function in developmentally regulated pruning of spines; defects in this process are associated with autism-like disorders [41]. Autophagy also modulates synaptic plasticity through the degradation of post-synaptic AMPA receptors [49], and has recently been shown to impact learning and memory in mice [52,53•].

Taken together, autophagy performs diverse and compartment-specific functions in neurons. These functions may depend on neuron age and can be specific to neuron-type [38••]. Thus, the function of autophagy in neurons may evolve to meet the demands of a developing and maturing nervous system. Additionally, the complexity of autophagic activity in the brain may be further revealed during conditions of stress. In fact, different regions of the brain regulate autophagy uniquely in response to nutrient deprivation [53•]. Furthermore, distinct roles for autophagy have been reported during the onset versus progression of neurodegenerative disease [40].

Regulation of neuronal autophagy by neighboring glia?

How is autophagy regulated in the brain where neurons are surrounded by glia? Glia represent an overwhelming ~90% of the cells in the brain, and are key regulators of neuronal homeostasis and function. Glia influence many aspects of neuronal development, metabolism, synaptic function, and repair after injury. During conditions of stress, glia may provide 'care packages' in the form of exosomes to neurons containing mRNA and translation machinery [54–56]. Further, alterations in neuron–glia communication are a significant contributing factor to the progression of neurodegeneration [57–59,60•]. Thus, do glia impact neuronal autophagy (Figure 2)?

Figure 2



Coordination of quality control pathways between neurons and glia that may facilitate neuronal function and survival. Glia may impact various branches of the endogenous quality control machinery in neurons. Additionally, unconventional pathways may shuttle cellular garbage from neurons to glia.

Surprisingly, the role of neuron–glia interactions in regulating autophagy in the brain is a nascent line of investigation. Preliminary evidence supports the possibility of non-cell autonomous regulation of autophagy by astrocytes. Conditioned media generated by astrocytes derived from ALS patient iPSCs decreases autophagy in HEK293T cells [61]. While patient iPSC-derived astrocyte conditioned media is toxic to iPSC-derived motor neurons, direct effects on neuronal autophagy need to be examined [61]. Non-cell autonomous regulation of neuronal autophagy by glia has been examined in models studying HIV-associated dementia [62]. Conditioned media extracted from microglia infected with simian immunodeficiency virus (SIV) decreases autophagic activity in primary cortical neurons [62]. SIV-infected microglial supernatant also decreases neuronal survival, and activation of neuronal autophagy abrogates this neurotoxicity [62]. Future experiments will need to examine the effects of glial-conditioned media on neuronal autophagy in the absence of SIV infection. In other studies, astrocyte-specific expression of a redox-sensitive transcription factor, Nrf2, decreases neurotoxicity in a mouse model of Parkinson's disease expressing mutant α-synuclein A53T specifically within neurons [63]. The mechanisms underlying this neuroprotective effect may involve glial-mediated restoration of autophagic flux in neurons to promote α-synuclein A53T degradation [63]. Together, these findings raise the possibility for the intercellular

coordination of autophagy between neurons and glia, which may be important for regulating homeostasis in the brain.

Intercellular transfer of cellular trash from neurons to glia

Emerging evidence supports the existence of novel, unconventional pathways for shuttling cellular garbage from neurons to glia (Figure 2). Axons of retinal ganglion cells of wild-type mice extrude mitochondria to adjacent astrocytes for degradation mediated by lysosomes resident in the recipient glial cell [64•]. Recent evidence from *C. elegans* demonstrates that neurons extrude protein aggregates and organelles in membrane-bound vesicles called exophers that are subsequently phagocytosed by other cell types [65••]. Exopher production increases when autophagy, the proteasome, or chaperone system is inhibited [65••]. Additionally, compromising mitochondrial health stimulates exopher release [65••], suggesting that this pathway provides a mechanism to eliminate damaged organelles from the neuron, particularly when the endogenous quality control machinery is compromised. Thus, neighboring cells, such as glia, may supplement neuronal degradation systems under normal conditions and this intercellular transfer of material may be enhanced in response to neurotoxic stress. Further, this pathway may not only transfer cellular trash, but also signaling information, to notify surrounding glia on the status of neuronal health. Given that many neurodegenerative diseases propagate through a prion-like cell-to-cell transfer of disease-associated proteins [1,66], an outstanding question is how do these intercellular pathways become altered or hijacked to facilitate disease progression?

