



decreased VLDL secretion and temporary storage of TG, which minimizes competition of VLDL and chylomicrons for catabolism. In the fed-to-fasting transition, stored TG is secreted with MTP, coordinating the intracellular coupling of TG with apoB to form VLDL, which is then secreted and thereby reduces accumulated TG. In insulin-resistant states, de novo lipogenesis is stimulated, and there is increased hepatic uptake of FAs released from fat. Dietary overindulgence increases apoB availability, enhances MTP expression, and increases lipogenesis, thereby maximizing VLDL secretion. It is critical to further investigate FoxO1 regulation of *Mttp* and coordination with other factors involved in regulating hepatic VLDL metabolism, as increased understanding of these events will provide rational interventional treatment strategies. Kamagate et al. (7) have demonstrated that FoxO1 is important in the regulation of hepatic VLDL-TG secretion, and in doing so have established a link among overindulgence, insulin resistance, and metabolic syndrome.

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## Regulation of A $\beta$ pathology by beclin 1: a protective role for autophagy?

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**The amyloid  $\beta$  (A $\beta$ ) peptide is thought to be a major culprit in Alzheimer disease (AD), and its production and degradation have been intensely investigated. Nevertheless, it remains largely unknown how A $\beta$  pathology is modulated by the autophagy pathway. The study by Pickford and colleagues in this issue of the *JCI* shows that beclin 1, a multifunctional protein that also plays an important role in the autophagy pathway, affects some aspects of A $\beta$  pathology in aged but not young transgenic mice expressing amyloid precursor protein (APP) (see the related article beginning on page 2190). These findings further support the notion that modulation of autophagy, in this case through beclin 1, may represent a novel therapeutic strategy for AD.**

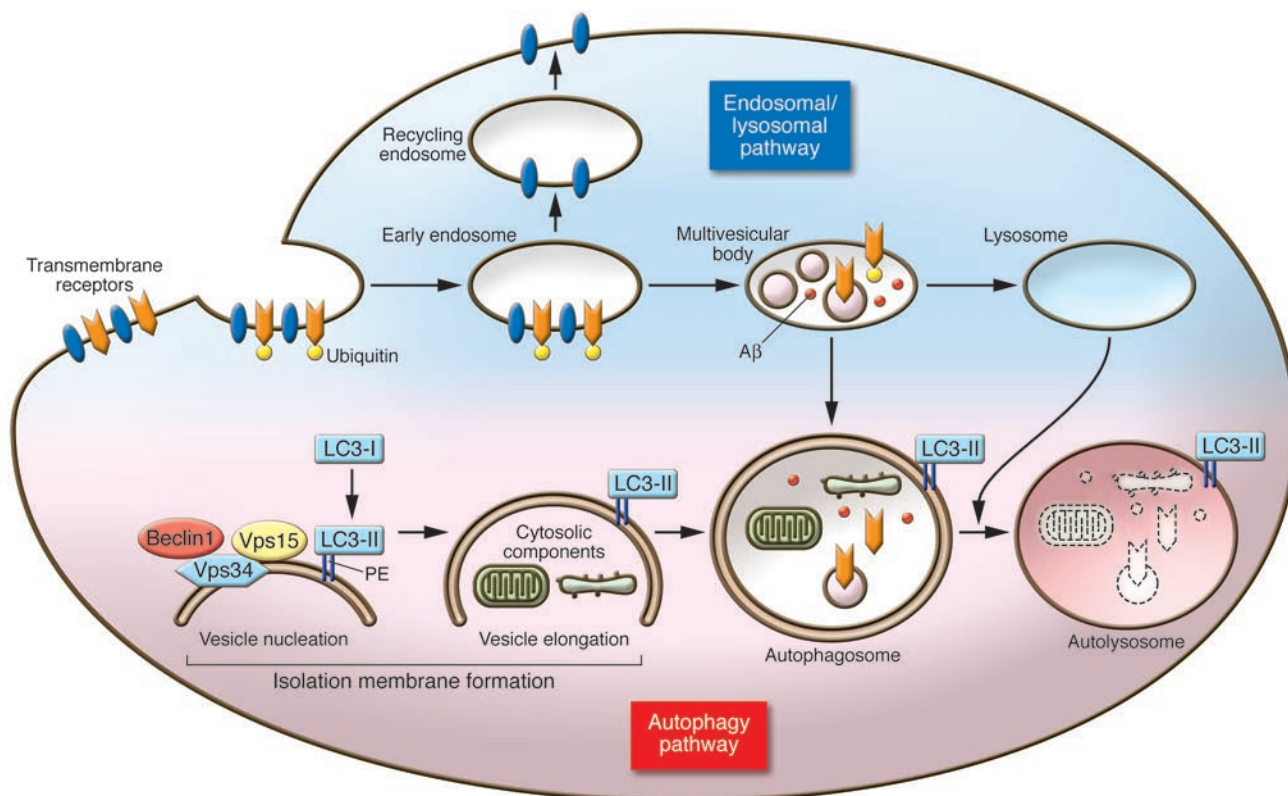
**Nonstandard abbreviations used:** A $\beta$ , amyloid  $\beta$ ; AD, Alzheimer disease; APP, amyloid precursor protein; LC3, microtubule-associated protein 1 light chain 3; MCI, mild cognitive impairment; PE, phosphatidylethanolamine.

