Beclin 1 Complex in Autophagy and Alzheimer Disease

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Beclin 1 is a protein involved in the regulation of autophagy and has been shown to be reduced in patients with Alzheimer disease. This review summarizes the current research data that link disturbances in autophagy, a cellular degradation and maintenance pathway, to the development of Alzheimer disease and related neurodegenerative diseases. It also provides a brief overview of the existing pharmacological interventions available to modulate autophagy activity in mammalian cells.

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Alzheimer disease (AD) is the most common form of dementia. It is a slowly progressive, neurodegenerative disorder that causes memory impairments and other cognitive dysfunctions. While numerous genetic risk factors for the development of AD have been identified over the past decades, our understanding of the underlying pathogenesis is still incomplete. No cure is available to date and current treatment strategies are mostly symptomatic. On the neuropathological level, the disease is identified by the presence of intracellular protein deposits (hyperphosphorylated tau protein in neurofibrillary tangles), extracellular aggregates (β-amyloid [Aβ] protein in amyloid plaques), and widespread brain atrophy. The Aβ protein, a small fragment cleaved off the amyloid precursor protein (APP), has received particular attention as a potential culprit. It exists in monomeric, oligomeric, and fibrillar form and has been implicated as a neurotoxic agent inside as well as outside the cell. More recently, other cleavage products of APP have been identified as possible players in AD pathology as well. Because APP is a transmembrane protein and many cleavage steps require the presence of specific proteolytic assemblies (secretases, proteases) and proper local pH value, the intracellular trafficking of APP through the membranous compartments could determine the production of APP cleavage products. This idea is supported by data showing that sortilin-related receptor mutations are genetically linked to AD and the resulting loss of endosomal sorting causes early AD pathology in mice. Now autophagy, another major vesicular trafficking pathway, has received increased attention in the AD research field.

AUTOPHAGY IS A VESICULAR DEGRADATION PATHWAY FOR CYTOSOLIC COMPONENTS

Autophagy (from Greek for “self-eating”) is a cellular process that allows degradation of large intracellular components and recycling of valuable anabolic resources (amino acids, lipids, sugars, etc). Different types of autophagy exist, but this review focuses on macroautophagy, the most extensively studied form of autophagy in the context of neurodegeneration. While the process had first been described in yeast, the last decade saw a dramatic increase of our understanding of the underlying molecular machinery in mammalian cells. In short, a double membrane-bound vesicle (autophagosome) forms in the cytosol...
and sequesters cellular debris such as large protein complexes, damaged mitochondria, pathogens, or bulk cytosol (Figure 1). In this way, autophagy can degrade cargo that is otherwise too large to be degraded by proteases or inserted into the proteasome. The source of the membrane used for autophagosome formation has been subject to an ongoing debate as either it could be synthesized locally as the nascent autophagosome grows or it could be derived from other membranous compartments like the endoplasmic reticulum through budding and fusion. A recent, elegant study using electron microscopy suggests that, at least in mammalian cells, autophagosome membranes can be derived from an endoplasmic reticulum subdomain through the formation of a spherical, cradlelike structure.\(^9\) While autophagy initially appeared to be a bulk degradation pathway, it is now clear that substrate specificity exists, especially for ubiquitinated or acetylated protein aggregates.\(^9,10\) Autophagy is a cellular stress response that is activated through a number of pathways,\(^7\) and the mammalian target of rapamycin (mTOR) signaling cascade integrates many autophagy-related stimuli such as starvation, hypoxia, growth factors, and infections.\(^11\) (Figure 1). After cargo sequestration, autophagosomes have to be transported to the perinuclear cytosol and fuse with endosomes and lysosomes for successful content degradation.\(^12,13\) Disruption of autophagosomal-endosomal-lysosomal trafficking can cause major changes in cellular vesicle turnover. Being a central metabolic pathway, autophagy plays an important role in a variety of human diseases, in cellular homeostasis, and in immunity, in both the central nervous system and other tissues.\(^14-18\) Accordingly, the latest research suggests that modulating levels of autophagy has beneficial effects on general cellular health and ameliorates the effects of aging in several experimental settings.\(^17-20\)

