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Autophagy, neuron-specific degradation and neurodegeneration

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Degradation of membrane compartments, organelles and other debris through macroautophagy (hereafter referred to as autophagy) is thought to occur in most, maybe all, cells. We recently reported the discovery of a neuron-specific endomembrane degradation mechanism that depends on the vesicle SNARE neuronal Synaptobrevin (n-Syb) and the vesicle ATPase component V100 (the V_0a1 subunit). Loss of *n-Syb* causes degeneration of adult photoreceptor neurons in Drosophila, reminiscent of adult-onset degeneration in neurons with defective autophagy. Here we explore the potential importance of this newly discovered neuron-specific degradation mechanism in comparison with ubiquitous autophagy machinery for adult-onset neurodegeneration.

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In the nervous system, loss of core autophagy gene function results in intracellular protein accumulation and adult-onset degeneration, as shown in two landmark papers in 2006. This finding supports the hypothesis that low levels of autophagic debris removal are required for neuronal maintenance. This hypothesis was already put forward prior to the 2006 studies and increasingly gained traction in recent years. There is an underlying idea that neurons are especially susceptible to proteasomal and autophagic dysfunction, possibly because they are long-lived cells with considerable specialized membrane and protein turnover.

Defective autophagy is also thought to render neurons more susceptible to neurotoxic insults. This idea feeds into the larger discussion of the cause of neurodegeneration in specific diseases. For example, Aβ42 in Alzheimer disease, tau in frontal-temporal dementia, and aberrant polyQ proteins in diseases like Huntington and several ataxias, to name but a few, have all been independently linked to abnormal autophagy. The fundamental question underlying these ideas concerns causality. Intracellular and extracellular accumulations are a principal hallmark of all neurodegenerative disorders; Aβ42, tau and polyQ aggregates are striking examples of this general pathological feature. Surprisingly, however, the toxicity of the actual accumulations is difficult to establish with certainty. Controversial evidence exists in most cases in support of potentially protective roles for both aberrant intracellular or extracellular inclusions. Consistent with such protective roles, autophagy is well characterized as a response to cellular stress with the dual effect of debris removal and provision of energy through recycling of valuable cellular resources. Taken together, autophagy has critically been linked to neurodegeneration in opposing roles—as both a primary cause and a secondary, protective response.

Studies using induction of autophagy have been only partially helpful to resolve this question. In support of the protective role, increased autophagy should increase neuronal viability. This may be especially true of neurons suffering from independent neurotoxic insults in known neurodegenerative diseases. Indeed, such protective functions have been successfully shown in several studies. On the other hand, induction of autophagy is itself a cause of cell death. The causative difference between the two opposite outcomes is

