

## Autophagy: A double-edged sword in Alzheimer's disease

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Autophagy is a major protein degradation pathway that is essential for stress-induced and constitutive protein turnover. Accumulated evidence has demonstrated that amyloid- $\beta$  (A $\beta$ ) protein can be generated in autophagic vacuoles, promoting its extracellular deposition in neuritic plaques as the pathological hallmark of Alzheimer's disease (AD). The molecular machinery for A $\beta$  generation, including APP, APP-C99 and  $\beta$ -/ $\gamma$ -secretases, are all enriched in autophagic vacuoles. The induction of autophagy can be vividly observed in the brain at early stages of sporadic AD and in an AD transgenic mouse model. Accumulated evidence has also demonstrated a neuroprotective role of autophagy in mediating the degradation of aggregated proteins that are causative of various neurodegenerative diseases. Autophagy is thus widely regarded as an intracellular hub for the removal of the detrimental A $\beta$  peptides and Tau aggregates. Nonetheless, compelling data also reveal an unfavorable function of autophagy in facilitating the production of intracellular A $\beta$ . The two faces of autophagy on the homeostasis of A $\beta$  place it in a very unique and intriguing position in AD pathogenesis. This article briefly summarizes seminal discoveries that are shedding new light on the critical and unique roles of autophagy in AD and potential therapeutic approaches against autophagy-elicited AD.

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### 1. Introduction

Autophagy is a highly conserved intracellular pathway involved in the organized elimination of proteins and organelles by lysosomes. The physiological functions of autophagy are required for cellular adaptations to nutrient deprivation and stress, and the constitutive activity of autophagy is also recognized as an arbitrator of neuronal survival. On the other hand, the pathophysiological roles of autophagy have been implicated in death decisions leading to neurodegenerative diseases. In a *Drosophila* model expressing amyloid- $\beta$ 42 (A $\beta$ 42), autophagy activation can further exacerbate A $\beta$ -induced neurotoxicity (Ling *et al.*

2009). It is believed that the abnormality of autophagic proteolysis can lead to a build-up of waste proteins or unwanted aggregates. The pathological functions of autophagy could then become a critical mediator of neurotoxicity elicited by these undigested protein aggregates, constituting a vicious cycle which further aggravates neuronal death. Emerging data thus support the view that dysregulation of autophagy could play a critical role in the pathogenesis of neurodegenerative disorders (Nixon and Yang 2011). In this review, we highlight the pathophysiological roles of autophagy and its potential therapeutic implications in Alzheimer's disease (AD) with emphasis on autophagy-localized  $\gamma$ -secretase-catalysed A $\beta$  production.

**Keywords.** Alzheimer's disease; amyloid precursor protein; amyloid- $\beta$ ; autophagy; secretases

## 2. Alzheimer's disease

AD, the most prevalent type of dementia in the elderly, affects more than 35 million people worldwide, and has become one of the most costly diseases to society. In brains of AD patients, the extracellular deposition of amyloid plaques and intracellular aggregation of neurofibrillary tangles (NFTs) are two major pathological hallmarks, and are widely regarded as the primary causes of neurodegeneration in AD.

Amyloid plaques are composed of fibrillar aggregates of the A $\beta$  peptide that is derived from the proteolysis of the A $\beta$  precursor protein (APP) through sequential cleavages by  $\beta$ - and  $\gamma$ -secretases. Extracellular A $\beta$  deposition surrounding damaged neurons in AD brains is believed to be a major contributing factor to AD pathogenesis. However, accumulating evidence shows that intracellular A $\beta$  aggregates in neurons are intimately correlated with cognitive deficits, suggesting that the production of intracellular A $\beta$  could also contribute to the disease progression of AD.

Although the prevailing amyloid cascade hypothesis suggests that A $\beta$  acts upstream of NFTs in AD pathogenesis (Hardy and Selkoe 2002), growing evidence supports that dysregulated production of both Tau and A $\beta$  can synergistically disrupt synaptic activity and mitochondrial function, resulting in the neurodegenerative deficits of AD (Roberson *et al.* 2007; Quintanilla *et al.* 2011). Therefore, delicate regulatory mechanisms of both A $\beta$  and Tau metabolism are crucial for normal neuronal function. Herein, we review recent findings supporting the view that autophagy, one of the major protein degradation systems, is critically involved in A $\beta$  homeostasis and AD pathogenesis, and discuss possible therapeutic strategies targeting autophagic activity in alleviating the A $\beta$ -associated pathogenesis of AD. A brief discussion of the correlation between autophagy and Tau-elicited neurodegeneration in AD is also presented. The two faces of autophagy on the homeostasis of A $\beta$  are the main focal points of discussion due to the unique features of autophagy in AD pathogenesis.

