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Targeting autophagy in Alzheimer's disease: Animal models and mechanisms

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ABSTRACT

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder that leads to cognitive impairment and memory loss. Emerging evidence suggests that autophagy plays an important role in the pathogenesis of AD through the regulation of amyloid-beta (Aβ) and tau metabolism, and that autophagy dysfunction exacerbates amyloidosis and tau pathology. Therefore, targeting autophagy may be an effective approach for the treatment of AD. Animal models are considered useful tools for investigating the pathogenic mechanisms and therapeutic strategies of diseases. This review aims to summarize the pathological alterations in autophagy in representative AD animal models and to present recent studies on newly discovered autophagy-stimulating interventions in animal AD models. Finally, the opportunities, difficulties, and future directions of autophagy targeting in AD therapy are discussed.

Keywords: Alzheimer's disease; Aβ metabolism; Tau pathology; Autophagy; Animal models

INTRODUCTION

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive and irreversible deterioration of the brain, leading to cognitive impairment and memory function decline (Graff-Radford et al., 2021; Querfurth & LaFerla, 2010). As the most common cause of dementia worldwide, AD currently afflicts approximately 40 million people globally, with its prevalence predicted to increase over the coming decades (Lynch, 2020). Neuropathologically, the disease is primarily defined by two hallmark lesions: intracellular neurofibrillary tangles (NFTs) arising from hyperphosphorylated tau protein and extracellular neurotic plaques composed of amyloid-beta (Aβ) and various other protein aggregates (Graff-Radford et al., 2021). The etiology of AD is complex, encompassing a combination of environmental and genetic factors, with various genes implicated in its pathogenesis (Zhang et al., 2019). Notably, *APP*, *PSEN1*, and *PSEN2* are considered the most commonly mutated genes in early-onset AD, while *APOEε4* is considered the strongest risk gene associated with late-onset AD (Li et al., 2017; Zare-Shahabadi et al., 2015). Given the absence of curative treatment strategies for AD, it is critical to advance research into the pathological mechanisms of the disease and to develop therapeutic interventions aimed at mitigating symptom progression (Knight et al., 2018).

Autophagy is a conserved catabolic process for intracellular substrate delivery and degradation, which maintains cellular homeostasis by constitutively degrading defective organelles or non-essential proteins and recycling components for energy and cellular remodeling. It can also be induced under starvation, oxidative stress, and a variety of disease conditions (Fleming et al., 2022; Klionsky et al., 2021; Levine & Kroemer, 2019; Wang et al., 2023). There are three main types of autophagy: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy (Figure 1) (Zare-Shahabadi et al., 2015; Zhang et al., 2021b). Of these, macroautophagy is considered predominant, contributing to the overall rate of autophagy and generally referred to as "autophagy". In the autophagic-lysosomal system, preautophagosomal structures (PAS) are formed to encapsulate selected substrates in the cytoplasm and subsequently develop into double-membrane autophagosomes. Lysosomes fuse with autophagosomes to form single-membrane autolysosomes, which eventually

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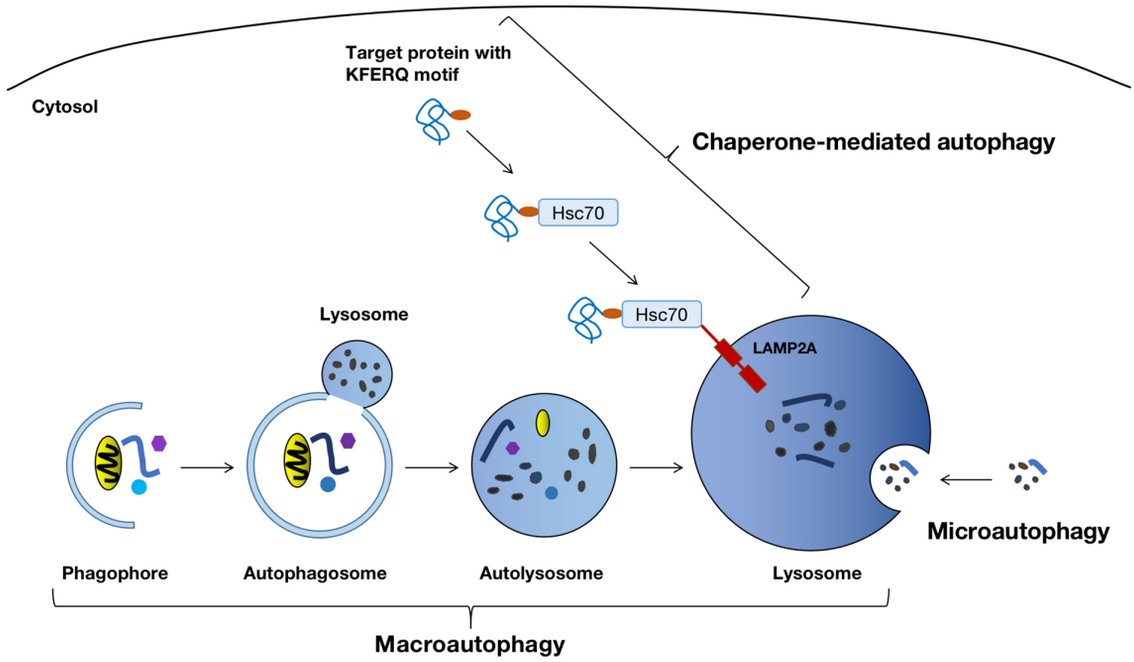

Figure 1 Schematic representation of three types of autophagy

In the macroautophagy pathway, preautophagosomal structures (PAS) are formed to engulf selected substrates in the cytoplasm and subsequently develop into double-membrane autophagosomes (AP). Lysosomes fuse with autophagosomes to form single-membrane autolysosomes (AL), which eventually evolve into lysosomes. In the chaperone-mediated autophagy (CMA) pathway, the Hsc70 chaperone protein complex recognizes target proteins in the cytoplasm with a KFERQ motif and delivers cargo to lysosomes for digestion via interaction with the lysosomal membrane protein LAMP2, which functions as a CMA receptor. Microautophagy is the simplest autophagic pathway, in which substrates are engulfed directly by lysosomes, independent of vesicles or protein targeting complexes.

evolve into lysosomes. Upon fusion with autophagosomes, lysosomal proteolytic enzymes carry out substrate degradation, while vesicular or vacuolar-type ATPase (V-ATPase) mediates acidification of the compartment (Colacurcio & Nixon, 2016). In recent years, accumulating studies have highlighted the critical role of the autophagy-lysosomal pathway in modulating cellular aging, the *sine qua non* for late-onset neurodegenerative diseases. Impaired autophagy is likely to contribute to the pathogenesis of many neurodegenerative diseases, including AD (Fleming et al., 2022; Litwiniuk et al., 2023; Miceli et al., 2023). Studies have reported that immature autophagosomes accumulate in the brains of AD patients and that the expression of certain autophagy-related proteins is down-regulated (Heckmann et al., 2020). Enlarged and dysfunctional autolysosomal vesicles accumulate in axons to form spheroids and network defects in AD progression (Yuan et al., 2022). Furthermore, electron microscopy has shown that failure of autolysosomal acidification precedes the formation of classic AD amyloid plaques and NFTs (Lee et al., 2022). Thus, these findings strongly suggest that targeting autophagy may be an effective approach for the treatment of AD.

