

REVIEW

Autophagic/lysosomal dysfunction in Alzheimer's disease

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Abstract

Autophagy serves as the sole catabolic mechanism for degrading organelles and protein aggregates. Increasing evidence implicates autophagic dysfunction in Alzheimer's disease (AD) and other neurodegenerative diseases associated with protein misprocessing and accumulation. Under physiologic conditions, the autophagic/lysosomal system efficiently recycles organelles and substrate proteins. However, reduced autophagy function leads to the accumulation of proteins and autophagic and lysosomal vesicles. These vesicles contain toxic lysosomal hydrolases as well as the proper cellular machinery to generate amyloid-beta, the major component of AD plaques. Here, we provide an overview of current research focused on the relevance of autophagic/lysosomal dysfunction in AD pathogenesis as well as potential therapeutic targets aimed at restoring autophagic/lysosomal pathway function.

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and cause of dementia in the older population. It targets brain regions responsible for complex cognitive function and gradually destroys patient memories and quality of life [1]. Neuropathologically, brains of patients with AD are characterized by the presence of two hallmark proteinaceous aggregates: extracellular amyloid-beta (A β) plaques and intracellular neurofibrillary tangles (NFTs). As the disease progresses, affected brain regions succumb to toxic insult as evidenced by gross neuronal loss and brain atrophy [1]. Autosomal dominant mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) cause early-onset familial AD. However, aging is the greatest risk factor for developing AD, and the vast majority (>95%) of AD cases develop sporadically without a clear genetic component or etiology.

The A β peptide is generated by sequential cleavage of transmembrane APP by integral membrane β - and γ -secretases. The multi-protein γ -secretase enzyme complex requires a catalytic presenilin (PS1 or PS2) protein.

Although A β generation can occur at the plasma membrane, the majority of A β is generated intracellularly via the endocytic and secretory pathways. As disease progresses, A β accumulates to form extracellular insoluble plaques [1,2]. NFTs are formed mainly of the hyperphosphorylated microtubule-associated protein tau. Physiologically, tau regulates microtubule stabilization; during pathological conditions, it becomes hyperphosphorylated and misfolded and aggregates to form intracellular inclusions [1]. Tau-positive inclusions are not unique to AD but can be found in other neurodegenerative disorders.

Prior to A β accumulation, neurons display endocytic pathway dysfunction, implicating it as a seminal event in pathogenesis [3]. The endocytic pathway merges with the autophagic-lysosomal system to degrade and recycle proteins. Autophagy is a highly conserved cellular catabolic process by which cytoplasmic material undergoes lysosomal degradation to clear long-lived proteins and organelles [4-7]. Mammalian autophagy occurs during physiologic conditions and becomes upregulated in response to certain cellular stressors, such as protein accumulation and aggregation as an attempt to clear excess protein burden [4,7].

The three forms of autophagy – macroautophagy, microautophagy, and chaperone-mediated autophagy – all target cytoplasmic content to the lysosome for degradation. Exclusively, this review will focus on macroautophagy, which will be referred to as autophagy from here forward. Autophagy induction involves the formation of