## 3. Autophagy: An intracellular machinery for protein degradation

Autophagy is regarded as a major protein degradation pathway that is critical for stress-induced and constitutive protein turnover as well as the maintenance of normal cellular homeostasis (Mizushima *et al.* 2008). Three types of autophagy have been identified in mammalian cells: macroautophagy is characterized by the formation of a double-membrane autophagosome that fuses with a lysosome to degrade its contents; chaperone-mediated autophagy (CMA) requires specific chaperone proteins to transport cytosolic molecules directly into lysosomes, without sorting

through autophagosomes; and microautophagy is the direct engulfment of molecules surrounding lysosomes by the dynamic activity of lysosomal membranes (Huang and Klionsky 2002; Knecht *et al.* 2009). Since macroautophagy is the best characterized type and is mostly discussed in relation to AD, we will hereafter simply refer to macroautophagy as autophagy.

Autophagy is initiated by the formation of a pre-autophagosomal structure (PAS) that encloses a portion of the cytoplasm, and which become a double-membrane-limited autophagosome (Mizushima *et al.* 2008). The identification of autophagy-related genes (ATGs), *Atg1~Atg35*, allowed the molecular mechanism underlying autophagosome formation to be delineated, and their functions are thought to be conserved from yeast to humans (Meijer *et al.* 2007). The translocation of *Atg8* or its mammalian homolog, LC3, to the autophagosome membrane is thus commonly used as a marker of autophagosome formation. The conversion of *Atg8* from an unlipidated (form I) to a lipidated species (form II) is closely correlated with autophagosome formation (Nakatogawa *et al.* 2007). Catabolism of confined materials within autophagosomes then ensues when their outer membranes are fused with lysosomes or late endosomes, enabling cells to survive during stressful conditions by recycling the degraded products for sources of energy production and macromolecule synthesis.

Although autophagic pathways appear to non-selectively engulf cytosolic molecules, autophagy can also specifically trap certain cargoes by the association between LC3, an autophagosomal membrane protein and a marker of autophagosomes, and a cargo receptor. The detailed mechanism is not well characterized yet, but several cargo receptors have been identified, including p62 and NRB1 (Pankiv *et al.* 2007; Knaevelsrud and Simonsen 2010). These cargo receptors are thought to link ubiquitinated cargo proteins to LC3 and entrap them in autophagosomes, leading to the degradation of the ubiquitinated cargoes (Pankiv *et al.* 2007; Ichimura *et al.* 2008; Kirkin *et al.* 2009; Tung *et al.* 2010).

The essential roles of autophagy in the homeostasis of protein metabolism have been intensively studied in various biological contexts. Increased autophagic activity has been shown to extend the lifespan of animals in various models (Melendez *et al.* 2003; Eisenberg *et al.* 2009; Bjedov *et al.* 2010). Conditional deletion of ATGs in the central nervous system of mice results in loss of autophagic activity and the concomitant accumulation of ubiquitinated proteins, leading to significant neurodegeneration (Hara *et al.* 2006; Komatsu *et al.* 2006). Those findings clearly suggest that autophagy-mediated clearance of unwanted aggregates is extremely crucial for neuronal survival, consistent with the notion that a decline in autophagy activity is tightly associated with normal aging (Lipinski *et al.* 2010). It is thus plausible that

autophagy could dictate normal and pathological aging through an intricate molecular machinery controlling intracytoplasmic levels of toxic protein aggregates in postmitotic neurons (Rubinsztein *et al.* 2011). The correlation between perturbed autophagy and aging may underscore the pathogenic events associated with AD and related neurodegenerative diseases.