Animal models are valuable tools for elucidating the pathological mechanisms of AD and for the development of novel therapeutic strategies (Chen & Zhang, 2022; Drummond & Wisniewski, 2017). At present, AD models are broadly categorized into spontaneous, drug-based, and transgenic models according to the methodology used to model the disease pathology (Esquerda-Canals et al., 2017). They are then evaluated using a comprehensive array of behavioral tests to assess learning, memory, and cognitive function. This review summarizes the pathological features of representative animal models of AD, evaluates the autophagic changes that contribute to the pathogenesis of these models, and discusses current investigations into therapeutic interventions targeting autophagy for the treatment of AD.

AUTOPHAGY IN PATHOGENESIS OF AD ANIMAL MODELS

Pathological features and mutated genes involved in AD

The formation of amyloid plaques and NFTs are two diagnostic hallmarks of AD pathology. The aggregation of extracellular Aβ peptides leads to the development of senile plaques and amyloid deposits on the cerebrovascular walls (Honjo et al., 2012; Trumbore, 2016). The Aβ-40 and Aβ-42 peptides, principal constituents of amyloid plaques, are generated by amyloid precursor protein (APP), a glycosylated receptor localized to the cell surface that undergoes proteolytic cleavage by β- and γ-secretases during endocytosis to produce intracellular Aβ, which is then secreted to the extracellular environment via exocytosis (Chen et al., 2017; De Strooper, 2003). The presenilin, nicastrin, aph-1, and pen-2 protein complex is responsible for γ-secretase activity, while β-site APP-cleaving enzyme 1 (BACE-1) mediates β-secretase activity (Zhang et al., 2017a). Autosomal dominant mutations in the genes encoding APP, presenilin-1 (PS1), and presenilin-2 (PS2) are known to promote the pathological accumulation of Aβ peptides at the molecular level. Elevated levels of Aβ can induce neuronal death due to amyloid toxicity, thereby accelerating the progression of familial AD (FAD) and late-onset AD (Armstrong, 2019). According to the amyloid hypothesis, dysregulated APP metabolism and Aβ peptide aggregation are posited as the initiating events in AD progression (Frisoni et al., 2022; Hardy & Allsop, 1991).

Insoluble NFTs, another representative microscopic brain lesion in AD, are primarily composed of tau, a microtubule-associated protein commonly found in axons. Neuronal tau plays a critical role in regulating microtubule stability and facilitates signal transduction-related protein trafficking through the microtubular network (Venkatramani & Panda, 2019). According to the tau propagation hypothesis, pathologic hyperphosphorylation of tau can lead to the formation of non-helical fibrils and depolymerized microtubules, resulting in the formation of intracellular NFTs (Frost et al., 2009; Sonawane & Chinnathambi, 2018). NFT pathology can disrupt cytoplasmic function and axonal transport between neurons, ultimately leading to neuronal dysfunction and degeneration in individuals with AD (Arnsten et al., 2021; Sexton et al., 2022; Tavares et al., 2013; Yang & Wang, 2018). Nevertheless, the molecular events underlying tau lesion formation and the mechanistic relationship between NFTs and amyloid pathology remain poorly understood.

Multiple AD-related genes are involved in autophagy regulation (Deng et al., 2022). Apart from its role in Aβ cleavage, PS1 is also an endoplasmic reticulum (ER) chaperone for the V-ATPase subunit V0A1 which is responsible for lysosomal acidification. Mutations in the *PS1* gene can lead to V-ATPase dysfunction and defective autolysosomal degradation in AD patient-derived cells (Lee et al., 2010). Mutations in *PS2*, another critical AD gene, can also impair autophagy by disturbing calcium (Ca^{2+}) homeostasis (Fedeli et al., 2019). Mutations in APOE4, encoded by the ε4 allele of the *APOE* gene and a primary risk factor for sporadic AD, can up-regulate the expression of endolysosomal protein RAB5 and endocytosis, resulting in an overload of autophagic cargo and accumulation of dysfunctional lysosomes (Shi et al., 2017). PICALM is a clathrin adaptor protein reported to confer dysfunction in the brains of AD patients. Variants in *PICALM* can disrupt VAMP protein endocytosis, thereby inducing impairment of autophagosomal maturation and autophagosome-lysosome fusion (Moreau et al., 2014).

Autophagy in Aβ metabolism and tau pathology

As autophagy transports cytoplasmic components to lysosomes for degradation and recycling, functional autophagy plays an important role in the production and clearance of Aβ peptides and the assembly of tau proteins in the mammalian brain (Figure 2 and 3). However, in the progression of AD, dysregulation of autophagy exacerbates amyloidosis and tau pathology (Zhang et al., 2021b).

Autophagy plays an essential role in the metabolism of Aβ, modulating both its production and clearance. The induction of ATG5-dependent autophagy facilitates the degradation of APP and Aβ production via the autophagy-lysosomal pathway (Cavieres et al., 2015), while inhibition of ATG7 impairs autophagic flux, leading to decreased extracellular Aβ plaque formation and increased intraneuronal Aβ accumulation,

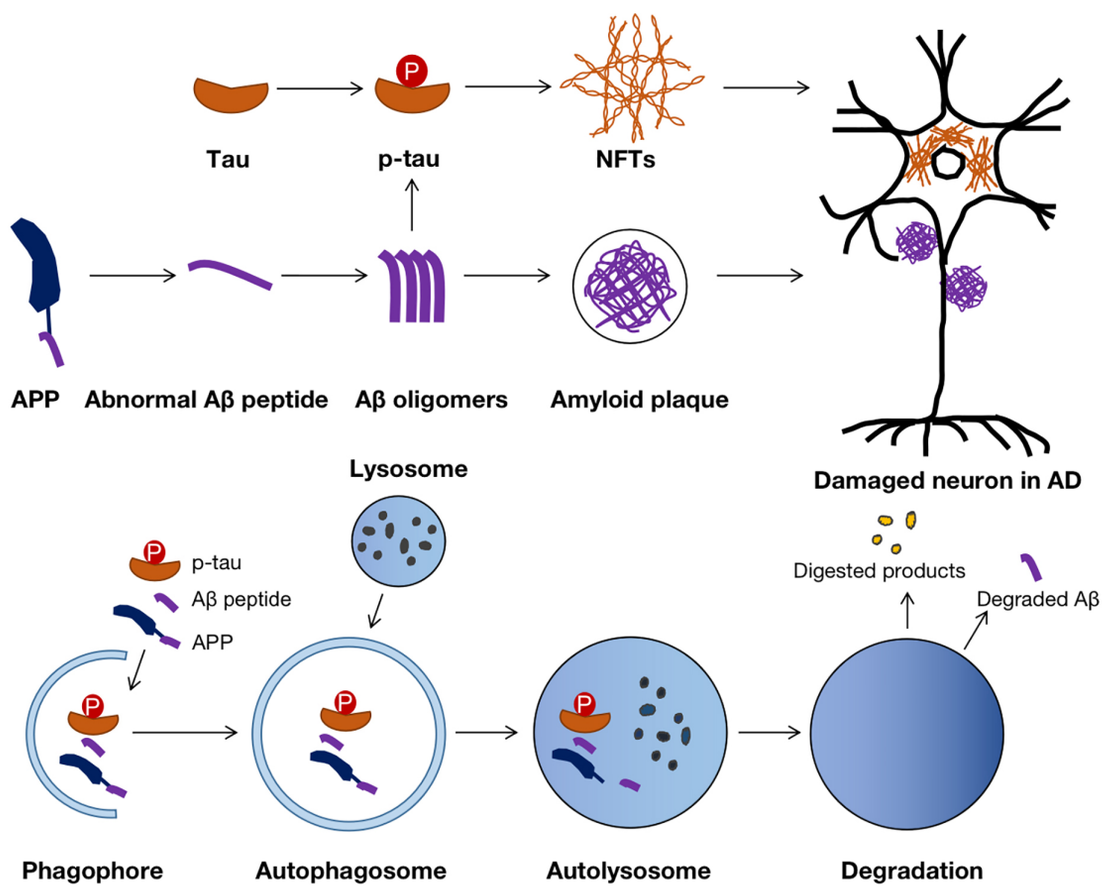

Figure 2 Role of autophagy in AD pathogenesis

Accumulation of aberrant Aβ peptides produced by APP and deposition of hyperphosphorylated tau leading to the formation of NFTs are fundamental pathological markers of AD. Abnormal Aβ peptides form oligomers and insoluble senile plaques and promote hyperphosphorylation and aggregation of tau (Zeng et al., 2019). Autophagy modulates Aβ metabolism and tau pathology by regulating their production, secretion, and clearance. Dysregulation of autophagy accelerates amyloidosis and tau pathology.