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The enormous interest in the autophagy pathway reflects its involvement in many different physiological and pathological conditions, including age-dependent neurodegenerative diseases. Autophagy (referring to macroautophagy herein) is an intracellular process that allows cells to engulf cytoplasmic contents — both

soluble molecules and large organelles — in specialized double membranes and deliver them to lysosomes for degradation (1). This self-eating process is often a nonselective stress response to many extracellular and intracellular stimuli. Autophagy is highly dynamic and involves multiple steps, including the initial formation of double membranes and autophagosomes and their maturation into autolysosomes (Figure 1). Whether autophagosomes are beneficial or detrimental to a cell depends on the context. For instance, defects in autophagosome formation and loss of basal autophagy cause neurodegeneration (2, 3), and increased autophagic activity helps to clear aggregated disease proteins, such as mutant  $\alpha$ -synuclein and huntingtin (proteins believed to contribute to the pathology of Parkinson



**Figure 1**

Steps in the autophagy pathway. Autophagy is a process by which cytoplasmic contents are sequestered by autophagosomes and degraded upon fusion with lysosomes. Autophagy occurs at a basal level and is regulated by several pathways. Once autophagy is induced, an isolation membrane is formed by vesicle nucleation. Beclin 1 interacts with the Vps34 protein complex and is involved in this initial step by increasing the activity of Vps34 (a type of PI3K). Therefore, beclin 1 is a positive regulator of the autophagy pathway and promotes its induction. PE is conjugated to cytosolic LC3-I and converts it into lipidated LC3-II. LC3-II localizes to both the outside and the inside membranes of autophagosomes and therefore is often used as a marker. After their formation, autophagosomes mature through fusion with endosomal compartments and with lysosomes to form autolysosomes for degradation of cytosolic components. In the endosomal/lysosomal pathway, mono-ubiquitination serves as a signal for targeting transmembrane cargo in early endosomes to multivesicular bodies. Aβ can be generated in multivesicular bodies and autophagosomes. The study by Pickford et al. in this issue of the *JCI* (10) reports that increased levels of beclin 1 reduces levels of Aβ, presumably through enhanced autophagic activity, although the detailed mechanism remains unclear.

and Huntington diseases, respectively) (4, 5). On the other hand, impaired maturation of autophagosomes may underlie, at least in part, the pathogenesis of Alzheimer disease (AD) (6), and excess accumulation of autophagosomes may contribute to neurodegeneration induced by dysfunctional endosomal sorting complex required for transport-III (ESCRT-III) and associated with frontotemporal dementia linked to chromosome 3 (7).

Brains of patients with AD contain many more autophagosomes and other vesicular structures than do brains of control patients, and the autophagosomes tend to accumulate markedly in dystrophic neurites (8, 9). This accumulation, resulting from increased autophagosome induction, impaired autophagosome maturation, or both, may well contribute to the pathogen-

esis of AD. Indeed, these abnormally accumulated autophagosomes are enriched in amyloid precursor protein (APP) and its processing enzymes and produce amyloid β (Aβ) peptides, the main constituents of amyloid plaques in the brains of AD patients (6). Moreover, in cell culture models, increased induction of the autophagy pathway through pharmacological manipulation leads to elevated Aβ accumulation (6).

To further define the role of the autophagy pathway in AD pathogenesis, Pickford et al. report in this issue of the *JCI* that the level of beclin 1 expression is lower in the brains of individuals with mild cognitive impairment (MCI) than in the brains of control patients, and is even lower in the brains of patients with severe AD (10). In transgenic mouse models of AD, partial reduction of beclin 1 increased Aβ lev-

els in aged (9-month-old) but not young (3.5-month-old) animals and enhanced several aspects of Aβ pathology. Conversely, increased expression of beclin 1 in 6-month-old APP transgenic mice did just the opposite.

Beclin 1 is an important multifunctional protein that also plays an important role in autophagy (11, 12). Therefore, the work presented by Pickford et al. (10) further contributes to the current debate about the precise roles of the autophagy pathway in AD. The authors' findings in animal models of AD suggest that modulation of beclin 1 activity may be a therapeutic strategy for AD, although the molecular and cellular mechanisms for the observed effects remain to be determined in detail, and other intriguing questions need to be answered.