Why do neurons transfer damaged cellular material to surrounding cells? Do neurons have a more limited capacity for quality control pathways and degradative activity as compared with glia? This possibility may explain why neurons are more susceptible to protein aggregation associated with neurodegenerative disease. In fact, Tydlacka *et al.*, have shown that glia exhibit higher levels of proteasomal activity as compared with neurons of the same age, and are able to more effectively clear huntingtin aggregates associated with Huntington's disease [67]. Future work will need to quantitatively compare other aspects of the proteastasis machinery between neurons and glia.

Future directions

We are only at the inception of our understanding of autophagy in neurons, and how neuron–glia interactions may coordinate autophagy in the context of the brain. Thus, many outstanding questions remain to fuel new avenues of research. First, how is autophagy regulated in glia? Similar to neurons, many glial populations also need to survive for an entire lifetime [68]. Thus, how is autophagy in glia adapted to accommodate this extended existence? Additionally, what is the role of autophagy in glia, and how does glial autophagy impact neuronal health and function? Initial studies have shown that autophagy in astrocytes may be important for astrocytic differentiation in the developing mouse cortex [69]. Other studies have shown that autophagy in Schwann cells, the myelinating glia of the peripheral nervous system, is important for degrading myelinating membranes after axonal injury [70,71]. Autophagy in microglia, the phagocytic macrophages of the central nervous system, may play an important role in the degradation of extracellular Aβ in Alzheimer's disease [72–74]. Lastly, microglial-specific loss of autophagy impairs developmental-based spine pruning, and results in autism-like behaviors in mice, linking glial autophagy with regulating proper connectivity of the developing brain [75]. Thus, the efficiency of glial autophagy may have profound implications on neuronal health, function, and response to stress. To examine this more completely, mouse models with glial-specific loss of autophagy in each glial population (e.g. astrocytes, oligodendrocytes, Schwann cells) will be necessary to fully elucidate how glial autophagy impacts neuronal development and survival.

A deeper understanding of the interplay between neurons and glia in the coordination of autophagy in health and disease is of crucial importance. A provocative hypothesis is whether autophagosomes are transferred from neurons to glia. Autophagosomes have been shown to be secreted from non-neuronal cells [76,77], raising the possibility that autophagosomes may shuttle trash, signaling information, or both between neural cells in the brain. Understanding these intercellular pathways for coordinating autophagy may provide a new avenue for therapeutic intervention to mitigate neurodegeneration.

Conflict of interest

Nothing declared.

Acknowledgements

We thank Vineet Vinay Kulkarni for comments on the manuscript. This work was funded by the McCabe Fund Fellow Award and NIH grants K99NS082619 and R00NS082619 to S.M.

References

1. Cushman M, Johnson BS, King OD, Gitler AD, Shorter J: **Prion-like disorders: blurring the divide between transmissibility and infectivity**. *J Cell Sci* 2010, **123**:1191-1201.

2. Harris JJ, Attwell D: **The energetics of CNS white matter**. *J Neurosci* 2012, **32**:356-371.

3. Cajigas IJ, Will T, Schuman EM: **Protein homeostasis and synaptic plasticity**. *EMBO J* 2010, **29**:2746-2752.

4. Wang YC, Lauwers E, Verstreken P: **Presynaptic protein homeostasis and neuronal function**. *Curr Opin Genet Dev* 2017, **44**:38-46.

5. Feng Y, He D, Yao Z, Klionsky DJ: **The machinery of macroautophagy**. *Cell Res* 2014, **24**:24-41.

6. Weidberg H, Shvets E, Elazar Z: **Biogenesis and cargo selectivity of autophagosomes**. *Annu Rev Biochem* 2011, **80**:125-156.

