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Review

The cellular pathways of neuronal autophagy and their implication in neurodegenerative diseases

Zhenyu Yue [a,*], Lauren Friedman [a], Masaaki Komatsu [b], Keiji Tanaka [b]

[a] Department of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY 10029, USA
[b] Laboratory of Frontier Science; Tokyo Metropolitan Institute of Medical Science; Bunkyo-ku, Tokyo, Japan

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ABSTRACT

Autophagy is a tightly regulated cell self-eating process. It has been shown to be associated with various neuropathological conditions and therefore, traditionally known as a stress-induced process. Recent studies, however, reveal that autophagy is constitutively active in healthy neurons. Neurons are highly specialized, post-mitotic cells that are typically composed of a soma (cell body), a dendritic tree, and an axon. Despite the vast growth of our current knowledge of autophagy, the detailed process in such a highly differentiated cell type remains elusive. Current evidence strongly suggests that autophagy is uniquely regulated in neurons and is also highly adapted to local physiology in the axons. In addition, the molecular mechanism for basal autophagy in neurons may be significantly divergent from "classical" induced autophagy. A considerable number of studies have increasingly shown an important role for autophagy in neurodegenerative diseases and have explored autophagy as a potential drug target. Thus, understanding the neuronal autophagy process will ultimately aid in drug target identification and rational design of drug screening to combat neurodegenerative diseases.

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1. Introduction

Autophagy is a conserved lysosomal degradation pathway. In mammals, three types of autophagy have been described: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). These three types of autophagy differ in their mode of delivery of their substrates to lysosomes for degradation [1]. While little is known about the microautophagy process, a large body of studies has contributed to the current understanding of the macroautophagy and CMA pathways. Macroautophagy is the prototype of autophagy involving formation, delivery, and degradation of autophagic vacuoles (also called autophagosomes) through lysosomes, and will be the only form discussed in this review (hereafter referred to as autophagy). Although autophagy occurs in virtually all cell types, and likely involves highly conserved molecular machinery, emerging evidence suggests cell type/tissue-specific regulation of autophagy.

Neurons were one of the few cell types that were used in the initial identification and characterization of autophagy. With early access to electron microscopy (EM) in the last century, Alex Novikoff, Christian De Duve, and colleagues discovered and described the cell "self-eating" process of autophagy in the form of distinct vacuoles through ultrastructural analysis [2,3]. The formation of the autophagosomes, which engulfed a portion of cytoplasm and occurred in a large number, especially following axotomy and excitotoxic insult to neurons, is associated with "chromatolysis", a phenomenon that describes the area in neuronal cytoplasm that is devoid of organelles and filled with various types of vesicles [4]. These initial observations of neuronal autophagic activity were followed by a series of EM studies that revealed the accumulation of autophagosomes in the neurons of several human neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). With little knowledge of autophagic process and regulation, especially in mammalian tissues, neuronal autophagy, marked by elevated levels of autophagosomes, was viewed traditionally as a cellular mechanism that was highly destructive, and therefore was suspected to be a driving force in cell death [5].

* Corresponding author. Tel.: +1 212 241 3155; fax: +1 212 348 1310.
E-mail address: zhenyu.yue@mssm.edu (Z. Yue).

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The arrival of the molecular era of autophagy study provided important evidence showing that autophagy is a primary stress response for cell survival. For example, loss-of-function studies demonstrate the essential role for autophagy-associated genes in the removal of "obsolete" proteins and organelles, thus protecting cell or neuron survival [6,7]. Therefore, in injured neurons or neurons bearing disease-related genes, altered autophagy, associated with increased numbers of autophagosomes, can be viewed as a beneficial response of neurons in repairing or remodeling damaged cellular components necessary for sustaining normal neuronal function and survival. However, other studies also provide genetic and cellular evidence that otherwise argues for a role of autophagy in promoting neuronal death, especially in neurons with acute injury [8].

More recent studies have begun to dissect the autophagic process in neurons under various stress or pathological conditions. These studies suggest that, while accumulation of autophagosomes can arise from increased production in some cases [9], it can be caused by a mechanism that blocks fusion and degradation of autophagosomes through lysosomes in other scenarios [10]. Given the current studies exploring the potential of autophagy as a drug target for the treatment of neurodegenerative diseases, a thorough investigation of the detailed mechanism whereby autophagy participates in each disease condition, would be critical for designing therapeutic intervention and evaluating the efficacy of an "autophagy drug" [11].

Over the past several years, characterization of autophagy in mammalian cells and animal models has greatly advanced our knowledge of the autophagy process in mammals. However, despite the recent effort and exponential growth in autophagy research as a whole, the progress in understanding the basic process and regulation of neuronal autophagy remains relatively slow. Recent studies have revealed the connections between autophagy and major neurological disorders such as (AD), (PD), and (HD) [12–14]. A common theme emerging in those studies is the role of autophagy in degrading disease-related, aggregate-prone mutant proteins such as tau, huntingtin and alpha-synuclein [15]. In addition, specific pathogenic mechanisms of AD, PD, or HD may profoundly alter autophagic activity. For example, while "inappropriate" autophagic induction may contribute to the increased synthesis of β-amyloid (Aβ) [16], blocked autophagic clearance is also implicated in cytotoxicity in AD [10]. Recently, genetic animal models containing reduced autophagic activity were used to examine the role of autophagy in the pathogenesis of AD, HD, and PD. These studies provided important evidence linking dysfunctional autophagy to the specific disease process [17,18], Friedman and Yue, unpublished). Due to numerous recent reviews on the study of autophagy in PD, AD, or HD [12–14,19–21], this review will instead summarize recent research in understanding the basis of neuronal autophagy, especially in primary neuronal cultures and the nervous system of animal models, and autophagic activity associated with other types of neuropathological conditions. Although limited and sometimes conflicting in their current forms, these studies nonetheless begin to shed light on specific cellular pathways and the connection of the physiological function of autophagy to disease mechanism.