### Is beclin 1 expression specifically decreased in neurons of AD brains?

Beclin 1 has tumor suppressor activity and binds to the antiapoptotic protein Bcl-2, and its expression is decreased in various types of tumor cell lines. More importantly, beclin 1 is required for the induction of autophagy in vivo (11, 12). In subjects with MCI or severe AD, Pickford et al. found that both mRNA and protein levels of beclin 1 are reduced only in affected brain regions, such as the entorhinal cortex (10). This decrease could largely result from loss of neurons or other cell types in AD brains. Indeed, Pickford et al. reported that the number of beclin 1-immunopositive cells was significantly reduced in the midfrontal cortex compared with control brains. Curiously, the level of a neuron-specific marker as measured by Western blot was the same in severe AD and control brains. Because beclin 1 seems to be expressed in both neurons and glial cells, especially after injury (13), and 90% of the cells in human brains are glial cells, it remains a technical challenge to determine quantitatively whether the level of beclin 1 expression is indeed lower in individual surviving neurons in human brains with severe AD than in age-controlled normal brains. This is an important issue, especially considering the finding reported by the authors that beclin 1 levels are normal in transgenic mouse models of AD in which neuronal cell loss is minimal (14). It will also be interesting to examine in more detail the number and size of autophagosomes and other parameters of the autophagy pathway in AD brains used in this study, as done in other reports (6, 9).

### Reduced beclin 1 activity promotes A $\beta$ pathology in APP transgenic mice

Pickford et al. (10) report the effects of reduced expression of beclin 1 (encoded by *Becn1*) on various aspects of A $\beta$  pathology in mouse models of AD in which human mutant APP was overexpressed specifically in neurons under the control of the *Thy1* promoter (15). Regardless of whether beclin 1 level is specifically reduced in neurons of AD brains, these findings in animal models may have important implications for our understanding of AD pathogenesis. The authors examined *APP<sup>+</sup>Becn1<sup>-/-</sup>* mice and found significant increases in extracellular A $\beta$  immunoreactive deposits, number of thioflavin S-positive plaques with globular shapes, and intraneuronal A $\beta$  levels. Moreover, lysosomal abnor-

malities were more pronounced, and the expression of CD68, a marker of increased phagocytic activity of macrophages and microglia, was higher in *APP<sup>+</sup>Becn1<sup>-/-</sup>* mice than in *APP<sup>+</sup>Becn1<sup>+/+</sup>* mice, probably as a result of increased A $\beta$  production.

Intriguingly, beclin 1 deficiency did not seem to affect the extent of synaptic and dendritic degeneration in APP transgenic mice nor calbindin immunoreactivity, a molecular indicator of neurodegeneration (14), even though the levels of extracellular and intracellular A $\beta$  were significantly higher in *APP<sup>+</sup>Becn1<sup>-/-</sup>* than in *APP<sup>+</sup>Becn1<sup>+/+</sup>* mice (10). Another interesting observation is that beclin 1 deficiency had age-dependent effects on A $\beta$  level: loss of one copy of *Becn1* correlated with increased levels of formic acid-soluble A $\beta$  in 9-month-old *APP<sup>+</sup>* mice but not in 3.5-month-old animals. In human brains, *BECN1* mRNA and protein levels in the prefrontal cortex were about 2-fold lower in older than younger people (16). Therefore, it is conceivable that the more pronounced effect of beclin 1 deficiency in older mice may reflect, at least in part, the lower beclin 1 levels in older animals.

These observations raise the question of how loss of one copy of *Becn1* altered A $\beta$  pathology so dramatically in this mouse model of AD (10). One plausible explanation is reduced autophagy. Indeed, Pickford et al. reported that both the number of microtubule-associated protein 1 light chain 3-positive (LC3-positive) vesicles in cultured primary hippocampal neurons and the ratio of LC3-II to LC3-I in lysates of mouse cortex were lower as a result of beclin 1 deficiency, consistent with a previous report (17). LC3 is the mammalian homolog of the autophagy-related protein 8 (Atg8), a ubiquitin-like protein conjugated to phosphatidylethanolamine (PE) during autophagosome formation. Therefore, PE-modified LC3 (i.e., LC3-II) is often used as a marker for isolation membranes and autophagosomes (18, 19). However, considering the potential caveats of using overexpressed GFP-LC3 (18, 19) and the subtle difference in the LC3-II/LC3-I ratio as shown by Western blot in the present study, it will be helpful to perform additional assays to measure the autophagy flux and activity. Moreover, it will be interesting in the future to determine whether partial reduction of the activities of some *Atg* genes, such as *Atg7* (2, 3), also enhances A $\beta$  pathology in APP transgenic mice.