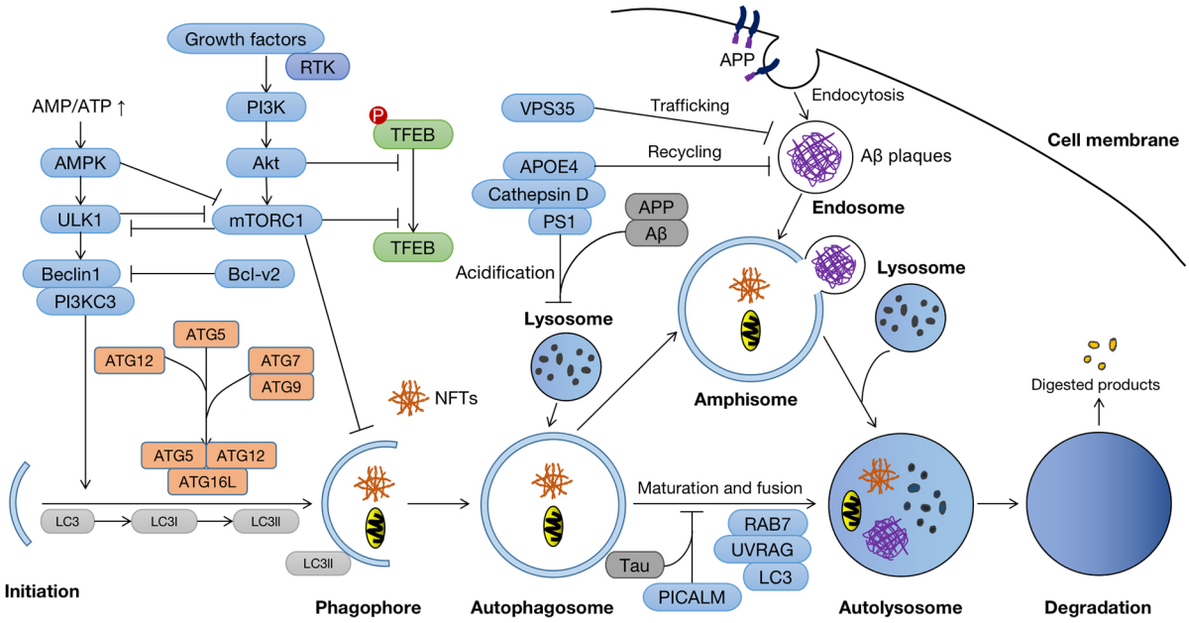

Figure 3 Regulatory mechanisms of autophagy in AD

Autophagy initiation is modulated by nutrient deprivation or cellular stress signals. Growth factor-activated PI3K induces the phosphorylation of downstream Akt, and p-Akt promotes the activation of mTORC1, which negatively regulates autophagic processes. AMPK is activated by up-regulated AMP/ATP and then phosphorylates the downstream ULK1 complex, which prevents the inhibitory effect of mTORC1 while promoting activation of Beclin-1, an essential autophagic initiator. Beclin-1/PI3KC3 complex regulates phagophore formation by recruiting autophagic proteins, which can be blocked by the anti-apoptotic protein Bcl-2. TFEB translocation from the cytoplasm to nucleus activates the transcription of autophagy-related genes. During phagophore formation, a series of autophagy-related proteins regulate the maturation of microtubule-associated protein 1A/1B light chain 3-II (LC3-II) on the phagophore membrane, which is necessary for membrane elongation (Di Meco et al., 2020). RAB7, UVRAG, and LC3 promote autophagosome maturation and fusion with lysosomes to form autolysosomes (Deng et al., 2022). AD-associated proteins and Aβ aggregation impair autolysosomal acidification, and tau deposition suppresses autophagy flux by disrupting autophagosome-lysosome fusion, which, in turn, exacerbates amyloidosis and tau pathology in AD.

suggesting that Aβ secretion is compromised under dysfunctional autophagy (Nilsson et al., 2015). Studies have shown that ATG5- and ATG7-dependent autophagy induced by morphine selectively affects dopaminergic neurons in the murine midbrain (Su et al., 2017). Autophagy potentially modulates Aβ clearance at various stages. Inhibition of mTOR-dependent pathways markedly increases autophagy and reduces both intracellular Aβ and extracellular amyloid deposition in the brain (Cai & Yan, 2013; Spilman et al., 2010). Furthermore, inhibition of Beclin-1 results in elevated APP, Aβ, and C-terminal fragment (CTF) expression, while its overexpression leads to stimulation of basal autophagy flux and significant remission of Aβ deposition and cognitive deficits (Rocchi et al., 2017; Salminen et al., 2013). Genetic ablation of cathepsin B, an essential lysosomal protease that degrades autophagic substrates, has been shown to exacerbate amyloid pathology in mouse models of AD (Mueller-Steiner et al., 2006). Accumulation of mutant APP and Aβ is also reported to induce mitochondrial, synaptic, and autophagic abnormalities in hippocampal neurons under AD pathology, leading to neuronal dysfunction (Reddy et al., 2018).

Tau pathology is also alleviated by autophagy induction. Studies have shown that hyperphosphorylated tau colocalizes with the autophagic marker LC3 and substrate p62/SQSTM1 in the brains of FAD patients and model mice (Piras et al., 2016). Inhibition of mTOR signaling using several identified compounds can significantly reduce tau phosphorylation and insoluble tau (Hamano et al., 2021). The autophagy receptor NDP52 recognizes phosphorylated tau in AD mouse brains, with its up-regulation found to enhance clearance of phosphorylated tau via autophagic degradation (Chesser et al., 2016). TFEB, a critical transcription factor for autophagy induction, mediates tau clearance by modulating its lysosomal exocytosis (Xu et al., 2021c). Defective CMA has also been implicated in many neurodegenerative diseases (Liu et al., 2015) and the degradation of pathogenic proteins, including tau. Tau contains two motifs in its C-terminus that can be recognized by CMA; however, mutant forms of tau exhibit resistance to CMA-mediated degradation due to the blockade of transport to the lysosomal lumen (Wang et al., 2009). Studies have demonstrated that blocking CMA accelerates tau aggregation and promotes disease progression, whereas increasing CMA activity with small molecules significantly suppresses tau pathology in several AD mouse models (Bourdenx et al., 2021). These findings suggest that both macroautophagy and CMA play critical roles in regulating Aβ metabolism and tauopathies.

