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Editorial

Autophagy in neurological diseases: An update

Over the past fifteen years, autophagy and neuronal quality control mechanisms have taken the limelight in neurological disease research. Autophagy, the process of "self-eating" by which cells digest unneeded, damaged or sacrificed parts of themselves is triggered by a wide variety of physiological and pathological stimuli. In many neurological diseases, dysregulated autophagy has been implicated in a pathogenic role. Processes that interrupt proper completion of basal or induced autophagy are observed in a growing number of diseases, sometimes leading to massive accumulation of undigested autophagosomes (Lee and Gao, 2009; Lee et al., 2011). Whereas successful completion of autophagy generally prevents or delays cell death (Boya et al., 2005; Dagda et al., 2009), chronic consequences of upregulated autophagy may contribute to muscle, nerve cell or organ-level dysfunction due to cellular atrophy (Ching and Weihl, 2013; Lum et al., 2005), mitochondrial depletion (Cherra III et al., 2013; Guo et al., 2016) or axonal-dendritic shrinkage (Cheng et al., 2011; Cherra III et al., 2010; Plowey et al., 2008).

There are three major forms of autophagy. Macroautophagy involves the formation of *de novo* organelles called autophagosomes, formed from extension of intracellular membranes around cellular constituents to be digested in the lysosome [See (Ejlerskov et al., 2019) in this issue for a summary of regulatory mechanisms]. Macroautophagy is capable of bulk turnover, as occurs during cellular starvation, as well as selective degradation of specific cargos [See (Chu, 2019)]. Chaperone-mediated autophagy involves the recognition of specific sequence motifs followed by translocation of the targeted proteins across the lysosome membrane [See (Li et al., 2019) for a summary of regulatory mechanisms]. Microautophagy involves delivery of cargo into the lysosomal lumen through invagination and budding of the lysosomal membrane itself. Although mainly studied in yeast with their large vacuoles, a similar process in mammals may occur through formation of multivesicular bodies (endosomal microautophagy) (Sahu et al., 2011). Unless otherwise specified, the term "autophagy" refers to macroautophagy in this issue.

In the seven or eight years that have elapsed since I edited the first special issue on *Autophagy and Protein Degradation in Neurological Diseases*, tremendous progress has been made in basic as well as translational autophagy research. The current issue begins with an article from Dr. Rubinsztein's group, which reviews a set of studies that utilize genetic methods to upregulate autophagy in models of neurodegeneration (Ejlerskov et al., 2019), fourteen years after their landmark paper demonstrated *in vivo* efficacy of pharmacological autophagy induction (Ravikumar et al., 2004). This is followed by an update on the still controversial role of autophagy in acute brain injuries from Dr. Clark's group (Wolf et al., 2019), which introduces the Janus-faced nature of autophagy touched upon further in the two mitophagy reviews below.

Whereas autophagy used to be regarded as a nonselective bulk degradation pathway, research in neurodegenerative diseases has led to a complete change in viewpoint with tremendous progress delineating mechanisms of selective autophagy. Polyglutamine-expanded huntingtin led the way as a canonical target of selective aggrephagy (Bjorkoy et al., 2005). In this issue, Dr. Yamamoto's group provides an update on new literature implicating mutant huntingtin in autophagy dysregulation at more than one step (Croce and Yamamoto, 2019). This is followed by a discussion of the growing repertoire of macomolecular interactions involving Atg8 family proteins that are used by mammalian cells to selectively target protein aggregates and mitochondria for autophagy (Chu, 2019), fifteen years after we first observed mitophagy in neurons from Parkinson's disease and Lewy body dementia patient brains (Zhu et al., 2003). Next, Dr. Holzbaur's group summarizes our current understanding of axonal autophagy and mitophagy in relation to genes implicated in amyotrophic lateral sclerosis, posing a set of unresolved questions (Evans and Holzbaur, 2019). A review of recent advances in chaperone-mediated autophagy (CMA) by Dr. Mao's group, discussing the crosstalk with ER stress and targeting CMA for therapy (Li et al., 2019), rounds out the discussion of selective autophagy.

Continuing upon a theme of synaptic dysfunction and autophagy that concluded the review articles in the last special issue (Plowey and Chu, 2011), in this issue, Dr. Sulzer's group highlights the role of autophagy in different types of brain cells in relation to synaptic pruning (Lieberman et al., 2019), shedding potential light on autism and other neuropsychiatric disorders. Since the seminal studies of Dr. Hollenbeck 25 years ago (Hollenbeck, 1993), it has been known that the endocytic and autophagic systems in neurons intersect extensively during retrograde axonal transport. Here, Dr. Yue's group reviews the recent genetic evidence linking synaptic vesicle endocytosis, autophagy and SNARE-mediated fusions in the presynaptic terminal and the possible role of these pathways in Parkinson's disease (Pan et al., 2019).

The final group of reviews focus upon lysosomal dysfunction in neurodegenerative diseases. The discoveries in yeast of conserved autophagy genes (Atg) in the 1990's (Tsukada and Ohsumi, 1993) led initially to a focus on regulatory mechanisms for autophagy induction. In 2011, the year of the last special issue, a landmark study showing coordinated regulation of lysosomal biogenesis and autophagy genes by the transcription factor TFEB (Settembre et al., 2011) revealed that lysosomal function and capacity may be just as tightly regulated. Based on observations in disease models, we now know that it is possible for autophagy induction to exceed the capacity of lysosomes to complete degradation, generating a state of autophagic stress (Chu, 2006). This may occur as a consequence of declining lysosomal function with aging (Cuervo and Dice, 2000), from impaired lysosomal acidification (Lee et al., 2010) and/or SNARE-dependent autophagosome-lysosome fusion (Fader et al., 2009), or in relation to lysosomal storage diseases. In this

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issue, Dr. Mazzulli's group discusses the intriguing relationship between Gaucher's disease and Parkinson's disease, and the use of patient-derived iPSC lines to study these processes (Pitcairn et al., 2019). Dr. La Spada's group reviews the evidence for TFEB disruption in multiple neurodegenerative diseases with a discussion of how TFEB might be targeted therapeutically (Cortes and La Spada, 2019). The issue closes with novel insights concerning the signaling role of lysosomes from a scientist that has been studying lysosomal pathobiology in Alzheimer's disease for 30 years. Dr. Nixon's group discusses the relationship between lysosomal transport and function in healthy or diseased neurons, and how lysosomes may be targeted for future disease-modifying interventions (Lie and Nixon, 2019).

Declaration

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