Beclin 1 is a multifunctional protein with many binding partners. For instance, beclin 1

may affect the endosomal/lysosomal pathway (20). A $\beta$  processing can occur in many subcellular compartments, including the endosomal/lysosomal pathway, which may – through unknown mechanisms – be influenced by beclin 1 deficiency. Also, beclin 1 is well known to interact with Bcl-2 (11, 12) and aged *Becn1<sup>-/-</sup>* mice exhibit a high incidence of spontaneous tumors (21). Therefore, aged *APP<sup>+</sup>Becn1<sup>-/-</sup>* mice may suffer more stress than *APP<sup>+</sup>Becn1<sup>+/+</sup>* mice. Finally, if the reduced induction of autophagy is indeed the direct underlying mechanism for observed higher levels of A $\beta$  peptides and aggregates, then the present model (10) appears to contradict previously published work (6). However, because the A $\beta$  level is affected by both production and clearance (22), reduced autophagy through beclin 1 deficiency in vivo may inhibit clearance of A $\beta$ , while defects in autophagosome maturation enhance A $\beta$  production. Additional experiments are needed to dissect the precise consequences of manipulating different steps of the autophagy pathway on A $\beta$  pathology and neurodegeneration associated with AD. As the authors discussed thoroughly, the exact molecular and cellular mechanisms linking beclin 1 deficiency and A $\beta$  level remain to be further investigated.

### Suppression of A $\beta$ pathology by ectopic beclin 1 expression

In AD patients, the maturation of autophagosomes may be impaired (6). Further induction of the autophagy pathway by enhancing beclin 1 activity may lead to unintended consequences. Nonetheless, regardless of the underlying molecular mechanism, the finding that beclin 1 overexpression reduces both the intracellular level and the extracellular deposition of A $\beta$  in a mouse model of AD is exciting (10). If this finding can be further confirmed by others in different cellular and animal models of AD, manipulating beclin 1 activity in combination with other interventions may be an attractive therapeutic approach for AD patients. The results described by Pickford et al. in this issue of the *JCI* will certainly spur more in-depth mechanistic studies of the specific roles of autophagy in AD, and those future studies will likely move us closer to our collective goal of finding a cure for this insidious disease.

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## A signaling pathway AKTing up in schizophrenia

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**The serine/threonine protein kinase AKT (also known as PKB) signaling pathway has been associated with several human diseases, including schizophrenia. Studies in preclinical models have demonstrated that impaired AKT signaling affects neuronal connectivity and neuromodulation and have identified AKT as a key signaling intermediary downstream of dopamine (DA) receptor 2 (DRD2), the best-established target of antipsychotic drugs. A study by Tan et al. in this issue of the JCI strengthens links among AKT signaling, DA transmission, and cognition in healthy individuals and offers potential avenues to explore in an effort to find more effective pharmacotherapies for schizophrenia and related disorders (see the related article beginning on page 2200).**

AKT (also known as PKB) is a key mediator of signal transduction processes mediated by protein phosphorylation and dephosphorylation (1) and a central node in cell signaling downstream of growth factors, cytokines, and other external stimuli. The AKT gene family includes three members (AKT1, AKT2,

AKT3), which possess partially redundant functions and contribute to several cellular functions including cell growth, survival, and metabolism. AKT has several substrates, most notable among them glycogen synthase kinase 3 $\alpha$  (GSK-3 $\alpha$ ) and GSK-3 $\beta$ , both of which are inhibited by AKT in response to various external cellular stimuli (1).

### AKT signaling and susceptibility to schizophrenia

Gain or loss of AKT activity has been associated with several human diseases, including cancer and type 2 diabetes (1). Since the initial report in 2004 from Emamian et al.

(2), accumulating evidence suggests that impaired AKT signaling also plays a role in the pathogenesis of schizophrenia. First, an association between schizophrenia and AKT1 genetic variants (Figure 1A) has been reported in several case/control samples and family cohorts (an updated compilation of such studies is now available; see ref. 3). Second, a number of studies have provided convergent evidence of a decrease in AKT1 mRNA, protein, and activity levels (reflected by changes in substrate phosphorylation) in brains of some individuals with schizophrenia (2, 4, 5). Negative findings have also been reported in some patient cohorts (3), but overall, an increasingly strong link between a dysregulation of AKT signaling and schizophrenia is emerging. Importantly, pharmacological evidence indicates that drugs used in the management of psychosis, such as the typical antipsychotic haloperidol as well as several atypical antipsychotics, can act as enhancers of AKT signaling in vivo or in vitro by directly activating AKT or by increasing the phosphorylation of its substrates GSK-3 $\alpha$  and GSK-3 $\beta$  (reviewed in ref. 6).

**Nonstandard abbreviations used:** COMT, catechol-O-methyltransferase; DA, dopamine; DRD2, dopamine receptor 2; GSK-3 $\alpha$ , glycogen synthase kinase 3 $\alpha$ ; PFC, prefrontal cortex.

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