7. Mizushima N, Yoshimori T, Ohsumi Y: **The role of Atg proteins in autophagosome formation**. *Annu Rev Cell Dev Biol* 2011, **27**:107-132.

8. Yang Z, Klionsky DJ: **Eaten alive: a history of macroautophagy**. *Nat Cell Biol* 2010, **12**:814-822.

9. Schneider JL, Cuervo AM: **Autophagy and human disease: emerging themes**. *Curr Opin Genet Dev* 2014, **26**:16-23.

10. Yamamoto A, Yue Z: **Autophagy and its normal and pathogenic states in the brain**. *Annu Rev Neurosci* 2014, **37**:55-78.

11. Ariosa AR, Klionsky DJ: **Autophagy core machinery: overcoming spatial barriers in neurons**. *J Mol Med (Berl)* 2016, **94**:1217-1227.

12. Kulkarni VV, Maday S: **Compartment-specific dynamics and functions of autophagy in neurons**. *Dev Neurobiol* 2018, **78**:298-310.

13. Komatsu M, Wang QJ, Holstein GR, Friedrich VL Jr, Iwata J, Kominami E, Chait BT, Tanaka K, Yue Z: **Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration**. *Proc Natl Acad Sci U S A* 2007, **104**:14489-14494.

14. Nishiyama J, Miura E, Mizushima N, Watanabe M, Yuzaki M: **Aberrant membranes and double-membrane structures accumulate in the axons of Atg5-null Purkinje cells before neuronal death**. *Autophagy* 2007, **3**:591-596.

15. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H *et al.*: **Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice**. *Nature* 2006, **441**:885-889.

16. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E *et al.*: **Loss of autophagy in the central nervous system causes neurodegeneration in mice**. *Nature* 2006, **441**:880-884.

17. •• Kim M, Sandford E, Gatica D, Qiu Y, Liu X, Zheng Y, Schulman BA, Xu J, Semple I, Ro SH *et al.*: **Mutation in ATG5 reduces autophagy and leads to ataxia with developmental delay**. *Elife* 2016:5. e12245.

In this study, the authors identify a mutation in Atg5 that decreases autophagic flux and leads to childhood ataxia. They provide the first evidence that mutations in core autophagy machinery lead to neurological disorders in humans.

18. Maday S: **Mechanisms of neuronal homeostasis: autophagy in the axon**. *Brain Res* 2016, **1649**:143-150.

19. Frake RA, Ricketts T, Menzies FM, Rubinsztein DC: **Autophagy and neurodegeneration**. *J Clin Invest* 2015, **125**:65-74.

20. Barmada SJ, Serio A, Arjun A, Bilican B, Daub A, Ando DM, Tsvetkov A, Pleiss M, Li X, Peisach D *et al.*: **Autophagy induction enhances TDP43 turnover and survival in neuronal ALS models**. *Nat Chem Biol* 2014, **10**:677-685.

21. Mizushima N, Yamamoto A, Matsui M, Yoshimori T, Ohsumi Y: **In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker**. *Mol Biol Cell* 2004, **15**:1101-1111.

22. Kabeya Y, Mizushima N, Ueno T, Yamamoto A, Kirisako T, Noda T, Kominami E, Ohsumi Y, Yoshimori T: **LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing**. *EMBO J* 2000, **19**:5720-5728.

23. Hollenbeck PJ: **Products of endocytosis and autophagy are retrieved from axons by regulated retrograde organelle transport**. *J Cell Biol* 1993, **121**:305-315.

24. Maday S, Wallace KE, Holzbaur EL: **Autophagosomes initiate distally and mature during transport toward the cell soma in primary neurons**. *J Cell Biol* 2012, **196**:407-417.

25. Maday S, Holzbaur EL: **Autophagosome biogenesis in primary neurons follows an ordered and spatially regulated pathway**. *Dev Cell* 2014, **30**:71-85.