In addition, emerging evidence suggests that defective mitophagy plays a critical role in AD occurrence and progression (Zeng et al., 2022). Mitophagy is a highly conserved process that recycles damaged mitochondria via autophagy, thereby maintaining balanced energy metabolism. Impairment in mitophagy can result from deficits in autophagosome-lysosome fusion and mitochondrial transport. Some AD patients with mild cognitive dysfunction exhibit higher transcriptional levels of mitophagy-related genes, such as *p62*, *parkin*, and *beclin 1* (Sorrentino et al., 2017), while other AD patients exhibit reduced levels of mitophagy proteins, including PINK1 and Bcl-2-like protein 13 (Fang

et al., 2019), which may reflect differences in disease stage. Mitochondrial dysfunction occurs in the early stages of AD, and Aβ toxicity and tau pathology cooperatively aggravate the accumulation of damaged mitochondria and mitophagy due to increased oxidative stress and disruption of PINK1/parkin localization, leading to a vicious cycle that induces neuronal damage and death (Cummins et al., 2019; Rhein et al., 2009).

Alterations in autophagy in AD animal models

Animal models are essential tools for the exploration of molecular mechanisms, behavioral functions, and therapeutic strategies of diseases. Three types of pathophysiologically based AD models exist: spontaneous, chemically induced, and transgenic (Esquerda-Canals et al., 2017). While certain mammals, such as tree shrews, macaques, and dogs (Beckman et al., 2021; Goodarzi et al., 2019; Li et al., 2023), exhibit natural development of Aβ deposition and tau hyperphosphorylation, their restricted reproductive output and relatively long lifespans limit their suitability in preclinical testing. Furthermore, chemically induced models, which employ the introduction of neurotoxic compounds into the animal brain to induce AD-like symptoms, cannot accurately replicate the pathogenesis of AD. Advancements in genetic engineering have enabled the generation of numerous transgenic AD models. Mice are extensively used as transgenic AD models due to their short lifespans, cost-effectiveness, and established manipulation procedures (Nakai et al., 2021). Rats are also widely used due to their larger brain size and superior performance in behavioral tests compared to mice. Invertebrate models, such as *Drosophila* or *Caenorhabditis elegans*, are noted for their short lifespans and simple requirements, but exhibit considerable neurological and physiological differences from mammals, constraining their applicability (Lu & Vogel, 2009).

Many transgenic (Tg) mice overexpressing mutated AD-related genes have been generated for disease research over the past several decades, which have mirrored the plaque formation, cognitive impairment, and defective adult hippocampal neurogenesis (AHN) in AD patients (Kim et al., 2022). Familial *APP*, *PSEN1*, and *PSEN2* mutations have been identified as major genetic risk factors for early-onset AD, while *APOE* and *TREM2* mutations have been implicated in the progression of late-onset AD (Cuyvers & Sleegers, 2016). This review provides a list of AD-related genes and details common transgenic mouse models employed in preclinical AD research, including a summary of their principal features (Tables 1, 2).

***APP* transgenesis:** The *APP* locus resides on human chromosome 21 and primarily encodes three isoforms, AβPP695, AβPP751, and AβPP770. The Swedish double mutation, *APPSwe* (*K670N/M671L*), is located at the β-cleavage site and favors β-secretase activity, contributing to increased production of Aβ. APPSwe (Tg2576) mice, serving as an early-onset Alzheimer's disease model, exhibit Aβ deposition by around 11 months and memory deficits as early as 10 months, attributed to the overexpression of the AβPP695 isoform under the regulation of the hamster prion protein (PrP) promoter (Lilja et al., 2013). APP23 mice exhibit overexpression of the AβPP751 isoform bearing the Swedish mutation under the control of the Thy1 promoter and show similar neuropathological and behavioral phenotypes as Tg2576, developing amyloid deposition at 6 months of age and memory impairment at approximately 3 months, followed by neuronal loss and synaptic degeneration with age (Bondolfi et al., 2002; Webster et al., 2014). TgCRND8 mice, which overexpress the Swedish and Indiana double mutations (*KM670/671NL* and *V717F*) of APP under the control of the PrP promoter, show Aβ deposition from 3 months of age and selective neuronal loss from 5 months of age, indicative of an earlier onset of pathology compared to single-mutation models (Kanemoto et al., 2014).

***Presenilin* transgenesis:** PSEN1 and PSEN2 form the catalytic core of the γ-secretase complex. Mutations in the *PSEN1* locus on human chromosome 14 are considered the most common cause of FAD. Specific mutations, including *M146V*, *M146L*, and *L286V*, can alter γ-secretase activity and induce the production of Aβ42, but not amyloid plaques (Edbauer et al., 2003). Mouse models with APP and PSEN1 mutations show a more rapid onset of pathogenesis compared to single mutation lines, both in terms of amyloid deposition and behavioral dysfunction. PSAPP mice overexpress both APP with the Swedish *KM670/671NL* mutation and PSEN1 with the *M146L* mutation (Roltsch et al., 2010), while APP/PS1 mice overexpress APP with the Swedish *KM670/671NL* mutation and PSEN1 with the *L166P* mutation, driven by the Thy1 promoter, leading to elevated Aβ42 levels at 2–3 months of age, hyperphosphorylated tau at 8 months, and cognitive impairment at 6–8 months of age (Lok et al., 2013). The 5×FAD transgenic mouse line carries the Swedish (*KM670/671NL*), Florida (*I716V*), and London (*V717I*) mutations of APP and the *M146L* and *L286V* mutations of PSEN1 under the control of the Thy-1 promoter. These mice represent a robust model for studying amyloidosis, with abundant Aβ accumulation in the brain at 6 months and

Table 1 Summary of representative genes implicated in risk of early and late-onset Alzheimer's disease (AD)

Gene	Location	Biological function	Involvement in AD pathology	Reference
APP	21q21.3	Aβ production, neuronal development, and synaptic formation	Swedish mutation (*KM670/671NL*): elevated Aβ levels; London mutation (*V717I*): increased Aβ42 with decreased Aβ40 levels; Flemish mutation (*A692G*): Aβ deposition in blood vessels of brain and senile plaques	Hinz & Geschwind, 2017; Lanoiselée et al., 2017
PSEN1	14q24.3	Aβ production, γ-secretase activity, and intracellular signaling	*PSEN1* mutation: increased Aβ42 with decreased Aβ40 levels, compromised neuronal function, and suppressed GSK-3β activity and kinesin-I-based motility	Hinz & Geschwind, 2017; Lanoiselée et al., 2017
PSEN2	lq42.13	Aβ production, β-secretase activity, and synaptic plasticity	*PSEN1* mutation: enhanced β-secretase activity, increased Aβ 42/40 ratio, neuritic plaque formation, NFT accumulation, and older age of onset	Hinz & Geschwind, 2017; Lanoiselée et al., 2017
APOE	19q13.2	Lipid metabolism, synaptic function, neurogenesis, as well as generation and trafficking of APP and Aβ	*APOE ε4* carriers: increased Aβ deposition, impaired glucose metabolism, cerebral amyloid angiopathy, and later onset of AD	Serrano-Pozo et al., 2021
TREM2	6q21.1	Phagocytosis and down-regulation of inflammation	Missense mutation R47H in *TREM2*: accelerated hyperphosphorylation of tau protein and later onset of AD	Zhou et al., 2019

Table 2 Summary of representative mouse models of Alzheimer's disease (AD), introduced mutations, pathogenic features, and alterations in autophagy