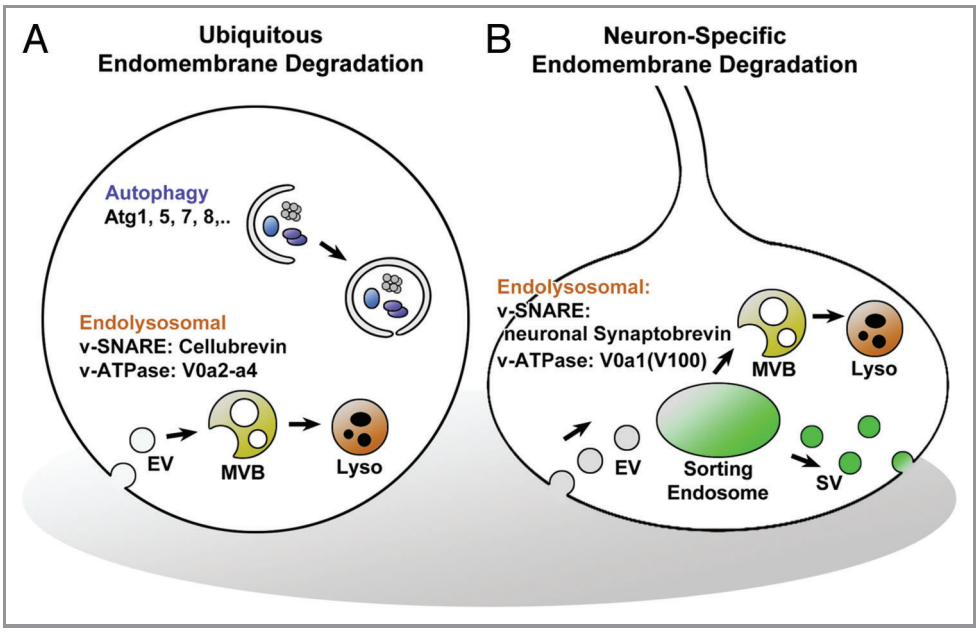

Figure 1. Comparison of ubiquitous and neuron-specific endomembrane degradation systems. (A) Autophagy and endolysosomal degradation are thought to operate in most, maybe all, cells. Core autophagy genes include numerous '*Atg*' genes, among other key regulators. Ubiquitous vesicle proteins that function in the endolysosomal system include the vesicle SNARE cellubrevin and at least one of the V_0-ATPase components V_0a2-a4 (*vha100-2, CG7678, CG12602*). (B) The neuron-specific 'sort-and-degrade' mechanism employs at least two proteins that are also implicated in neurotransmitter release: the synaptic vesicle SNARE n-Syb and the synaptic vesicle ATPase component V_0a1 (V100). The neuron-specific endolysosomal degradation mechanism most likely operates in parallel to the ubiquitous machinery shown on the left. EV, endosomal vesicle; MVB, multivesicular body; Lyso, lysosome; SV, synaptic vesicle.

likely due to different levels of autophagy, with low levels being potentially protective, and high levels inducing cell death.

We have recently described an endolysosomal degradation mechanism that, in contrast to autophagy, functions specifically in neurons. Our recent paper reports adult-onset degeneration in Drosophila photoreceptors in the absence of the neuron-specific synaptic vesicle SNARE protein neuronal Synaptobrevin (n-Syb). n-Syb is the target of tetanus toxin and was previously thought to specifically function in neurotransmitter release. Similarly, our preceding companion paper in 2010 presented a very similar degenerative phenotype after loss of the neuron-specific vesicle ATPase component V100 (**Fig. 1A and B**). V100, like n-Syb, has previously been shown to function in neurotransmitter release. However, loss of neurotransmitter release does not cause degeneration in fly photoreceptors. Instead, both n-Syb and V100 function in the sorting and degradation of endosomal compartments independent of their roles in neurotransmitter release. Consequently, we termed this mechanism a form of neuron-specific 'sort-and-degrade.' Both *n-syb* and *v100* have direct neuronal orthologs in mice and humans that have known equivalent functions in neurotransmitter release. To our knowledge, the 'sort-and-degrade' mechanism defined by n-Syb and V100 represents the first neuron-specific endomembrane degradation system whose loss causes neurodegeneration.

What can we learn from neuron-specific endolysosomal degradation about the role of autophagy, and intracellular degradation generally, in neurodegeneration? Loss of either *n-Syb* or *V100* results in substantially elevated levels of autophagy, visible both as large numbers of autophagosomes in electron micrographs as well as in the upregulation of the autophagy marker Atg8. However, accumulation of autophagosomal structures does not necessarily indicate autophagic defects but may also result from an upregulation of functional autophagy due to other defects. Indeed, in the *n-syb* mutant the accumulating autophagosomes are acidified and typically include late, degraded materials. In addition, induction of autophagy through expression of *Atg1* is functional in *n-syb* mutant photoreceptors, where it leads to early cell death independent of the presence of n-Syb. It is possible that the observed increase in autophagy is a compensatory response of neurons to the loss of the neuronal 'sort-and-degrade' mechanism in a manner similar to other cellular stresses known to induce autophagy. Furthermore, increased autophagy may exceed the capacity of lysosomal enzyme activity to keep pace in clearing out autophagosomes. We propose that the neuron-specific 'sort-and-degrade' mechanism is functionally independent of autophagy. We further proposed that this mechanism is required for neuronal survival, and that its loss leads to adult-onset degeneration.

Neither the core genes of autophagy, nor *n-syb* or *v100* are 'disease genes' for neurodegeneration in the strict definition, because no mutations are known in these genes, at least so far, that are directly linked to human neurodegenerative diseases. Instead, the finding of adult-onset degeneration in the cases of defective autophagy or neuron-specific degradation

may mostly highlight the original hypothesis, namely that neurons are cells with considerable specialized membrane trafficking that require an 'extra effort' in membrane degradation for long-lived maintenance. Any defect that places an additional burden on the neuronal cell biology may interfere with neuronal longevity. This burden may come in two flavors, either as neurotoxic insults like Aβ42 or polyQ proteins that require increased degradative capacity, or as a decrease of neuronal degradative capacity itself. Interestingly, the neuron-specific 'sort-and-degrade' mechanism puts the focus of such an increased neuron-specific degradative capacity at synapses, since both n-Syb and V100 are predominantly synaptic proteins that likely function at the interface of synaptic vesicle cycling and synaptic endolysosomal function. It will therefore be interesting to see how the newly discovered neuron-specific endomembrane degradation system integrates into our understanding of neuronal maintenance in health and disease.

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