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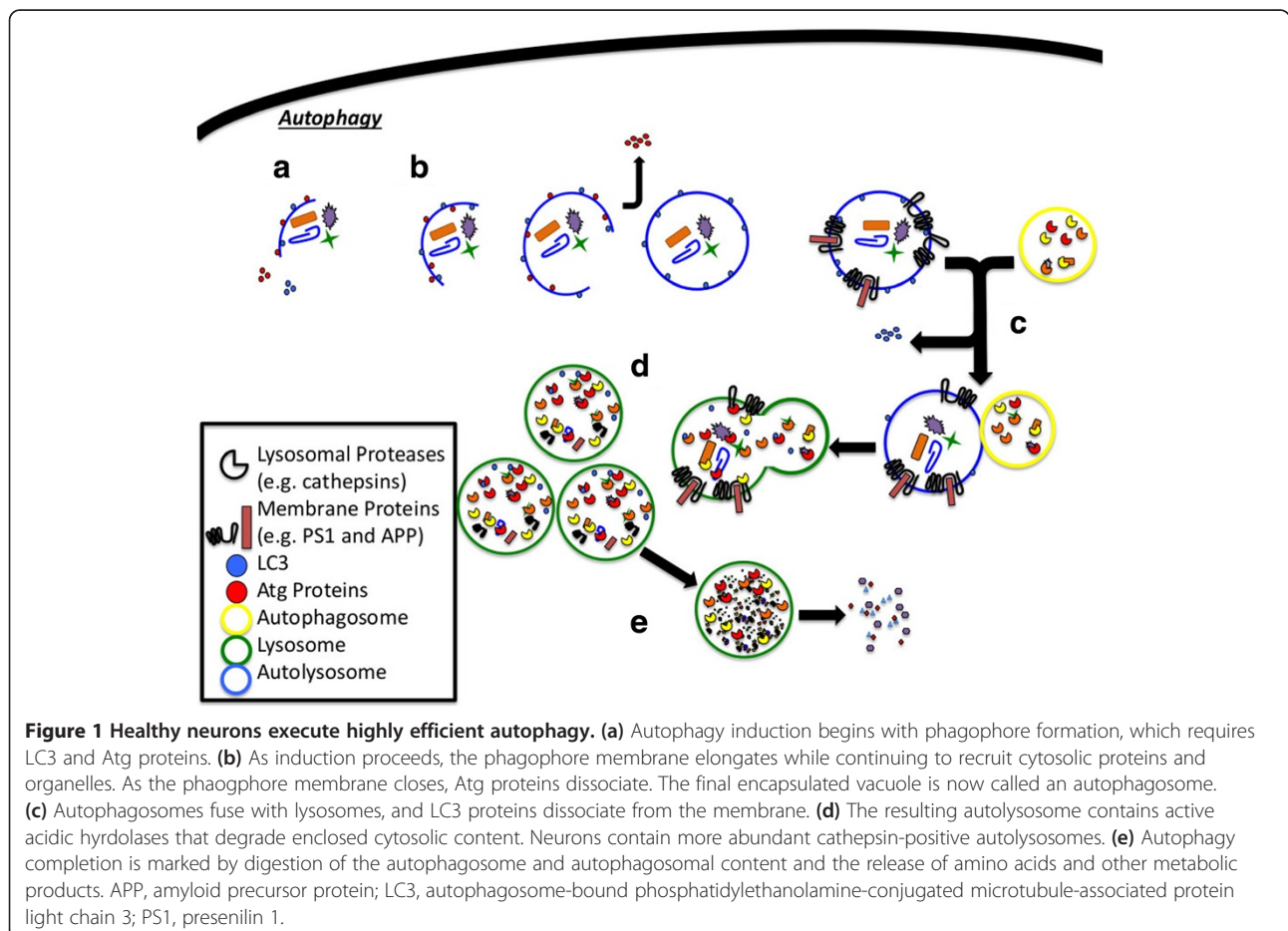
a double-membranous structure, the phagophore, which elongates and fuses around the cytoplasmic content targeted for degradation [4]. The membranous source for phagophores may arise *de novo* from pre-existing intracellular materials such as the endoplasmic reticulum (ER), golgi apparatus, and mitochondrial and plasma membranes [4,8]. The fused structure, now called an autophagosome, delivers its contents to the lysosome through autophagosomal-lysosomal fusion to form an autolysosome, where protein degradation occurs (Figure 1). Amino acids and other metabolic products generated by this digestion are released for reuse, marking the completion of autophagy [4,7,8].

The endosomal-lysosomal system inherently bears potential to participate in AD pathogenesis as it is a prominent site of APP processing, A β uptake, and A β production. Here, we will review the mounting evidence implicating autophagic/lysosomal dysfunction in AD. Additionally, we will highlight therapeutic targets aimed to restore autophagic/lysosomal protein degradation that prove efficacious in animal models and hold potential to translate to patients with AD.