Mouse line	Transgenic mutation	Amyloid deposition	Phosphorylated tau	Behavioral dysfunction	Alteration of autophagy	Reference
Tg2576	APP Swedish mutation	5-fold increase in Aβ40 and 14-fold increase in Aβ42/43 at 11 months	Not detected	Spatial learning and memory impairment by10 months	Deficient autolysosomal acidification and selective accumulation of Aβ/APP-βCTF within pa-AL before extracellular Aβ42 deposits; 'PANTHOS'	Lee et al., 2022; Lilja et al., 2013
APP23	APP Swedish mutation	7-fold overexpression of AβPP at 6 months	6 months	Early cognitive impairment from 3 months	Not reported	Bondolfi et al., 2002; Webster et al., 2014
TgCRND8	APP Swedish and Indiana mutations	Elevated levels of Aβ42 at 3 months	7–12 months	Early cognitive impairment from 3 months	Deficient autolysosomal acidification and selective accumulation of Aβ/APP-βCTF within pa-AL before extracellular Aβ42 deposits; 'PANTHOS'	Kanemoto et al., 2014; Lee et al., 2022
PSAPP	APP Swedish and PS1 M146L mutations	Elevated levels of Aβ42 detected earlier than in Tg2576	Not detected	Spatial learning and memory impairments at 12–15 months	Deficient autolysosomal acidification and selective accumulation of Aβ/APP-βCTF within pa-AL before extracellular Aβ42 deposits; 'PANTHOS'	Lee et al., 2022; Roltsch et al., 2010
APP/PS1	APP Swedish and PS1 L166P mutations	Elevated levels of Aβ42 at 2–3 months	8 months	Spatial learning and memory impairments at 6–8 months	Up-regulated levels of P62Increased autophagy and mitophagy at early ages of mice	de la Cueva et al., 2022; Lok et al., 2013; Xu et al., 2021a
5×FAD	APP Swedish, Florida, London, PS1 M146V and L286V mutations	High levels of Aβ42 in the brain at 6 months	Not detected	Cognitive impairment at 4–6 months	Deficient autolysosomal acidification and selective accumulation of Aβ/APP-βCTF within pa-AL before extracellular Aβ42 deposits; 'PANTHOS'Altered transcription and expression levels of ATGs: BECN1-PIK3C3, ULK1/2-FIP200, DEF8, and ATG5	Lachance et al., 2019; Lee et al., 2022; Leyton et al., 2021; Oakley et al., 2006; Yelleswarapu et al., 2022
3×Tg-AD	APP Swedish, PS1 M146V, and Tau P301L mutations	High intracellular levels of Aβ42 at 3-4 months, and extracellular Aβ deposits at 6 months	12 months	Progressive cognitive and memory impairments with age	Defective CMA	Bourdenx et al., 2021; Falangola et al., 2020; Webster et al., 2014

cognitive impairment detected at 4–6 months (Oakley et al., 2006; Yelleswarapu et al., 2022). Triple Tg (3×Tg-AD) mice overexpress APP with the Swedish *K670N/M671L* mutation, PSEN1 with the *M146V* mutation, and protein tau with the *P301L* mutation, establishing a robust model for studying tau pathology and amyloidosis. These mice display intracellular Aβ accumulation in the brain at 3 months, as well as extracellular Aβ deposition with age and intracellular NFT formation in the hippocampus at 12 months (Falangola et al., 2020; Webster et al., 2014).

***APOE* transgenesis:** *APOE* is a lipid metabolism-associated gene located on chromosome 19 and exhibits three principal allelic forms, *ε2*, *ε3*, and *ε4*. The presence of the *ε4* allele is considered a strong genetic risk factor for late-onset AD (Liu et al., 2013; Serrano-Pozo et al., 2021). Mice carrying *APOE* modifications (*APOE* knock-in, *APOE* knock-out, and *APOE*-targeted replacement) combined with *APP* mutations serve as useful models for studying AD pathology. For example, APOE KO/PDAPP mice show reduced Aβ deposition at 6 months of age, while APOE4-KI/5×FAD mice demonstrate delayed Aβ deposition compared to 5×FAD mice (Liao et al., 2015).

***TREM2* transgenesis:** Mutation of the *TREM2* gene on human chromosome 6 is another critical risk factor for late-onset AD (Zhou et al., 2019). *TREM2* is highly expressed in microglial cells, which play an important role in promoting Aβ clearance and suppressing tau propagation (Zhou et al., 2019). Crossing mice carrying *TREM2* modifications with those carrying mutant APP genes, such as TREM2 KO/APP/PS1 mice, leads to a reduction in the accumulation of Aβ and tau, suggesting that targeting microglial activity may be a novel therapeutic approach for AD (Jay et al., 2015).

Due to the complex role of autophagy in the pathogenesis of AD, changes in autophagy in AD animal models have been extensively studied to verify the credibility of models and to investigate the underlying regulatory mechanisms. Recent research identified similar autophagy dysregulation in neurons in five different AD mouse models *in vivo*, including early-onset (5×FAD, TgCRND8, and PSAPP mice) and late-onset (Tg2576 and APP51 mice) models (Lee et al., 2022). Autolysosomal acidification declines in vulnerable neuronal populations well before extracellular amyloid deposition, associated with deficiencies in V-ATPase activity and accumulation of Aβ/APP-βCTF selectively within poorly acidified autolysosomes (pa-AL). In more damaged neurons, Aβ-filled autophagic vacuoles (AVs) cluster into large membrane blebs and the fluorescent petal-like blebs surrounding DAPI-positive nuclei form flower-like perikaryal rosettes, termed 'PANTHOS' (poisonous flower). Quantitative analysis revealed that PANTHOS neurons are the source of most senile plaques in AD mouse models, prompting a re-evaluation of the traditionally known sequence of events in amyloid plaque deposition in AD pathology (Lee et al., 2022).

The expression level of p62, an essential autophagy receptor, is markedly elevated in APP/PS1 mice due to impaired neuronal autophagic flux. Overexpression of p62 regulates TNF-α signaling through its interaction with RIPK1,

contributing to neuronal death in AD (Xu et al., 2021a). Accumulation of autophagy-related proteins, including p62, has also been observed in microglial cells within the hippocampus of aged PDAPP-J20 mouse models of AD, associated with prolonged exposure to Aβ peptides (Pomilio et al., 2020).

Autophagic dysfunction is induced by the accumulation of microtubule-associated protein tau (MAPT) in HsMAPT transgenic mice, which exacerbates tau aggregation, leading to synaptic and behavioral dysfunction. Tau accumulation suppresses autophagy flux by disrupting the formation of the IST1-regulated ESCRT-III complex, which is required for autophagosome-lysosome fusion. Up-regulation of IST1 facilitates autophagic clearance of insoluble tau, thereby improving synaptic plasticity and ameliorating cognitive deficits in HsMAPT mice (Feng et al., 2020).

Differential expression of several autophagy-related genes (ATGs) has been demonstrated in the brains of AD mice. Analysis has shown that the expression of genes encoding the autophagy kinase complexes BECN1-PIK3C3 and ULK1/2-FIP200 is significantly down-regulated in the parahippocampal gyrus of 5×FAD mice, while deletion of NRBF2, a component of the BECN1-PIK3C3 complex that also interacts with ULK1/2-FIP200, leads to reduced autophagic clearance of Aβ in the hippocampus and cognitive impairment (Lachance et al., 2019). DEF8 is a member of the Rubicon protein family implicated in the final step of autophagy and the endolysosomal pathway. Its gene expression is altered in AD models along with other ATGs, which present as reduced transcriptional levels of *DEF8* mRNA but increased protein levels of DEF8 in 5×FAD mice (Leyton et al., 2021).