#### 4. The role of autophagy in the homeostasis of A $\beta$ production

The role of autophagy in the pathogenesis of AD has recently been elucidated. The expression of Beclin-1, an essential regulator for initiating the autophagic process, is decreased in AD patients (Pickford *et al.* 2008; Jaeger *et al.* 2010). This depletion of Beclin-1 is believed to be caused by caspase-mediated cleavage (Rohn *et al.* 2011). Macroautophagic markers of Atg5, Atg12, and LC3 are found to be associated with plaque and tangle pathologies in AD (Ma *et al.* 2010). Interestingly, a recent study implicates that Herpes simplex virus type 1 in the brain disrupts autophagy and contributes to AD progression (Itzhaki *et al.* 2008). Morphological evidence also reveals that APP and A $\beta$  peptides can co-localize with LC3-positive autophagosomes in an APP-overexpressing cell line as well as in AD mouse models (Yu *et al.* 2004; Lunemann *et al.* 2007), suggesting that A $\beta$  could be an autophagic substrate and be subject to autophagy-mediated clearance. Consistent with this concept, cells depleted of Beclin-1, an initiator of autophagy, exhibit significant accumulation of A $\beta$ , full-length APP, and APP C-terminal fragments (APP-CTFs), concomitant with inhibition of autophagosome turnover (Jaeger *et al.* 2010). This finding is nicely confirmed by downregulation of Beclin-1 in an APP transgenic mouse model, in which evident accumulation of both intraneuronal and extracellular A $\beta$  deposition is accompanied by marked neurodegeneration (Pickford *et al.* 2008). Together, these data firmly support the model in which autophagy is essential for the removal of detrimental A $\beta$  peptides and aggregates.

A $\beta$ , on the other hand, has also been implicated in modulating autophagy, despite being an autophagy substrate. Cells overexpressing mutant APP (APP<sup>swe</sup>) are found to carry large numbers of double-membrane autophagic vacuoles, where A $\beta$  accumulates (Pajak *et al.* 2009). The build-up of intracellular A $\beta$  could thus regulate cellular autophagy through either an Akt-dependent pathway or induction of mitochondrial reactive oxygen species (ROS) generation (Hayashi *et al.* 2009; Lipinski *et al.* 2010). In addition, cells treated with A $\beta$  show an attenuated activation of mammalian target of rapamycin (mTOR) (Lafay-Chebassier *et al.* 2005), a negative regulator of autophagy (Caccamo *et al.* 2010). Together, it is plausible that A $\beta$

could act through diverse pathways to induce autophagy and create a feedback loop to promote its own degradation, constituting an intrinsic checkpoint for the homeostasis of A $\beta$  production (Hung *et al.* 2009).

The intrinsic A $\beta$ -elicited regulation of autophagy is also a very delicate system, because excessive amounts of intracellular A $\beta$  can lead to disruption of the lysosomal degradative system. In cultured cells, an ROS-induced increase in A $\beta$  accumulation in lysosomes could result in lysosomal membrane permeabilization, augmenting cellular sensitivity to ROS-induced apoptosis (Zheng *et al.* 2006a, b, 2009). Furthermore, exogenous expression of intracellular human A $\beta$  in *Caenorhabditis elegans* and *Drosophila* results in significant accumulation of autophagosomes due to impairment of autophagosome maturation (Florez-McClure *et al.* 2007; Ling *et al.* 2009).

Given that autophagosomes and other prelysosomal autophagic vacuoles are abundant in dystrophic neocortical and hippocampal pyramidal neurons from AD patients (Nixon *et al.* 2005), an alternative role of autophagy in sustaining A $\beta$  production has been proposed. This hypothesis concurs with similar findings in brains of PS1/APP transgenic mice at an early stage prior to extracellular A $\beta$  deposition (Yu *et al.* 2005). In healthy primary cortical neurons, active cathepsin-positive autolysosomes, rather than LC3-II-positive autophagosomes, predominate as the machinery for protein degradation, suggesting that newly formed autophagosomes efficiently fuse to lysosomes. Disruption of autophagosome-lysosome fusion results in marked accumulation of autophagosomes that resembles the ultrastructure observed in AD brains and in an AD mouse model (Boland *et al.* 2008). Moreover, immunostaining and subcellular fractionation analyses show that not only A $\beta$  peptides are located in autophagosomes/lysosomes, APP,  $\beta$ -CTF, and  $\gamma$ -secretase are also enriched in these organelles (Yu *et al.* 2004). Translocation of  $\gamma$ -secretase complexes from an endosome/endoplasmic reticulum (ER) pool to autophagosomes is highly enhanced by the induction of autophagy, concomitant with a dramatic increase in A $\beta$  production (Yu *et al.* 2005). *In vitro* assays further confirmed that  $\gamma$ -secretase can actively process  $\beta$ -CTFs to produce A $\beta$  inside autophagosomes, and modulation of autophagy can significantly affect A $\beta$  generation through alterations in  $\gamma$ -secretase activity, suggesting that these autophagic vacuoles could account for a significant source of intracellular A $\beta$  production in AD (Yu *et al.* 2005; Ohta *et al.* 2010). Interestingly, more A $\beta$ 42 than A $\beta$ 40 is produced by autophagosomes. It is believed that in healthy brains, efficient clearance of autophagic vacuoles by the autophagosome-lysosome maturation process prevents the accumulation of intracellular A $\beta$ . This notion is further corroborated by data that defective lysosomal catabolism of cholesterol and glycosphingolipids in neurons of Niemann-