Autophagic/lysosomal dysfunction in Alzheimer's disease

Heritable mutations that alter lysosomal degradation cause dozens of disorders collectively referred to as lysosomal storage disorders (LSDs). Most often, mutations occur in genes encoding lysosomal hydrolases, resulting in excess lysosomes with abundant undegraded content [9]. Interestingly, AD and LSDs display strong phenotypic overlap, including neuronal accumulation of lysosomal vesicles, dystrophic axons, ectopic dendrites, cognitive deficits, and neurodegeneration [1,9]. Lysosomal pathology occurs earliest in mice expressing mutant presenilin, which likely correlates with its role in lysosomal function (for example, [10,11]) and is the topic of discussion in a later section.

When dysfunction in the autophagic-lysosomal system began gaining traction in the AD field, early hypotheses predicted that enhanced, not impaired, neuronal autophagy initiated pathogenesis. These assertions arose from initial investigations that reported low basal autophagic activity in neurons [12-14]. However, methodologies used to detect autophagic flux captured only snapshots of autophagosome vacuole (AV) density and



autophagosome-bound phosphatidylethanolamine-conjugated microtubule-associated protein light chain 3. At any given time, healthy neurons contain very few of these canonical autophagy markers [15-17]. Until studies examined the effects of inhibiting basal neuronal autophagy on neuronal viability, reports consistently underestimated neuronal autophagic function in healthy cells. The generation of transgenic mice with impaired central nervous system autophagy revealed ubiquitinated protein inclusions and neurodegeneration to conclusively expose a necessary role of autophagy in neuronal health [18,19]. Subsequent studies revealed that neurons maintain constitutively active, highly efficient autophagy. Instead of containing numerous AVs, healthy neurons contain high levels of cathepsin-rich autolysosomes [20], suggesting that soon after autophagosome formation they fuse with lysosomes.

Proper autophagic flux involves the execution of autophagosome formation and clearance by lysosomes. Understanding pathogenesis requires an evaluation of both processes; indeed, dysfunction in multiple steps of the autophagic pathway has been implicated in AD, and often contradictory reports have been published. Some studies have associated AD with impaired autophagic induction and report decreased expression of autophagy-inducing proteins and increased activity of autophagy-suppressing molecules [21-23]. Other studies report intact autophagy induction, as evidenced by accumulating intermediate AVs (that is, autolysosomes and autophagosomes) containing improperly digested autophagic substrates and lysosomal hydrolase upregulation, indicating a failure of substrate clearance [16,24]. Since numerous pathological changes in the lysosomal network occur in AD neurons, it is likely that these changes may relate to different stages in AD progression. Interestingly, transcriptional upregulation of autophagy occurs in AD brains, which contrasts with normal healthy aging, where autophagy is downregulated [24,25]. Since defective autophagosomal maturation occurs in AD neurons resulting in AV accumulation, autophagic upregulation may represent a compensatory attempt to increase autophagic flux and could help explain some discrepancies reported in the literature. Impaired autophagy may occur early in disease, with dysregulated overcompensation in advanced AD.