26. Lee S, Sato Y, Nixon RA: **Lysosomal proteolysis inhibition selectively disrupts axonal transport of degradative organelles and causes an Alzheimer's-like axonal dystrophy**. *J Neurosci* 2011, **31**:7817-7830.

27. Yue Z: **Regulation of neuronal autophagy in axon: implication of autophagy in axonal function and dysfunction/degeneration**. *Autophagy* 2007, **3**:139-141.

28. Murdoch JD, Rostosky CM, Gowrisankaran S, Arora AS, Soukup SF, Vidal R, Capece V, Freytag S, Fischer A, Verstreken P *et al.*: **Endophilin-A deficiency induces the Foxo3a-Fbxo32 network in the brain and causes dysregulation of autophagy and the ubiquitin-proteasome system**. *Cell Rep* 2016, **17**:1071-1086.

29. Soukup SF, Kuenen S, Vanhauwaert R, Manetsberger J, Hernandez-Diaz S, Swerts J, Schoovaerts N, Vilain S, Gounko NV, Vints K *et al.*: **A LRRK2-dependent EndophilinA phosphoswitch is critical for macroautophagy at presynaptic terminals**. *Neuron* 2016, **92**:829-844.

30. Vanhauwaert R, Kuenen S, Masius R, Bademosi A, Manetsberger J, Schoovaerts N, Bounti L, Gontcharenko S, Swerts J, Vilain S *et al.*: **The SAC1 domain in synaptojanin is required for autophagosome maturation at presynaptic terminals**. *EMBO J* 2017, **36**:1392-1411.

31. Okerlund ND, Schneider K, Leal-Ortiz S, Montenegro-Venegas C, Kim SA, Garner LC, Gundelfinger ED, Reimer RJ, Garner CC: **Bassoon controls presynaptic autophagy through Atg5**. *Neuron* 2017, **93**:897-913.

32. Fu MM, Nirschl JJ, Holzbaur EL: **LC3 binding to the scaffolding protein JIP1 regulates processive dynein-driven transport of autophagosomes**. *Dev Cell* 2014, **29**:577-590.

33. Cheng XT, Zhou B, Lin MY, Cai Q, Sheng ZH: **Axonal autophagosomes recruit dynein for retrograde transport through fusion with late endosomes**. *J Cell Biol* 2015, **209**:377-386.

34. •• Maday S, Holzbaur EL: **Compartment-specific regulation of autophagy in primary neurons**. *J Neurosci* 2016, **36**:5933-5945.

In this study, the authors use live-cell imaging of the autophagosome marker GFP-LC3 to demonstrate that autophagy is a compartmentalized process in primary neurons under basal versus stress conditions.

35. Farias GG, Guardia CM, Britt DJ, Guo X, Bonifacino JS: **Sorting of dendritic and axonal vesicles at the pre-axonal exclusion zone**. *Cell Rep* 2015, **13**:1221-1232.

36. Song AH, Wang D, Chen G, Li Y, Luo J, Duan S, Poo MM: **A selective filter for cytoplasmic transport at the axon initial segment**. *Cell* 2009, **136**:1148-1160.

37. •• Gowrishankar S, Yuan P, Wu Y, Schrag M, Paradise S, Grutzendler J, De Camilli P, Ferguson SM: **Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques**. *Proc Natl Acad Sci U S A* 2015, **112**:E3699-E3708.

In this study, the authors demonstrate that lysosomes accumulate in axonal swellings located near extracellular amyloid plaques in models of Alzheimer's disease. These accumulated lysosomes are deficient for proteases, suggesting that defects in retrograde transport prevent lysosomal maturation and subsequent cargo degradation in Alzheimer's disease.

38. •• Stavoe AK, Hill SE, Hall DH, Colon-Ramos DA: **KIF1A/UNC-104 transports ATG-9 to regulate neurodevelopment and autophagy at synapses**. *Dev Cell* 2016, **38**:171-185.