Pick disease type C (NPC) augments  $\gamma$ -secretase-dependent A $\beta$  production (Mattsson *et al.* 2011). It has also been reported that autophagy is involved in hypoxia-induced increases in A $\beta$  production (Li *et al.* 2009). Emerging evidence suggests that the accumulation of intracellular A $\beta$  precedes the formation of extracellular A $\beta$  deposits and leads to the early progression of AD (LaFerla *et al.* 2007). The majority of intracellular A $\beta$  is identified as A $\beta$ 42 (Gouras *et al.* 2000; Takahashi *et al.* 2002). Thus, the pathological accumulation of intracellular A $\beta$  could wreak havoc on a variety of cellular functions, resulting in such insults as disruption of synaptic activity, proteasome dysfunction, calcium dyshomeostasis, and Tau hyperphosphorylation. However, another study shows that although APP-CTFs and A $\beta$  can readily be digested by lysosomal proteolysis, APP metabolism does not seem to occur in autophagic vacuoles (Boland *et al.* 2010). The exact role of autophagy in the homeostasis of A $\beta$  production in neurons still requires further investigation.

A recent study demonstrates that PS1, one of the  $\gamma$ -secretase core subunits, can function as an ER chaperone to assist with the *N*-glycosylation of the v-ATPase V0a1 subunit (Lee *et al.* 2010). Loss of PS1 expression results in the accumulation of immature unglycosylated v-ATPase. Since v-ATPase is required for the acidification of autolysosomes/lysosomes, the aberrant accumulation of late-stage autophagosomes containing undigested contents can thus be vividly observed in PS1-null cells, reminiscent of the ultrastructures present in AD neurons (Nixon *et al.* 2005). In line with those findings, two recent reports show that autophagy-mediated clearance of telencephalin and  $\alpha$ -synuclein is impaired in neurons from PS1<sup>-/-</sup> mice (Esselens *et al.* 2004; Wilson *et al.* 2004). This notion is further substantiated by another independent study showing that PS1 is indispensable for autophagosome-lysosome fusion independent of  $\gamma$ -secretase activity (Neely *et al.* 2011), suggesting that autophagy-localized PS1 may

have a distinctive function in neurons. Together, these findings support a model in which dysregulation of the autophagic system is an upstream event in AD pathogenesis and contributes to neuronal deficits in AD.

### 5. Potential anti-A $\beta$ therapeutic strategies for AD that target autophagy

Several studies focus on autophagy as a potential therapeutic target to decrease abnormal aggregates in neurons and alleviate neurotoxicity. Small-molecule compounds that can activate autophagy through either mTOR-dependent or mTOR-independent pathways are identified through cell-based screening systems (Sarkar *et al.* 2007; Williams *et al.* 2008; Balgi *et al.* 2009), and are shown to be protective in models of polyglutamine diseases (Jimenez-Sanchez *et al.* 2011). Rapamycin, an mTOR inhibitor which also functions as a tumor suppressor and an autophagy inducer, is able to reduce A $\beta$  and Tau pathology in animal models of AD (Bove *et al.* 2011). In addition, a small-molecule enhancer of rapamycin (SMER)28 has recently been proven to promote the clearance of A $\beta$  and APP-CTFs from cultured cells (Tian *et al.* 2011). Coincidentally, some drugs used in AD clinical trials are found to be effective in regulating autophagy (table 1), further suggesting that autophagy could be a legitimate pharmacological target of AD.