Presenilin effect on lysosome

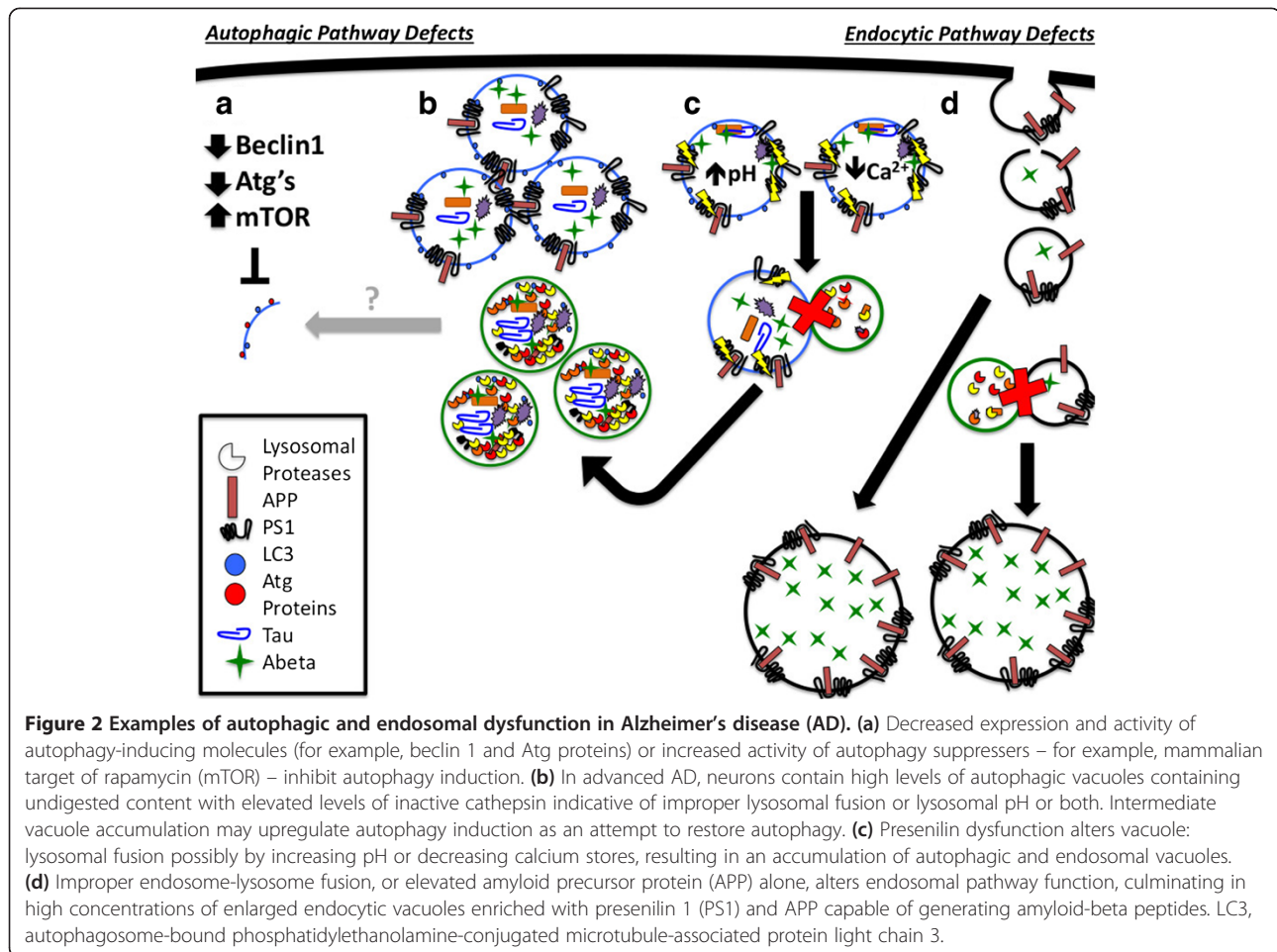
Autosomal dominant mutations in genes encoding PS1 or PS2 are the most common cause of early-onset familial AD [1]. As a component of the γ -secretase complex, they participate in cleaving type I transmembrane proteins, including APP. In addition, both PS1 and PS2 contribute to other cellular pathways [26].

Many AD-linked presenilin mutations enhance the disproportionate release of aggregation-prone A β_{1-42} peptide,

but not all have this effect [1]. Toward this end, recent studies suggest that PS1 may play disparate roles in AD pathogenesis. For example, strong evidence implicates presenilin function in calcium homeostasis independent of its γ -secretase role [27]. Indeed, calcium flux regulates autophagy induction as well as vacuole fusion, and presenilin mutations exacerbate autophagic-lysosomal system dysfunction [10]. Presenilin dysfunction may represent a mechanistic link unifying these pathologies, and recently several groups have aimed to gain insight into this connection.