**Figure 1.** Autophagy in mammalian cells. Autophagy can be triggered through a variety of upstream signaling events such as starvation, insulin, growth factors, hypoxia, or pathogens. Many of these events converge in an inhibition of mammalian target of rapamycin (mTOR) activity, which in turn initiates autophagy. Numerous autophagy-related proteins participate in the initiation and formation of autophagosomes and in cargo recognition (see references for details). The complete autophagosome is then transported to fuse with lysosomes, and degradation of the content releases valuable anabolic compounds. PI3K indicates phosphatidylinositol 3-kinase.

**Figure 2.** The role of Beclin 1 in autophagy and Alzheimer disease (AD). A, Beclin 1 is reduced in human AD brains, at both the messenger RNA and protein levels. Accumulated autophagosomes indicate stalled autophagosomal degradation. \(\beta\)-Amyloid (\(\beta\)) is produced and accumulates in amyloid plaques. Beclin 1-deficient transgenic mice expressing human amyloid precursor protein (hAPP) exhibit disturbances in their autophagosomal-lysosomal degradation and have increased amyloid plaque load. Inhibition of autophagy in hAPP-expressing cells leads to an accumulation of APP and its metabolites, while autophagy activation can reduce the levels of APP and its metabolic products. CTF indicates C-terminal fragment. B, Beclin 1 has multiple binding partners, and the composition of proteins in the Beclin 1 complex appears to determine its function. Reduced availability of Beclin 1 may cause a destabilization of the complex and could impair autophagy on multiple levels.

**THE BECLIN 1 CONNECTION: AUTOPHAGY, NEURODEGENERATION, AND AD**

The creation of autophagy-specific knockout mice in 2006 and the observation of their neurodegenerative phenotype brought autophagy to the attention of the broader neuroscience community.\(^21,22\) The accumulation of autophagosomes and nondegraded material in neurons of brains in patients with AD and the presence of APP-processing secretases in autophagosomes had already indicated that autophagy participates in the turnover of APP and its metabolites and that it might be deregulated in AD.\(^23-25\) Additionally, changes in autophagy and endosomal sorting-related messenger RNAs had been reported in AD brain tissues of patients with AD.\(^26\) A study from our laboratory then identified Beclin 1, a protein involved in the initiation and execution of autophagy, to be reduced in AD brain tissue, linking the disease to an autophagy defect (Figure 2A).\(^27\) Accordingly, APP-transgenic mice with a heterozygous deletion of Beclin 1 have an increase in \(\beta\) plaque deposition, neuronal loss, and the accumulation of abnormal lysosomes containing electron-dense material.\(^27\) These findings indicate that autophagy plays a central role in APP transport and metabolism, a hypothesis that is further supported by new cell culture data from our laboratory: APP
and APP metabolites are degraded via the autophagy pathway, and Beclin 1 reduction increases APP, APP C-terminal fragment, and Aβ accumulation in cell culture.28 Interestingly, APP overexpression, both in cells and in mice, causes no detectable change in Beclin 1 levels.27,28 This suggests that disturbances in autophagy preceede the pathological disruption of APP processing. Beclin 1 had initially been identified as a tumor suppressor gene29 and is now at the center of research aiming to understand the complex molecular events surrounding autophagy initiation and execution. A series of landmark studies published in the last 3 years showed that Beclin 1 is at the core of a large protein complex that regulates multiple aspects of autophagy, depending on its subunit composition (Figure 2B).30-36 The question is, to what extent is autophagy involved in the development or prevention of neurotoxic events, and can modulating autophagy cause or rescue neurodegeneration? Autophagy appears impaired in presenilin 1/APP mice and contributes to neuronal apoptosis,24,37 while it is constitutively active in healthy neurons.38 In addition, Aβ1-42 has been reported to directly impair the autophagosomal-lysosomal system in flies,39 and Aβ oligomers interfere with mTOR signaling.40 On the other hand, activation of autophagy or overexpression of Beclin 1 can prevent neuronal cell death and promote clearance of toxic protein aggregates.41-43 These data suggest a model where basal autophagy plays an important role in neuronal protein housekeeping and vesicular turnover. Disruption of autophagy would lead to an accumulation of abnormal subcellular vesicles (endosomes, lysosomes, multivesicular bodies, autophagosomes), which are part of the native APP trafficking system and present the right microenvironment to produce potentially toxic APP metabolites. Increasing levels of these toxic species, including Aβ, could then contribute further to an escalating disruption of the autophagosomal system and ultimately to cell death. A rescue of autophagy levels or a mild overactivation appears to have beneficial effects, while extreme autophagy activation can lead to cell death by itself.