2. Biosynthesis of autophagosomes is conserved from yeast to human

Morphological evidence for autophagy was first reported in the 1960s [3], but the underlying molecular mechanisms were not elucidated for another three decades. In the early 1990s, genetic screens of yeast mutants identified a number of *au*tophagy-related (*ATG*) genes essential for the autophagic molecular machinery [22,23]. Currently, 31 autophagy genes are known, many of which are required for autophagosome formation, at the nucleation, elongation, and/or fusion steps. Upon induction, an isolation membrane or phagophore forms and elongates, enveloping a portion of the cytosol, and encloses to form a double-membrane vacuole. Its outer membrane subsequently fuses with the lysosome, where its contents, together with the inner membrane, are digested by acidic hydrolases within the lysosomes (Fig. 1). Up to now, at least 14 mammalian homologues of yeast *ATG* genes have been identified, and characterization of their functions suggests that the autophagic machinery is highly conserved in mammals [24].

Studies in yeast revealed that, unlike endosomes and secretory vesicles, autophagosome formation does not require budding from existing organelles as its membrane source. Rather, autophagosomes may form from *de novo* membrane cisternae in the pre-autophagosomal structure (PAS), which contains several Atg protein complexes, and resides adjacent to the yeast vacuole [25–27]. It was shown that Atg9, the only known integral membrane protein associated with autophagic membranes, shuttles between a peripheral site in the cytoplasm and the PAS, therefore regulating the delivery of membrane to the PAS for expansion [27,28]. The Atg1 kinase complex, which contains regulatory subunit, Atg13, is involved in the retrieval of Atg9 from the PAS and is required for autophagosome formation [28,29]. Interestingly, the mammalian homologue of Atg9 (mAtg9) was shown to cycle between the trans-Golgi network (TGN) and late endosomes, which may serve as sources for membrane elongation. Starvation or rapamycin treatment induced redistribution of mAtg9 from TGN to peripheral late endosome membranes. Knock-down of Atg1 human homolog, ULK1, prevented this starvation-induced redistribution, suggesting that mAtg9 trafficking is ULK1-dependent [30].

In addition to the recruitment of membranes, Atg9 may also play a role in assembling protein complexes at the PAS [31]. Vps34, a class III phosphatidylinositol (PtdIns) 3-kinase mediates vesicular trafficking through its interactions with Vps15 and Atg6, and forms two distinct complexes: one with Atg14, which regulates autophagy-specific function, and the other with Vps38, for endosome-to-Golgi trafficking [32]. The PtdIns 3-kinase complex produces phosphatidylinositol 3-phosphate (PtdIns(3)P) which may recruit effector proteins, such as the Atg18–Atg2 complex, and together, both complexes are essential for nucleation [25]. The mammalian homologues of Vps34, Vps15 and Atg6 are hVps34, p150 and Beclin 1, respectively. Recent studies have found additional proteins that interact with the hVps34–p150–Beclin 1 complex: UVRAG [33], Atg14L (putative yeast Atg14 homologue) [34] and Rubicon [35]. These studies suggest the existence of multiple hVps34–Beclin 1 kinase complexes, which are involved in specific membrane trafficking mechanisms, including autophagy [35].

Two ubiquitin-like conjugation systems mediate autophagic membrane elongation; one involving the conjugation of Atg5 with Atg12 [36] and the other involving the covalent linkage of Atg8 with phosphatidylethanolamine (PE) [37]. Both Atg12 and Atg8 modifications share a single E1-like activating enzyme, Atg7, but are processed by two separate E2-like conjugating enzymes; Atg10 and Atg3 respectively [38]. The two ubiquitin-like conjugation systems are highly conserved from yeast to mammals [36,39]. The majority of Atg5 and Atg12 exists in the conjugated form and interacts noncovalently with multimeric protein, Atg16, in yeast and its functional counterpart, Atg16L, in mammals [40]. In one of the first studies linking the small GTPase Rab family to Atg proteins, Atg16L was shown to directly interact with Golgi-resident Rab33 and modulates autophagosome formation [41]. The Atg5–Atg12·Atg16 complex is essential for autophagosome formation and facilitates Atg8 conjugation with PE [40] through E3-like activity of Atg5–Atg12 for Atg8 conjugation [42].

Microtubule-associated protein 1 light chain 3 (LC3) is a mammalian homolog of yeast Atg8 and is cleaved at its C-terminal region by cysteine protease Atg4. This processed form (LC3-I) resides in the cytoplasm until it undergoes two ubiquitin-like modifications to become covalently linked to PE. Both the lipidated form LC3 (termed LC3-II) and Atg12–Atg5·Atg16 are recruited to the isolation membrane [38]. Whereas Atg12–Atg5·Atg16 dissociates upon autophagosome completion, LC3-II remains coupled to the autophagic

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