A recent report suggests that patients with chronic lithium treatment, a mood-stabilizing drug, exhibit a significantly lower prevalence of AD (Nunes *et al.* 2007). The protective effect of lithium may partly be through modulation of autophagy, since inhibition of inositol monophosphatase by lithium can result in a decrease in myo-inositol-1,4,5-triphosphate (IP<sub>3</sub>) and in turn activates autophagy (Sarkar *et al.* 2005). Nilvadipine, a calcium channel blocker used to treat hypertension, is also evaluated as a possible treatment for AD in a clinical trial (Kennelly

**Table 1.** A partial list of small-molecule compounds being evaluated in clinical trials or approved as Alzheimer's disease (AD) therapies that can modulate autophagic activity

Drug in clinical use or a trial	Primary pharmacological target	Effect on autophagy	Mode of action in autophagic regulation	References
Lithium	IMPase inhibitor	Activator of autophagy	Reduces inositol and IP <sub>3</sub> levels	Sarkar <i>et al.</i> 2005
Nilvadipine	Ca <sup>2+</sup> channel blocker	Activator of autophagy	Reduces intracytosolic Ca <sup>2+</sup> levels	Williams <i>et al.</i> 2008; Zhang <i>et al.</i> 2007
Nicotinamide	Histone deacetylase inhibitor	Activator of autophagy	Up-regulates ATG12	Kang and Hwang 2009
Galanthamine hydrochloride	Agonist of the nicotinic acetylcholine receptor	Inhibitor of autophagy	Possibly down-regulates autophagy-related genes	Lipinski <i>et al.</i> 2010
Ghrelin	Natural ligand for the growth hormone secretagogue receptor	Inhibitor of autophagy	Possibly down-regulates autophagy-related genes	Lipinski <i>et al.</i> 2010



*et al.* 2011). Interestingly, two independent screens identify similar calcium channel blockers that can enhance autophagic activity (Zhang *et al.* 2007; Williams *et al.* 2008), suggesting that the efficacy of nilvadipine on AD could be due to its effect on autophagy enhancement. In addition, nicotinamide, an histone deacetylase (HDAC) inhibitor that selectively reduces a specific form of phospho-tau (Thr<sup>231</sup>) in an AD mouse model (Green *et al.* 2008), can enhance autophagy activation in human cells and prevent cognitive decline in AD patients (Demarin *et al.* 2004; Kang and Hwang 2009). However, clonidine, a noradrenergic receptor agonist that activates autophagy through an mTOR-independent pathway (Williams *et al.* 2008), can worsen the attention and memory deficits in AD patients (Riekkinen *et al.* 1999). Furthermore, an AD drug, galanthamine, and an AD drug candidate, ghrelin, can inhibit autophagy through targeting autophagy-related genes in a genome-wide screen (Lipinski *et al.* 2010). These discrepancies may be due to the combined effects of various pharmacological targets or the different extents of autophagic modulation by these drugs. Together, these findings further substantiate the proposed 'double-edged sword model' of autophagy in AD, and suggest that a delicate governance of autophagic activity is needed for AD therapy.

Previous studies have found that the fusion between autophagosomes and lysosomes during the autophagic process and the acidification of lysosomes could be impaired in AD (Lee *et al.* 2010, 2011). Consistent with those findings, the genetic ablation of cystatin B, an endogenous inhibitor of lysosomal cysteine proteases, enhances lysosomal activities and ameliorates amyloid pathologies and memory deficits in an AD mouse model (Yang *et al.* 2011). We thus reason that activation of autophagy at an early stage might not be sufficient to ameliorate autophagy-associated deficits in AD. Strategies that can enhance lysosomal activity and/or autophagosome/lysosome fusion could be keys to developing novel therapeutic interventions against AD.

## 6. The autophagy-dependent clearance of Tau as a therapeutic target of AD

Neurotoxicity downstream of Tau aggregates is believed to be essential for A $\beta$ -elicited neurodegeneration in AD (Querfurth and LaFerla 2010). Strategies targeting the molecular mechanisms underlying the Tau-mediated formation of neurofibrillary tangles, including the abnormal hyperphosphorylation of Tau, the misfolding and aggregation of Tau, and the defective clearance of Tau aggregates, have been proposed to be legitimate alternatives to anti-A $\beta$  approaches (Gong *et al.* 2010).