In this article, the authors demonstrate that autophagy is required for assembly of pre-synaptic compartments, and axonal outgrowth. Different neuron types exhibit these distinct phenotypes in response to autophagy loss, providing evidence that autophagy plays neuron-type-specific roles.

39. Shen W, Ganetzky B: **Autophagy promotes synapse development in Drosophila**. *J Cell Biol* 2009, **187**:71-79.

40. Rudnick ND, Griffey CJ, Guarnieri P, Gerbino V, Wang X, Piersaint JA, Tapia JC, Rich MM, Maniatis T: **Distinct roles for motor neuron autophagy early and late in the SOD1G93A**

mouse model of ALS. *Proc Natl Acad Sci U S A* 2017, **114**:E8294-E8303.

41. Tang G, Gudsnuk K, Kuo SH, Cotrina ML, Rosoklija G, Sosunov A, Sonders MS, Kanter E, Castagna C, Yamamoto A *et al.*: **Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits**. *Neuron* 2014, **83**:1131-1143.

42. Hernandez D, Torres CA, Setlik W, Cebrian C, Mosharov EV, Tang G, Cheng HC, Kholodilov N, Yarygina O, Burke RE *et al.*: **Regulation of presynaptic neurotransmission by macroautophagy**. *Neuron* 2012, **74**:277-284.

43. Wang T, Martin S, Papadopulos A, Harper CB, Mavlyutov TA, Niranjan D, Glass NR, Cooper-White JJ, Sibarita JB, Choquet D *et al.*: **Control of autophagosome axonal retrograde flux by presynaptic activity unveiled using botulinum neurotoxin type A**. *J Neurosci* 2015, **35**:6179-6194.

44. •• Dragich JM, Kuwajima T, Hirose-Ikeda M, Yoon MS, Eenjes E, Bosco JR, Fox LM, Lystad AH, Oo TF, Yarygina O *et al.*: **Autophagy linked FYVE (Alfy/WDFY3) is required for establishing neuronal connectivity in the mammalian brain**. *Elife* 2016:5. e14810.

Here, the authors demonstrate that loss of Alfy, an axon-enriched protein involved in the selective autophagy of ubiquitinated substrates, results in axonal guidance defects and perinatal lethality in mice. These findings suggest a critical role for selective autophagy in establishing proper connectivity of the developing nervous system.

45. Kannan M, Bayam E, Wagner C, Rinaldi B, Kretz PF, Tilly P, Roos M, McGillewie L, Bar S, Minocha S *et al.*: **WD40-repeat 47, a microtubule-associated protein, is essential for brain development and autophagy**. *Proc Natl Acad Sci U S A* 2017, **114**:E9308-E9317.

46. Ban BK, Jun MH, Ryu HH, Jang DJ, Ahmad ST, Lee JA: **Autophagy negatively regulates early axon growth in cortical neurons**. *Mol Cell Biol* 2013, **33**:3907-3919.

47. Kononenko NL, Classen GA, Kuijpers M, Puchkov D, Maritzen T, Tempes A, Malik AR, Skalecka A, Bera S, Jaworski J *et al.*: **Retrograde transport of TrkB-containing autophagosomes via the adaptor AP-2 mediates neuronal complexity and prevents neurodegeneration**. *Nat Commun* 2017, **8**:14819.

48. Ashrafi G, Schlehe JS, LaVoie MJ, Schwarz TL: **Mitophagy of damaged mitochondria occurs locally in distal neuronal axons and requires PINK1 and Parkin**. *J Cell Biol* 2014, **206**:655-670.

49. Shehata M, Matsumura H, Okubo-Suzuki R, Ohkawa N, Inokuchi K: **Neuronal stimulation induces autophagy in hippocampal neurons that is involved in AMPA receptor degradation after chemical long-term depression**. *J Neurosci* 2012, **32**:10413-10422.

50. Baas PW, Deitch JS, Black MM, Banker GA: **Polarity orientation of microtubules in hippocampal neurons: uniformity in the axon and nonuniformity in the dendrite**. *Proc Natl Acad Sci U S A* 1988, **85**:8335-8339.