### CLINICAL RELEVANCE AND CURRENT BASIC RESEARCH

Autophagy is a major pathway of cellular homeostasis. It is regulated by a variety of important signaling cascades, and pharmacological intervention to alter autophagy levels without disrupting other main pathways may prove difficult. However, a number of studies have shown that it is possible to screen for autophagy-inducing drugs using simple cell or animal model systems of neurodegeneration (Table). Current research on the precise role of Beclin 1 and other autophagy-initiating and autophagy-modulating protein complexes will hopefully allow us to develop better drugs to fine-tune autophagy activity depending on the specific disease settings. Surprising off-target effects of established drugs for cancer treatment should be evaluated for their usefulness in autophagy modulation because many cancer and autophagy pathways overlap. Also, aging is the major risk factor for AD, and enhancing autophagy has been shown to ameliorate some age-related phenotypes and promote longevity. Thus, progress in our understanding of the role of autophagy in neurodegeneration may yield valuable insight in a multitude of geriatric conditions.

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## Table. Selection of Drugs With Autophagy-Inducing Effects in Cell Culture or Animal Models

<table>
<thead>
<tr>
<th>Drug Name, Use</th>
<th>Autophagy Target Pathway</th>
<th>Disease Model</th>
<th>Source</th>
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<tbody>
<tr>
<td>Amiodarone, antiarrhythmic agent; nicosamide, tenaciade, perhexiline, antianiral agent; sirolimus, immunosuppressant; temsirolimus, anticancer agent</td>
<td>Inhibition of mTOR</td>
<td>HD, PD, Tau, SCA3, AD</td>
<td>Jaeger et al,28 2010; Rubinsztein et al,45 2007; Menzies et al,46 2010; Balgi et al,47 2009; Sarkar et al,48 2007; Zhang et al,49 2007</td>
</tr>
<tr>
<td>Carbamazepine, anticonvulsant; lithium, antidepressant; sodium valproate, anticonvulsant</td>
<td>Phosphoinositol signaling</td>
<td>HD, PD, ALS</td>
<td>Sarkar et al,48 2005; Sarkar et al,49 2008; Fornai et al,11 2008</td>
</tr>
<tr>
<td>Trehalose, food/pharmaceutical supplement</td>
<td>Unknown</td>
<td>HD, PD</td>
<td>Tanaka et al,12 2004; Sarkar et al,13 2007</td>
</tr>
<tr>
<td>Amiodarone, antiarrhythmic agent; loperamide, antidiarrheal agent; nifedipine, antihypertensive agent; pimozide, antipsychotic agent</td>
<td>Unknown, blocking of calcium ion channels</td>
<td>HD</td>
<td>Zhang et al,46 2007</td>
</tr>
<tr>
<td>Fluspirilene, antipsychotic agent; trifluoperazine, antipsychotic agent</td>
<td>Unknown, dopamine antagonists</td>
<td>HD</td>
<td>Zhang et al,46 2007</td>
</tr>
<tr>
<td>Clonidine, several uses; minoxidil, vasodilator; verapamil, several uses</td>
<td>cAMP-IP3-calpain signaling</td>
<td>HD</td>
<td>Williams et al,46 2008</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; cAMP, cyclic adenosine monophosphate; HD, Huntington disease; IP3, inositol triphosphate; mTOR, mammalian target of rapamycin; PD, Parkinson disease; SCA3, spinocerebellar ataxia type 3; Tau, tauopathies.
REFERENCES