It is suggested that the intracellular clearance of soluble Tau and aggregated NTFs is at least partially mediated by

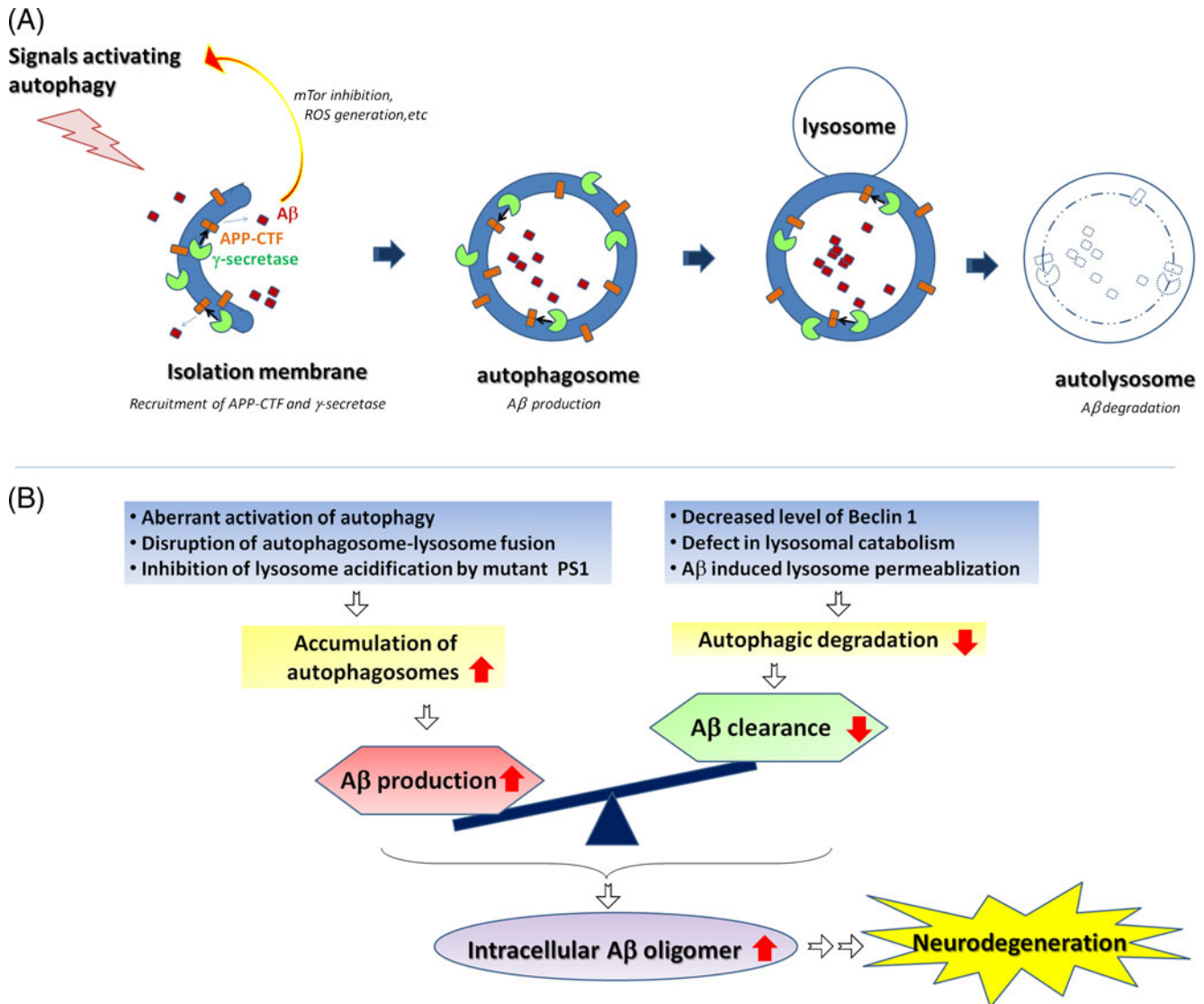
autophagy. Tau-enriched granules are detected in lysosomes of neurons from human brains (Ikeda *et al.* 1998, 2000). Inhibition of autophagy by 3-methylamphetamine (3-MA) leads to enhanced Tau aggregation and Tau-elicited neurotoxicity (Wong *et al.* 2008; Wang *et al.* 2009). When lysosomal hydrolases are inhibited by either an acidotropic agent, chloroquine (CQ), or a cathepsin B/L inhibitor in neuroblastoma cells overexpressing Tau, levels of Tau and Tau aggregates are significantly increased (Hamano *et al.* 2008). Tau-overexpressing *Drosophila* treated with rapamycin, an autophagy inducer, exhibits reduced aggregation of Tau and Tau-induced neurotoxicity (Berger *et al.* 2006). Recently, phospholipase D1 (PLD1) is identified as acting downstream of Vps34 to regulate autophagosome maturation, and blockade of PLD1 activity results in higher levels of Tau and p62 aggregates in the brain, strongly favouring a role of autophagy in the degradation of Tau (Dall'Armi *et al.* 2010). Interestingly, it has been demonstrated that full-length Tau is preferentially degraded through macroautophagy, while Tau<sub>RD</sub> $\Delta$ K280, a truncated Tau containing pro-aggregated repeat domains and which functions as a seed for initiating Tau aggregate formation, is translocated to lysosomes through CMA machinery (Wang *et al.* 2009), suggesting that different Tau fragments might be degraded through distinct autophagic pathways. In agreement with this notion, another caspase-cleaved Tau, which is present in AD brains and is more prone to aggregate and induce neurotoxicity than natural Tau, is preferentially degraded through autophagy in a faster turnover rate than the full-length Tau (Dolan and Johnson 2010). Together, these data strongly favour a model in which the autophagy-mediated degradation of Tau could be pivotal for the homeostasis of intracellular Tau (Gong *et al.* 2005). A deficiency in autophagy-mediated Tau degradation could tip the balance toward the formation of neurofibrillary tangles, resulting in the Tau-elicited neurotoxicity that further exacerbates A $\beta$ -induced neurodegeneration in AD. Therapeutic strategies that can simultaneously block A $\beta$ - and Tau-elicited neurotoxicity could become an ideal approach for developing next-generation anti-AD drugs.