51. Kleele T, Marinkovic P, Williams PR, Stern S, Weigand EE, Engerer P, Naumann R, Hartmann J, Karl RM, Bradke F *et al.*: **An assay to image neuronal microtubule dynamics in mice**. *Nat Commun* 2014, **5**:4827.

52. Zhao YG, Sun L, Miao G, Ji C, Zhao H, Sun H, Miao L, Yoshii SR, Mizushima N, Wang X *et al.*: **The autophagy gene Wdr45/Wipi4 regulates learning and memory function and axonal homeostasis**. *Autophagy* 2015, **11**:881-890.

53. • Nikoletopoulou V, Sidiropoulou K, Kallergi E, Dalezios Y, Tavernarakis N: **Modulation of autophagy by BDNF underlies synaptic plasticity**. *Cell Metab* 2017, **26**:230-242.

Here, the authors demonstrate that BDNF suppresses autophagy levels in the brain, and this inhibition of autophagy is important for learning and memory. They find that autophagy is regulated differently in each region of the brain, and this may have profound functional consequences for the brain.

54. Court FA, Hendriks WT, MacGillavry HD, Alvarez J, van Minnen J: **Schwann cell to axon transfer of ribosomes: toward a novel understanding of the role of glia in the nervous system**. *J Neurosci* 2008, **28**:11024-11029.

55. Fruhbeis C, Frohlich D, Kuo WP, Amphornrat J, Thilemann S, Saab AS, Kirchhoff F, Mobius W, Goebbels S, Nave KA *et al.*: **Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication**. *PLoS Biol* 2013, **11**:e1001604.

56. Lopez-Verrilli MA, Picou F, Court FA: **Schwann cell-derived exosomes enhance axonal regeneration in the peripheral nervous system**. *Glia* 2013, **61**:1795-1806.

57. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang PW *et al.*: **Oligodendroglia metabolically support axons and contribute to neurodegeneration**. *Nature* 2012, **487**:443-448.

58. Boillee S, Yamanaka K, Lobsiger CS, Copeland NG, Jenkins NA, Kassiotis G, Kollias G, Cleveland DW: **Onset and progression in inherited ALS determined by motor neurons and microglia**. *Science* 2006, **312**:1389-1392.

59. Di Malta C, Fryer JD, Settembre C, Ballabio A: **Astrocyte dysfunction triggers neurodegeneration in a lysosomal storage disorder**. *Proc Natl Acad Sci U S A* 2012, **109**:E2334-E2342.

60. • Liu L, Zhang K, Sandoval H, Yamamoto S, Jaiswal M, Sanz E, Li Z, Hui J, Graham BH, Quintana A *et al.*: **Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration**. *Cell* 2015, **160**:177-190.

Here, the authors report that mitochondrial damage specifically within neurons results in the accumulation of lipids in glia, leading to neurodegeneration. These findings emphasize the complexity of intercellular communication between neurons and glia and how theses interactions impact neuronal health.

61. Madill M, McDonagh K, Ma J, Vajda A, McLoughlin P, O'Brien T, Hardiman O, Shen S: **Amyotrophic lateral sclerosis patient iPSC-derived astrocytes impair autophagy via non-cell autonomous mechanisms**. *Mol Brain* 2017, **10**:22.

62. Alirezaei M, Kiosses WB, Flynn CT, Brady NR, Fox HS: **Disruption of neuronal autophagy by infected microglia results in neurodegeneration**. *PLOS ONE* 2008, **3**:e2906.

63. Gan L, Vargas MR, Johnson DA, Johnson JA: **Astrocyte-specific overexpression of Nrf2 delays motor pathology and synuclein aggregation throughout the CNS in the alpha-synuclein mutant (A53T) mouse model**. *J Neurosci* 2012, **32**:17775-17787.

64. • Davis CH, Kim KY, Bushong EA, Mills EA, Boassa D, Shih T, Kinebuchi M, Phan S, Zhou Y, Bihlmeyer NA *et al.*: **Transcellular degradation of axonal mitochondria**. *Proc Natl Acad Sci U S A* 2014, **111**:9633-9638.