Amyloidosis precipitates dysfunction in mitochondrial biogenesis and dynamics in APP/PS1 murine models. Concurrently, Aβ pathology prompts the early induction of both autophagy and mitophagy, mirroring the up-regulation of autophagic processes observed in the early stages of AD in humans (de la Cueva et al., 2022).

Defective CMA is also observed in various AD models (Caballero et al., 2021; Wang & Lu, 2022). Notably, CMA activity is inhibited in hTauP301L AD mice, whereas neuronal loss of CMA significantly increases the accumulation of phosphorylated tau, APP CTFs, and Aβ42 peptides in 3×Tg mice. Conversely, chemical activation of CMA improves behavior and neuropathology in PS1 mice with frontotemporal dementia-related proteotoxicity (Bourdenx et al., 2021).

The role of dysfunctional autophagy in the pathogenesis of *Drosophila* models is similar to that in mammalian systems. Reduced levels of Atg1 or Atg18 increase neurotoxicity in *Drosophila* overexpressing Aβ42, whereas knockdown of Atg5 or Atg12 significantly mitigates amyloid accumulation, suggesting a dual nature of autophagic pathway components involved in AD progression (O'Keefe & Denton, 2018).

TARGETING AUTOPHAGY IN THE TREATMENT OF AD MODELS

Substantial efforts have been made in the development of effective pharmacological interventions to slow or reverse the progression of AD (Jucker & Walker, 2023; Long & Holtzman, 2019; Sose et al., 2023; Thakral et al., 2023). Nonetheless, drugs currently approved by the US FDA for the treatment of AD exhibit limited efficacy and pronounced inter-individual variability (Knight et al., 2018). Accumulating evidence highlights the potential of autophagy-mediated degradation of amyloid and tau pathologies, as well as impaired organelles, as a promising therapeutic approach for AD. Autophagy-stimulating strategies to ameliorate neuropathology have been extensively studied in AD animal models. Although many novel therapies, such as immunotherapy and gene therapy, have emerged as potential options for AD intervention in preclinical trials, small molecule autophagy stimulators are still preferred due to their relatively high bioactivity and proficiency in crossing the blood-brain barrier (BBB) (Zhang et al., 2021b). Endogenous genes and components involved in the regulation of autophagy in AD have also been screened, with their therapeutic effects verified in many animal studies, identifying potential autophagy modulating targets for the development of agonists or antagonists for the treatment of AD. The following section summarizes the performance of recently discovered autophagy-stimulating interventions used in the treatment of AD and introduces their possible underlying mechanisms.

Pharmacological interventions

Most autophagy-stimulating agents studied in AD animal models enhance autophagy by inhibiting mTOR or activating AMPK signaling pathways (Table 3). However, mTOR and AMPK may also be dispensable targets for autophagy induction.

Current research indicates that caloric restriction and its mimetics, including compounds such as resveratrol, spermidine, rapamycin, metformin, and curcumin, exert significant effects on autophagic modulation (Yang & Zhang, 2020). Rapamycin, also known as sirolimus, is a well-described autophagy stimulator through inhibition of mTOR. Administration of rapamycin in hTauP301S mice alleviates amyloidosis and tauopathies and improves cognitive function (Yang & Zhang, 2020). Resveratrol, a natural polyphenol found in grape skins and seeds, induces autophagy by controlling sirtuin 1 (SIRT1)-mediated transcriptional regulation or AMPK/mTOR-dependent signaling pathways, leading to a reduction in amyloid deposition in the brains of APP transgenic mice and improvement in memory in ovariectomized AD rats (Kou & Chen, 2017). Spermidine, a small endogenous polyamine required for cell proliferation, differentiation, and apoptosis, activates autophagy by modulating Beclin-1. Oral administration of spermidine in APP/PS1 mice reduces neurotoxic soluble Aβ expression and attenuates AD-associated neuroinflammation (Freitag et al., 2022). Metformin, a biguanide compound widely used in the treatment of type 2 diabetes, induces autophagy via activation of AMPK and inhibition of mTORC1. Notably, metformin induces CMA via activation of the TAK1-IKKα/β signaling pathway, leading to the phosphorylation of Hsc70. In APP/PS1 mice, metformin-mediated activation of CMA potently reduces Aβ plaque accumulation in the brain and ameliorates molecular and behavioral AD phenotypes (Xu et al., 2021b). Curcumin, a natural polyphenolic compound extracted from *Curcuma longa*, enhances autophagy by suppressing the PI3K-Akt-mTOR signaling pathway. Curcumin treatment in APP/PS1 mice significantly reduces amyloid aggregation and improves memory deficits (Salehi et al., 2019).

Lithium is an antipsychotic drug that induces autophagy by activating AMPK. Lithium treatment significantly ameliorates tauopathies in 3×Tg AD mice but shows no significant inhibitory effects on tau phosphorylation in clinical trials (Matsunaga et al., 2015). Lychee seed fraction-enriched polyphenol (LSP), reported to have anti-neuroinflammatory

Table 3 Summary of autophagy-stimulating agents with therapeutic potential in Alzheimer's disease (AD) animal models

Compound	Mechanism of action	Pharmacological activity	AD animal model	Reference
Rapamycin	mTOR inhibition	Reduces Aβ deposition and tauopathies, improves cognitive dysfunction	hTauP301S mice	Yang & Zhang, 2020
Resveratrol	mTOR inhibition and/or AMPK activation	Reduces Aβ deposition Improves cognitive dysfunction	APP transgenic mice Ovariectomized AD rats	Kou & Chen, 2017
Spermidine	modulation of Beclin-1	Reduces neurotoxic soluble Aβ, attenuates AD-associated neuroinflammation	APP/PS1 mice	Freitag et al., 2022
Metformin	Inducing autophagy via mTOR inhibition and AMPK activation; Inducing CMA via TAK1-IKKα/β pathways	Reduces Aβ deposition and tauopathies, ameliorates behavioral AD phenotypes	APP/PS1 mice	Xu et al., 2021b
Curcumin	mTOR inhibition	Reduces Aβ aggregation, improves memory deficits	APP/PS1 mice	Salehi et al., 2019
Lithium	AMPK activation and GSK3 inhibition	Ameliorates tauopathies	3×Tg AD mice	Matsunaga et al., 2015
Lychee seed fraction enriched polyphenol (LSP)	AMPK activation	Ameliorates cognitive dysfunction	APP/PS1 mice	Qiu et al., 2020
Oleuropein	mTOR inhibition and AMPK activation	Reduces Aβ deposition, improves synaptic plasticity	TgCRND8 mice	Nediani et al., 2019
Carbamazepine	Activating autophagy in an mTOR-dependent or -independent manner	Reduces Aβ deposition, improves cognitive dysfunction	3×Tg AD mice	Li et al., 2013
Magnolol	Activation of AMPK/mTOR/ULK1 pathway	Reduces Aβ deposition, improves cognitive impairment	APP/PS1 mice	Wang & Jia, 2023
Hederagenin (HD)	PPARα/TFEB activation	Improves cognitive dysfunction	APP/PS1 mice	Xie et al., 2023
Bergaptene (BG) Tadalafil (TAD)	Modulation of PI3K/Akt, Wnt/β-catenin, and AMPK/mTOR pathways	Reduces Aβ deposition and tauopathies, improves cognitive dysfunction	STZ-induced AD mice	Salem et al., 2021
Trehalose	TFEB activation	Reduces Aβ deposition and tauopathies, improves behavioral deficits	Aβ-injected mice	Pupyshev et al., 2022
LH2-051	DAT-TFEB axis regulation	Reduces Aβ deposition, improves cognitive dysfunction	APP/PS1 mice	Yin et al., 2023
HEP14 and HEP15	PKC/TFEB activation	Reduces Aβ deposition	APP/PS1 mice	Li et al., 2016
Lactulose	Not reported	Improves cognitive dysfunction	APP/PS1 mice	Lee et al., 2021
Anthocyanin-rich blueberry extracts (BE) and protocatechuic acid (PCA)	Not reported	Reduces neuronal damage	APP/PS1 mice	Li et al., 2022
Cannabidiol (CBD)	Not reported	Improves the immune response	APP/PS1 mice	Hao & Feng, 2021
UMI-77	Activation of mitophagy via the ATG5 pathway	Reverses the inflammatory response and improves cognitive dysfunction	APP/PS1 mice	Cen et al., 2020
Melatonin	Modulation of mitophagosome-lysosome fusion	Reduces Aβ deposition and improves cognitive dysfunction	5×FAD mice	Chen et al., 2021a
β-Asarone and icariin	Mitophagy stimulation	Reduces Aβ deposition, improves cognitive impairment	APP/PS1 mice	Wang et al., 2021
Kaempferol and rhapontigenin	Mitophagy stimulation	Ameliorates Aβ and Tau pathologies, forestalls memory deficits	3×Tg AD mice	Xie et al., 2022