## 7. Conclusions

It is now clear that autophagy plays a crucial role in maintaining the homeostasis of A $\beta$  production in neurons. Impairment of the autophagosome-lysosome system in AD neurons is proven to result in accumulation of detrimental A $\beta$  aggregates, and is also instrumental in causing ROS insults and neuronal death. These events in combination contribute to neurodegeneration and the pathogenesis of AD. Given that A $\beta$ <sub>42</sub> is the primary form of intracellular A $\beta$  and has a higher propensity to form oligomers (Gouras *et al.*

2000; Takahashi *et al.* 2002), autophagy may thus occupy a unique position in deciding the ratio of A $\beta$ 40 to A $\beta$ 42 and the formation of oligomeric A $\beta$  versus monomeric A $\beta$ . It is conceivable that the pathological insults leading to AD could breach the physiological role of autophagy in maintaining the homeostasis of A $\beta$  production in neurons, tipping the balance toward increased production of A $\beta$ 42

and A $\beta$  oligomers due to unrestrained pathological activity of autophagy. It is the authors' opinion that the molecular mechanism underlying the autophagosome-lysosome system in the nervous system could lay the foundation for the development of therapeutic strategies against AD and related neurodegenerative diseases. Identification of this hypothetical 'master switch' of autophagy that governs its



**Figure 1.** A 'double-edged sword' model for the role of autophagy in the homeostasis of amyloid- $\beta$  (A $\beta$ ) in Alzheimer's disease. (A) Diagram of two faces of autophagy (production vs. degradation) on the homeostasis of intracellular A $\beta$  under normal physiological condition. Intracellular A $\beta$  inhibits mammalian target of rapamycin (mTOR) and simultaneously elicits reactive oxygen species (ROS) production to synergistically activate autophagy, a feedback control critical for maintaining A $\beta$  at a physiological level (balanced A $\beta$  production vs. A $\beta$  clearance).  $\gamma$ -Secretase, A $\beta$  precursor protein (APP)-C-terminal fragments (CTFs), and A $\beta$  are respectively shown in green, orange, and red. Note that isolation membrane and autophagosomes are double-membrane structures and that  $\gamma$ -secretase and APP-CTFs are depicted as evenly distributed on the membrane. (B) Aberrant autophagic activity in pathological conditions leads to inhibition of A $\beta$  clearance and/or enhancement of A $\beta$  (especially A $\beta$ 42) generation. The net accumulation of intracellular A $\beta$  may further disrupt the autophagic system, constituting a vicious cycle that could tip the balance toward the formation of A $\beta$  oligomers and adversely lead to neurodegeneration.

physiological versus pathological activities would certainly help to unveil the machinery that dictates autophagy as either a gatekeeper of cell survival or a culprit of neurotoxicity (figure 1). The development of selective autophagy modulators that would only alleviate pathological autophagy activity without affecting its physiological functions could represent tremendous therapeutic potential for AD and related neurodegenerative diseases.

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