In this study, the authors demonstrate the transfer of mitochondria from neuronal axons to surrounding glia which then degrade enveloped mitochondria via lysosomes. This article provides exciting new evidence for the co-operation between neurons and glia in eliminating cellular material from the neuron.

65. •• Melentijevic I, Toth ML, Arnold ML, Guasp RJ, Harinath G, Nguyen KC, Taub D, Parker JA, Neri C, Gabel CV *et al.*: ***C. elegans* neurons jettison protein aggregates and mitochondria under neurotoxic stress**. *Nature* 2017, **542**:367-371.

Here, the authors show that organelles are secreted from neurons in membrane-bound vesicles called exophers. Exopher secretion is enhanced with mitochondrial damage, and in autophagy mutants. These findings establish a novel mechanism for how neurons can eliminate cellular trash in response to stress such as organelle damage or compromised endogenous quality control systems.

66. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM: **Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice**. *Science* 2012, **338**:949-953.

67. Tydlacka S, Wang CE, Wang X, Li S, Li XJ: **Differential activities of the ubiquitin-proteasome system in neurons versus glia may account for the preferential accumulation of misfolded proteins in neurons**. *J Neurosci* 2008, **28**:13285-13295.

68. Fuger P, Hefendehl JK, Veeraraghavalu K, Wendeln AC, Schlosser C, Obermuller U, Wegenast-Braun BM, Neher JJ, Martus P, Kohsaka S *et al.*: **Microglia turnover with aging and in an Alzheimer's model via long-term in vivo single-cell imaging**. *Nat Neurosci* 2017, **20**:1371-1376.

69. Wang S, Li B, Qiao H, Lv X, Liang Q, Shi Z, Xia W, Ji F, Jiao J: **Autophagy-related gene Atg5 is essential for astrocyte differentiation in the developing mouse cortex**. *EMBO Rep* 2014, **15**:1053-1061.

70. Gomez-Sanchez JA, Carty L, Iruarrizaga-Lejarreta M, Palomo-Irigoyen M, Varela-Rey M, Griffith M, Hantke J, Macias-Camara N, Azkargorta M, Aurrekoetxea I *et al.*: **Schwann cell autophagy, myelinophagy, initiates myelin clearance from injured nerves**. *J Cell Biol* 2015, **210**:153-168.

71. Jang SY, Shin YK, Park SY, Park JY, Lee HJ, Yoo YH, Kim JK, Park HT: **Autophagic myelin destruction by Schwann cells during Wallerian degeneration and segmental demyelination**. *Glia* 2016, **64**:730-742.

72. Ries M, Sastre M: **Mechanisms of Aβ clearance and degradation by glial cells**. *Front Aging Neurosci* 2016, **8**:160.

73. Lucin KM, O'Brien CE, Bieri G, Czirr E, Mosher KI, Abbey RJ, Mastroeni DF, Rogers J, Spencer B, Masliah E *et al.*: **Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease**. *Neuron* 2013, **79**:873-886.

74. Cho MH, Cho K, Kang HJ, Jeon EY, Kim HS, Kwon HJ, Kim HM, Kim DH, Yoon SY: **Autophagy in microglia degrades extracellular beta-amyloid fibrils and regulates the NLRP3 inflammasome**. *Autophagy* 2014, **10**:1761-1775.

75. Kim HJ, Cho MH, Shim WH, Kim JK, Jeon EY, Kim DH, Yoon SY: **Deficient autophagy in microglia impairs synaptic pruning and causes social behavioral defects**. *Mol Psychiatry* 2017, **22**:1576-1584.

76. Pfeffer SR: **Unconventional secretion by autophagosome exocytosis**. *J Cell Biol* 2010, **188**:451-452.

77. Jiang S, Dupont N, Castillo EF, Deretic V: **Secretory versus degradative autophagy: unconventional secretion of inflammatory mediators**. *J Innate Immun* 2013, **5**:471-479.