properties in AD, ameliorates cognitive dysfunction by promoting LRP1/AMPK-mediated autophagy in APP/PS1 mice (Qiu et al., 2020). Oleuropein, extracted from green olives, stimulates autophagy by inhibiting mTOR and activating AMPK. Notably, oleuropein treatment significantly reduces Aβ deposition and improves synaptic plasticity in TgCRND8 mice (Nediani et al., 2019). Carbamazepine, an FDA-approved antiepileptic drug that induces autophagy through mTOR-dependent or independent pathways, promotes autophagic clearance of amyloid plaques and cognitive improvement in 3×Tg AD mice (Li et al., 2013). Bergaptene (BG), found in a variety of medicinal plants, and phosphodiesterase 5 inhibitors such as tadalafil (TAD) exhibit neuroprotective effects. Of note, administration of TAD or BG in streptozotocin (STZ)-induced AD mice ameliorates tau pathology, amyloidosis, and associated cognitive deficits via modulation of neuroinflammation and crosstalk between PI3K/Akt, Wnt/β-catenin, AMPK/mTOR pathways (Salem et al., 2021). Magnolol, an active ingredient isolated from *Magnolia officinalis*, decreases amyloid pathology and improves cognitive impairment in APP/PS1 mice by promoting autophagy through activation of the AMPK/mTOR/ULK1 signaling pathway (Wang & Jia, 2023). Hederagenin (HD), a triterpene compound isolated from a variety of foods, ameliorates cognitive impairment and pathological changes in APP/PS1 mice by enhancing PPARα/TFEB-mediated autophagy (Xie et al., 2023). Trehalose, a natural disaccharide, activates autophagy by modulating the transcription factor TFEB. Notably, trehalose treatment in Aβ-injected mice prolongs autophagy induction and transcriptional activation of autophagy-related genes, prevents amyloid deposition and tau pathology, and effectively reverses behavioral deficits, with the best results achieved in combination with rapamycin (Pupyshev et al., 2022). The

small-molecule compound LH2-051, an inhibitor of the dopamine transporter (DAT), mediates lysosome biogenesis by negatively regulating TFEB activity. Administration of LH2-051 significantly promotes the clearance of Aβ aggregates and improves memory function in APP/PS1 mice (Yin et al., 2023). As small-molecule compounds isolated from *Euphorbia peplus* Linn, HEP14 and HEP15 regulate lysosomal biogenesis through protein kinase C (PKC)-dependent TFEB activating pathways. These PKC activators can facilitate clearance of Aβ accumulation in APP/PS1 mouse brains (Li et al., 2016). The prebiotic lactulose, an analog of trehalose, ameliorates cognitive deficits in AD mice through autophagy and CMA pathways, and exhibits better inducing effects than trehalose in enhancing synaptic protein expression level (Lee et al., 2021). Anthocyanins, a group of naturally occurring phenolic compounds, can also promote autophagy. Anthocyanin-rich blueberry extract and protocatechuic acid, a major anthocyanin metabolite, alleviate the Aβ-induced inhibitory effects of autophagy and reduce neuronal damage in APP/PS1 mice (Li et al., 2022). Cannabidiol (CBD), a natural component isolated from the cannabis plant, exerts neuroprotective effects in AD, with treatment in APP/PS1 mice significantly improving immune response and autophagy (Hao & Feng, 2021).

In addition, emerging evidence suggests that small molecules enhancing neuronal aggregation and mitophagy may also be considered as therapeutic targets for AD (Zeng et al., 2022). UMI-77, an established BH3 mimetic, selectively targets MCL-1, a receptor that directly interacts with LC3A to promote mitophagy. UMI-77 induces mitophagy via the ATG5 pathway and significantly reverses the inflammatory response and cognitive deficits in APP/PS1 mice (Cen et al., 2020). Melatonin, a hormone secreted by the pineal gland, exerts protective effects in mitochondria-related diseases and neurodegenerative disorders, attenuating neurotoxicity via regulating the aberrant activation of autophagy mediated by cyclin-dependent kinase 5 (CDK5) (Feng et al., 2013; Su et al., 2015). Oral treatment with melatonin in 5×FAD mice improves mitophagy by enhancing mitophagosome-lysosome fusion, attenuating amyloid pathology and cognitive deficits (Chen et al., 2021a). β-Asarone is an essential component of *Acorus tatarinowii* Schott volatile oil and icariin is a flavonoid constituent of *Epimedium* species exhibit pharmacological effects in neurodegenerative diseases, inhibiting Aβ deposition and reversing cognitive dysfunction by promoting mitophagy in APP/PS1 mice (Wang et al., 2021). Recent combined usage of machine learning and cross species validation have identified several novel mitophagy stimulators for AD treatment. Among the AI-selected candidates, kaempferol and rhapontigenin induce mitophagy, restore memory deficits, and abrogate pathologies in 3×Tg AD mice (Xie et al., 2022).

Endogenous autophagy modulators in AD

Recent investigations have revealed a number of endogenous genes and components, including microRNAs (Zhang et al., 2022a), transcription factors, and cytosolic and membrane proteins, involved in the regulation of autophagy. These components, as verified in AD animal studies, are posited as prospective therapeutic targets for AD intervention via modulation of autophagy (Kou et al., 2020; Martini-Stoica et al., 2016; Salminen et al., 2013; Zhang et al., 2021a).

UVRAG mediates the recognition and fusion of autophagosomes and lysosomes (Xu et al., 2021a). Notably, its transcriptional down-regulation in AD leads to impaired autophagic flux and neuronal necroptosis, while its overexpression in APP/PS1 AD mice significantly rescues learning and memory deficits and reverses neuronal necroptosis (Xu et al., 2021a). Overexpression of *UBE4B*, a *miR-9* target gene, promotes the autophagic degradation of oligomeric tau in tau-BiFC mice (Chen et al., 2021b). The microRNAs *miR-331-3p* and *miR-9-5p*, which target the autophagy receptors Sqstm1 and Optn, respectively, display lower expression in early-stage AD mice but higher expression in late-stage AD mice. Inhibition of late-stage *miR-331-3p* and *miR-9-5p* improves mobility and cognitive dysfunction by enhancing autophagic clearance of Aβ in APP/PS1 mice (Chen et al., 2021b; Subramanian et al., 2021).