To better understand the role of endogenous wild-type presenilin in the autophagic-lysosomal system, proteostasis was investigated in presenilin-null model systems or in the presence of γ -secretase inhibitors [28,29]. Autophagy was not altered in wild-type fibroblasts treated with γ -secretase inhibitors. In contrast, presenilin-null fibroblasts displayed deficiencies in clearing long-lived proteins and regulating autophagosome levels [29]. These changes were specific as protein degradation through the ubiquitin-proteasome system remained unaffected [29]. Pharmacologic induction of autophagy caused an additional accumulation of autophagosomes in presenilin-null fibroblasts, revealing that presenilin is not necessary for this step in autophagy. However, protein degradation deficits persisted, indicating that presenilin is required for proper autophagic flux and functions downstream of autophagic induction [29]. Furthermore, lysosomal inhibitors failed to exacerbate autophagosome accumulation [29]. Given these results, it is tempting to speculate that presenilins affect autophagy flux by facilitating vesicle fusion and/or lysosomal function, although future studies are needed to better elucidate this point. Despite the high cellular concentration of lysosomes, presenilin-null fibroblasts contained low lysosomal calcium stores [28,30]. Mechanistic studies revealed improper expression and dimerization of the endosomal/lysosomal calcium efflux channels, two-pore channels (TPCs) 1 and 2, leading the authors to propose a necessary role for presenilin in TPC processing [30]. TPCs have been linked to several steps of autophagy, including endosomal/lysosomal vesicular trafficking, lysosomal biogenesis [31], and response to second messengers known to regulate autophagy in astrocytes [32]. These studies gave rise to a new hypothesis proposing that presenilin plays a necessary role in lysosomal calcium storage and release; without proper presenilin function, cells experience defective endosomal-lysosomal fusion accompanied by the accumulation of endosomes and autophagosomes and severely deficient autophagy (Figure 2 and [28,30]).

Controversial results from investigating γ -secretase-independent presenilin function indicated a necessary role of PS1 in lysosomal acidification via a novel mechanism [33]. Deficits in lysosomal acidification occurred in



presenilin hypomorph, knockout, and AD-mutant PS1-expressing cells [11,33,34]. Interestingly, Lee and colleagues [33] described that PS1 holoprotein, not its better-characterized cleavage fragment involved in γ -secretase activity, performed this function. They also reported an interaction between PS1 holoprotein and the V0a1 subunit of the vesicular ATPase, an intracellular proton pump responsible for acidifying autophagosomes and lysosomes. This interaction appeared necessary for the glycosylation of V0a1 in the ER. In the absence of PS1, V0a1 maturation failed, which enhanced its susceptibility to degradation and prevented it from reaching autolysosomes/lysosomes at appropriate levels to facilitate acidification [33]. Since the maturation/activation of cathepsin proteases within these degradative compartments requires acidification, the altered pH ultimately resulted in greatly reduced protein degradation [33]. The necessity of V0a1 in neuronal lysosomal acidification was independently confirmed by a separate group in *Drosophila* photoreceptor neurons lacking V0a1 [35]. The V0a1-null neurons contained lysosomal compartments with high pH and increased AV density

containing undegraded substrates that coincided with slow, adult-onset neurodegeneration [35]. Although dysfunction did not cause AD-associated A β and tau protein misprocessing, further studies revealed that V0a1 deficiency increased cellular sensitivity to exogenously applied AD-associated A β and tau variants in their *Drosophila* model [35].

These data are consistent with a recent report showing that lysosomal acidification is defective in PS1 knockout primary neurons and fibroblasts from AD patients with PS1 mutations [34]. However, they and others failed to corroborate the necessity of presenilins in V0a1 N-glycosylation, targeting, function, or lysosomal acidification [28,29]. The reason underlying these discrepancies is not clear, but differences in model systems and methodologies are likely culprits. Likewise, not all studies on presenilin-null model systems find evidence for slowed turnover of autophagic substrates or changes in lysosomal acidification/function [36]. Although conclusions from recent studies do not flawlessly overlap, they consistently demonstrate presenilin function in the lysosomal-autophagic system separate from their γ -secretase activity

and agree that their precise role in autophagy requires further attention.

Cathepsins and cystatins

Lysosomal proteases play pivotal roles in regulating and executing several steps in the autophagic pathway from initial autophagic vesicle formation through final lysosomal proteolysis [37]. Owing to their proteolytic and apoptotic potential, lysosomal proteases must remain under tight regulatory control, and their dysregulation contributes to the overall lysosomal pathology in numerous diseases, including AD.

The cathepsin lysosomal acidic proteases participate directly in lysosomal substrate clearance by degrading vesicular content [37]. Toward this end, strong evidence supports a role of cathepsins in autophagic clearance of APP metabolites, including A β . Indeed, mice with genetically ablated cathepsin, or treated with lysosomal protease inhibitors, develop autophagy pathology similar to patients with AD [20,38,39]. Correspondingly, enhancing neuronal cathepsin activity significantly decreased A β levels and accumulation, mitigated autophagic-lysosomal pathology, and improved cognition in transgenic mice overexpressing APP [40,41].

Most APP processing occurs in endosomal/lysosomal vesicles, which uniquely positions lysosomal proteases for a role in APP fate. Cathepsins play a dual function in APP processing, which complicates their role in AD. In addition to their A β catabolic role described above, they exhibit β -secretase activity. Canonical A β peptide production occurs through the sequential cleavage of APP by β - and γ -secretases [1]. The β -site APP-cleaving enzyme 1 (BACE-1) cleaves APP and participates in the production of elevated A β . However, BACE-1 does not cleave wild-type APP as efficiently as mutant APP variants [42]. Since the vast majority of patients with AD carry wild-type APP, the most suitable therapeutic targets are β -site-cleaving enzymes that preferentially recognize wild-type APP, such as cathepsin B. Cathepsin B cleaves wild-type APP more efficiently than BACE-1, and cathepsin B inhibitors lowered A β levels and plaque burden and improved memory in transgenic mice overexpressing wild-type APP [43]. Consistent with cathepsin cleaving wild-type APP more efficiently than mutant APP, cathepsin B inhibitors did not benefit mice expressing mutant APP [43]. Collectively, these studies have brought much attention, and debate, to cathepsins as viable pharmacological targets to modulate APP processing and turnover in AD. Since cathepsin B plays a dual role in APP processing (that is, lysosomal degradation versus A β generation from wild-type APP cleavage), it appears to be an interesting potential therapeutic target. Opposing effects of cathepsin B modulation may depend in part on the stage of disease (that is, mouse age, APP

transgene/isoform) as well as mouse genetic background. Indeed, more studies are required to better understand how to regulate its function.

Cathepsin regulation occurs primarily through their endogenous inhibitors, the cystatin proteases. Cystatin C, a potent inhibitor of cathepsin B, is expressed ubiquitously in all tissues and secreted into all body fluids [44]. Cystatin C upregulation occurs after neurotoxic insults; however, whether it plays a neuroprotective or neurotoxic role has been unclear. In terms of AD, cystatin C polymorphisms are associated with late-onset AD [45,46]. Additionally, extracellular cystatin C co-localizes with A β in vascular walls and dense plaques, and intracellular cystatin C immunoreactivity appears in neurons especially susceptible to AD neurotoxicity [47]. To examine the correlative effects of cystatin C and AD, two independent research groups either overexpressed or ablated cystatin C in AD transgenic mice expressing human APP variants [48,49]. Both groups reported that overexpressing human cystatin C at twice the endogenous level decreased A β plaque load without altering APP processing or total A β levels. Cystatin C ablation did not increase A β plaque levels in the parenchyma, but the authors observed a significant increase in the amount of A β in neocortical vasculature, which could contribute to cerebral amyloid angiopathy frequently seen in AD [48]. In a separate study, cystatin C upregulation activated mammalian target of rapamycin (mTOR)-dependent autophagy while pharmacologic block of autophagy prevented the cystatin C-induced protein clearance [50]. In these studies, cathepsin B activity remained unaltered, revealing this as a unique activity of cystatin C independent of its cathepsin B regulatory role. By directly binding A β , reducing plaque accumulation, and activating autophagy, cystatin C appears beneficial for AD; however, more studies are required to fully understand its potential.

Therapeutic targets

Several groups have reported dysfunction in the endosomal-autophagic-lysosomal pathway occurring prior to the development of other canonical AD pathologies. Implicated as an underlying factor in disease pathogenesis and known to metabolize APP, this highly complex vacuolar system is a prime target for AD intervention. However, since both the production and degradation of A β occur here, therapeutic strategies require careful consideration.