The peroxisome proliferator-activated receptor alpha (PPARA/PPARα) transcription factor regulates autophagic activity in the nervous system. Pharmacological activation of PPARA with gemfibrozil or Wy14643 promotes Aβ clearance and reverses memory impairment in APP/PS1 mice by inducing autophagosome biogenesis (Luo et al., 2020; Raha et al., 2021). Activating transcription factor 6 (ATF6), a key sensor of ER stress, and cystathionine γ-lyase (CTH), which mediates endogenous signal H2S production, are both reduced in AD models. ATF6 enhances autophagy via the regulation of CTH expression, thereby rescuing memory impairment in APP/PS1 ATF6 knockout mice (Zhang et al., 2022b). Myocardin and myocardin-related transcription factor-A (MRTF-A), both co-activators of the serum response factor (SRF) that regulates the transcription of genes involved in cytoskeletal organization and muscle cell differentiation, are down-regulated in AD models. Overexpression of MRTF-A reverses Aβ-induced autophagy deficits by targeting the miR-1273g-3p/mTOR axis and protects against neuronal apoptosis in Tg2576 mice (Zhang et al., 2022c).

SIRT5 is a mammalian sirtuin that removes lysine acylation from proteins and is often considered an autophagy inducer. SIRT5 expression is impaired in APP695/PS1dE9 mice, while overexpression of ectopic SIRT5 suppresses microglial and astrocyte activation and oxidative stress-induced damage and apoptosis in mice (Wu et al., 2021). Transmembrane glycoprotein NMB (GPNMB) is highly expressed in the brains of AD mice. Overexpression of GPNMB enhances autophagic clearance of Aβ via suppression of mTOR signaling and ameliorates cognitive dysfunction in APP/PS1 mice (Zhu et al., 2022). IKKβ, a constituent of the IκB kinase complex, modulates activity of the NF-κB pathway, which is intricately linked to inflammatory processes. Inhibition of IKKβ increases Aβ accumulation and RIPK1-mediated necroptosis via suppression of autophagy in APP/PS1 mice, while IKKβ overexpression restores impaired autophagy caused by Aβ and mitigates tau pathology in these AD models (Wang et al., 2022). Ryanodine receptors (RyanRs) with increased basal activity in AD inhibit autophagy via repression of the AMPK/ULK1 pathway mediated by activated calcineurin. The *RyanR2-E4872Q* mutation, which reduces basal activity of RyanR2 in APPKI and APP/PS1 mice, markedly disinhibits the autophagic pathway for amyloid clearance and rescues AD phenotypes (Zhang et al., 2023). The CCZ1-MON1A complex functions as the guanine nucleotide exchange factor (GEF) for RAB7, a small GTPase essential for the maturation of endosomes and autophagosomes. The active form of RAB7 is decreased in AD, accompanied by impaired CCZ1-MON1A

activity, whereas overexpression of CCZ1-MON1A increases RAB7 activity, enhances autophagosome maturation, promotes autophagic degradation of Aβ, and alleviates cognitive dysfunction in 3×Tg AD mice (Cai et al., 2022). Lysosomal two-pore segment channel 2 (TPCN2/TPC2) mediates the excessive release of Ca^{2+} that causes autophagy-lysosomal pathway impairment in AD. Genetic knockdown or pharmacological inhibition of the TPCN2 channel in 5×FAD mice significantly reduces amyloid accumulation and ameliorates cognitive deficits by restoring autophagy-lysosomal pathway function (Tong et al., 2022). The metabotropic glutamate receptor 5 (mGluR5) is a member of the G protein-coupled receptor (GPCR) superfamily, implicated as an extracellular scaffold for Aβ oligomers. mGluR5 is highly expressed on the cell surface in AD and associated with impaired autophagic flux, whereas pharmacological or genetic inhibition of mGluR5 signaling facilitates ULK1 activation, thereby activating autophagy in APPswe/PS1ΔE9 and 3×Tg-AD mice (Abd-Elrahman et al., 2018).

Stem cell stimulations

Stem cell therapy has shown efficacy in enhancing memory and cognitive functions in animal models of AD, with extensive preclinical research dedicated to elucidating the mechanisms involved (Chang et al., 2024; Temple, 2023). Transplanted bone marrow-derived mesenchymal stem cells (BMMSCs) stimulate neurogenesis and inhibit apoptosis, regulated by crosstalk between apoptosis and autophagy (Qin et al., 2021a). BMMSCs can activate autophagy by increasing the expression of BECN1/Beclin-1 and LC3-II-positive autophagosomes in the hippocampus of APP/PS1 mice, thereby ameliorating Aβ accumulation, hyperphosphorylated tau pathology, and cognitive deficits (Qin et al., 2021b).

CONCLUSIONS

Neurodegenerative diseases are characterized by the accumulation of insoluble and toxic protein aggregates in the brain. Although therapeutic interventions targeting amyloid and tau pathologies in AD have been investigated for many years, no effective strategies for curing AD have been discovered in clinical trials (Knight et al., 2018). Recent research suggests that autophagy dysregulation may play a critical and complex role in the pathogenesis of AD. Various mutated genes relevant to AD risk, including *PSEN1* and *PSEN2*, are implicated in the modulation of autophagy (Deng et al., 2022). Autophagy impairment is positively correlated with Aβ production and tau pathology, with Aβ deposits known to further exacerbate impairment of autophagic flux (Fleming et al., 2022) and autophagy-stimulating interventions found to reverse synaptic plasticity and cognitive function in AD (Zhang et al., 2021b). These findings suggest a dual functional role for autophagy, both upstream and downstream of Aβ metabolism and tau pathology. Therefore, targeting autophagy to enhance clearance of toxic protein aggregates is a potential approach for the treatment of AD. Various stimulators and endogenous targets of autophagy have been discovered in recent years (Kou et al., 2020; Salminen et al., 2013), although their underlying mechanisms and therapeutic potential remain to be verified at the preclinical stage in AD animal models. Animal studies are essential for bridging the gap between basic and clinical drug-screening applications (Chen & Zhang, 2022), thus streamlining the translation of drug candidates into clinical AD treatment. AD transgenic mice show similar neuropathologies and autophagy impairments as AD patients (Nakai et al., 2021), offering valuable models for investigating the molecular mechanisms of autophagy involved in AD progression and autophagy-stimulating strategies in the treatment of AD.

AD is a complex multifactorial disease, and research into appropriate therapeutics still faces many challenges. As classic autophagy-stimulating agents mainly regulate autophagy through mTOR inhibition (Yang & Zhang, 2020), the discovery of novel mTOR-independent drug targets is imperative. Elucidating the molecular basis of endogenous autophagy modulation in AD may also help to achieve precise autophagy regulation in the nervous system (Kou et al., 2020). For autophagy modulators that cannot cross the BBB, nanocapsule applications may be an effective approach to achieve targeted brain therapy (Zhang et al., 2017b). In addition, more reliable means of monitoring *in vivo* autophagy flux need to be investigated for more precise modulation of autophagy for AD treatment.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

X.W.Z. wrote the first draft of the manuscript. J.H.L., X.X.Z., and D.S.T. contributed to the conception, design, and revision of the manuscript. All authors read and approved the final version of the manuscript.

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