A possible therapeutic approach aimed at ameliorating protein accumulation in AD is to enhance lysosomal production or function or both. Toward this end, an elegant study by Yang and colleagues [41] showed that genetically enhancing lysosomal activity in the brain of a transgenic mouse model of AD significantly reduced A β

deposits and levels. These results are consistent with a recent study showing that promoting lysosomal biogenesis facilitates A β turnover [51].

Accumulating evidence implicates dysregulation of endogenous modulators of autophagy, such as Beclin-1 and mTOR, in AD [52]. mTOR, a ubiquitously expressed serine/threonine kinase, serves as a key gatekeeper of autophagy. It functions as the regulatory core subunit of larger protein complexes (mTORC1 and mTORC2) that respond to several stress conditions and growth factor signals; when fully associated in mTORC1, mTOR suppresses autophagy by blocking its induction [53]. Conversely, mTORC1 disruption results in mTOR inhibition and increased autophagic induction [53,54]. Recently, mTORC1 was shown to inhibit lysosome function, thereby revealing a dual mechanism by which mTORC1 negatively regulates autophagy [54,55]. Specifically, the authors used multiple complementary approaches to demonstrate that decreasing the activity of mTORC1, but not mTORC2, leads to lysosomal activation. Furthermore, by deleting either Atg5 or Atg7 to inhibit autophagic induction, lysosomal activity was significantly reduced, suggesting that lysosomes require autophagy-associated activation for proper function [55]. Overall, the changes in lysosomal functions were linked to an mTORC1-mediated activation of transcription factor EB (TFEB) [55]. This is consistent with an earlier report showing that mTOR colocalizes with TFEB and that inhibition of mTOR activates TFEB, which in turn facilitates lysosomal biogenesis [56].

Rapamycin, a US Food and Drug Administration-approved antibiotic and immunosuppressant drug initially used to prevent organ transplant rejections, inhibits mTOR by disrupting mTORC1 formation. Rapamycin promotes longevity and beneficial effects on aging in a variety of organisms and has potential to decrease toxicity in proteinopathies by increasing autophagy via mTOR inhibition [57]. We investigated its efficacy to alter AD-like pathology in a widely used animal model of AD, 3xTgAD mice. In an early study, we treated 3xTg-AD mice with rapamycin for 10 weeks starting at 6 months of age [58]. At this age, the 3xTg-AD mice have cognitive deficits associated with elevated soluble A β , but plaques and tangles have not yet developed [59]. We found that rapamycin administration decreased mTOR activity and enhanced autophagy and coincided with decreased A β and tau pathology and improved behavioral deficits [58]. We further showed that autophagy induction was necessary for rapamycin's effects on A β [58]. The effects of rapamycin on early AD pathology have been independently replicated in a different mouse model [60]. More recently, we found that rapamycin administration effectively reduced tau pathology and improved motor deficits in a mouse model

overexpressing mutant human tau [61]. These results suggest that autophagy-mediated protein turnover may directly control tau accumulation as well as regulating A β levels.

Whereas mTOR negatively regulates initial autophagosome formation, Beclin-1 regulates multiple steps of autophagy. Patients with AD express lower levels of Beclin-1 than age-matched controls and patients with other neurological disorders [21]. Notably, APP overexpression does not alter Beclin-1 expression *in vitro* or *in vivo* [21], suggesting that Beclin-1 downregulation occurs upstream of APP misprocessing. To investigate the relationship between Beclin-1 expression and AD pathogenesis, Pickford and colleagues [21] decreased Beclin-1 expression in the TgAPP/PS1 AD mouse model. Lower Beclin-1 levels caused neuronal autophagy deficits with enhanced AV accumulation. Additionally, the mice developed an increase in A β that inversely correlated with Beclin-1 protein levels. In a complementary experiment, the authors increased brain Beclin-1 expression via viral delivery and saw decreased amyloid pathology [21]. Overall, these experiments demonstrate that, although defective autophagy exacerbates and may even initiate AD pathology, the effects are reversible through autophagy restoration. Others have shown Beclin-1 involvement in endocytic trafficking [62,63], suggesting that the effects of Beclin-1 on A β and APP processing might also be mediated by changes in the endocytic pathway, which clearly is involved in A β generation [2]. Further studies are needed to dissect the molecular mechanisms linking Beclin-1 to A β production.

Accumulating evidence from patients and model systems suggests that deficits in autophagy induction occur early in disease but that lysosomal clearance deficits occur in more advanced stages of disease. It is tempting to speculate that the transcriptional upregulation of autophagy-related proteins seen in patients with AD might represent a compensatory attempt of the system to cope with the accumulation of abnormal proteins (Figure 2). We conducted a study to compare the effects of using rapamycin as an advanced-stage treatment therapy with that of using it prophylactically. We found that rapamycin treatment mitigated protein aggregation and cognitive decline only when treatment began prior to the onset of widespread plaque and tangle accumulation [64]. Specifically, we found that treating 3xTg-AD mice with rapamycin starting at 2 months of age for 16 months greatly reduced the number of plaques and tangles and soluble A β and tau levels. Consistently, cognitive performance was improved compared with mice on a control diet. In contrast, when we administered the rapamycin-encapsulated diet to mice with manifest pathology (15-month-old mice), despite clear autophagy upregulation, rapamycin did not lower A β or tau or

improve cognition [64]. These findings are somewhat inconsistent with data showing that acute rapamycin treatment in Tg2576 AD mice increased A β [65]. Differences in length of treatment (acute versus chronic), rapamycin formulation, and/or route of administration may have contributed to the different outcomes. Interestingly, in a Parkinson's disease model, in addition to increasing autophagy induction, rapamycin treatment enhanced lysosomal biogenesis and enhanced clearance of autophagosomes [66]. Furthermore, we recently showed that rapamycin directly decreases tau pathology in a tau transgenic mouse [61]. These effects appeared to be mediated by changes in autophagy induction and in the activity of key kinases involved in tau phosphorylation [61]. Taken together, these results highlight the pleiotropic effects of rapamycin, making it difficult to fully resolve the contribution of each molecular pathway targeted by its action. Perhaps dose-dependent effects contribute to some of the reported differences and, if so, could be manipulated to upregulate different phases of autophagy.

Conclusions

Growing interest suggests an involvement of autophagy in several neurodegenerative disorders, especially those characterized by protein accumulation, including AD and Huntington's disease [67]. This is not surprising given the role of autophagy in protein turnover. Facilitating autophagy-mediated protein degradation is an attractive therapeutic intervention in AD and related disorders. However, the dichotomy between the beneficial effects of upregulating autophagy induction early in disease, and ineffective or perhaps even detrimental effects in late disease, underscore the need for further studies [16,20,52,64]. Therefore, therapeutic strategies require careful consideration as enhancing autophagy induction in patients with advanced disease may exacerbate pathology; indeed, upregulating autophagy in other diseases with lysosomal impairment exacerbates pathology and behavior deficits [68]. Suppressing autophagy has beneficial effects on enzyme replacement therapy for Pompe disease, a type of lysosomal storage disorder providing evidence that in certain situations blocking autophagy may prove beneficial [69]. Although an appreciation of autophagic dysfunction in AD certainly has grown over the past several years, the field remains in its infancy. More studies are needed to fully elucidate the potentials of modulating autophagy as a viable therapeutic approach for AD.

Note: This article is part of a series on A β Catabolism, edited by Elizabeth Eckman. Other articles in this series can be found at http://alzres.com/series/Abeta_catabolism.

Abbreviations

AD: Alzheimer's disease; APP: Amyloid precursor protein; AV: Autophagosome vacuole; A β : amyloid-beta; BACE-1: β -site amyloid precursor protein-cleaving enzyme 1; ER: Endoplasmic reticulum; LSD: Lysosomal storage disorder; mTOR: Mammalian target of rapamycin; NFT: Neurofibrillary tangle; PS1: Presenilin 1; PS2: Presenilin 2; TFEB: Transcription factor EB; TPC: Two-pore channel.

Competing interests

The authors declare that they have no competing interests.

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