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Review

Autophagy in Alzheimer's disease pathogenesis: Therapeutic potential and future perspectives

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A B S T R A C T

Alzheimer's disease (AD) is a complex neurodegenerative disease in the elderly and the most common cause of human dementia. AD is characterized by accumulation of abnormal protein aggregates including amyloid plaques (composed of beta-amyloid (Aβ) peptides) and neurofibrillary tangles (formed by hyper-phosphorylated tau protein). Synaptic plasticity, neuroinflammation, calcium signaling etc. also show dysfunction in AD patients. Autophagy is an evolutionarily conserved lysosome-dependent cellular event in eukaryotes. It is closely linked to modulation of protein metabolism, through which damaged organelles and mis-folded proteins are degraded and then recycled to maintain protein homeostasis. Accumulating evidence has shown that impaired autophagy also contributes to AD pathogenesis. In the present review, we highlight the role of autophagy, including bulk and selective autophagy, in regulating metabolic circuits in AD pathogenesis. We also discuss the potential and future perspectives of autophagy-inducing strategies in AD therapeutics.

1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder and the most common cause of human dementia, accounting for approximately 60%−80% of cases (Crous-Bou et al., 2017). It is estimated that more than 30 million individuals are living with AD worldwide, with the number likely to increase to over 100 million by 2050 (ADI, 2019). Despite the extensive research since its first description in 1906, the molecular basis ~~of~~ underlying AD pathogenesis is still not fully understood and there are no effective interventions to block or reverse AD progression.

Two disease-defining pathological features of AD are: the extracellular senile plaques and intracellular neurofibrillary tangles (NFTs). Senile plaques consist of short beta-amyloid (Aβ) peptides and NFTs are

Abbreviations: AD, Alzheimer's disease; Alfy, autophagy-linked FYVE protein; ALS, amyotrophic lateral sclerosis; AMBRA1, activating molecule in Beclin-1 regulated autophagy; AMPK, AMK-activated protein kinase; APOE, apolipoprotein E; APP, amyloid precursor protein; ATG, autophagy-related genes; ATG14L, ATG14-like protein; BACE1, β-site APP cleaving enzyme 1; Bcl2, B-cell lymphoma 2; Bif-1, BAX interacting factor 1; BIN1, bridging integrator 1; CLU, Clusterin; CMA, chaperone-mediated autophagy; DFCP1, double FYVE-containing protein 1; EOAD, early-onset Alzheimer's disease; ER, endoplasmic reticulum; FIP200, focal adhesion kinase family-interacting protein of 200 kDa; GTP, guanosine-5'-triphosphate; GWAS, genome-wide association studies; HOPS, homotypic fusion and protein sorting; HSPA8, heat shock protein family A member 8; IKK, IκB kinase; LAMP2, lysosome-associated membrane protein 2; LC3, microtubule-associated protein 1 light chain 3; LIR, LC3-interacting region; LOAD, late-onset Alzheimer's disease; MAPT, microtubule associated protein tau; mTORC1, mammalian target of rapamycin complex 1; NBR1, neighbor of BRCA1 gene 1; NDP52, nuclear dot protein 52 kDa; NFT, neurofibrillary tangle; OPTN, optineurin; PD, Parkinson's disease; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol-3-phosphate kinase; PI3P, phosphatidylinositol 3-phosphate; PICALM, phosphatidylinositol-binding clathrin assembly protein; PINK1, PTEN induced putative kinase 1; PTEN, phosphatase and tensin homolog; PTEN-L, phosphatase and tensin homolog-long; PSEN, presenilin; PtdIns, phosphatidylinositol; Rab5, Ras-related protein 5; Rag, Ras-related GTPase; Raptor, regulatory-associated protein of mammalian target of rapamycin; Rheb, Ras homolog enriched in brain; SNARE, soluble NSF attachment protein receptor; SNX18, Sorting Nexin 18; SQSTM1, phosphotyrosine-independent ligand for the Lck SH2 domain of 62 kDa/sequestosome; TAK1, transforming growth factor beta-activated kinase 1; TFEB, transcription factor EB; TRAF6, TNF receptor-associated factor 6; TREM2, triggering receptor expressed on myeloid cells 2; UBD, ubiquitin-binding domain; ULK1, uncoordinated-51-like kinase 1; UVRAG, ultraviolet irradiation resistance-associated gene; v-ATPase, vacuolar-type H^+ ATPase; VPS34, vacuolar protein sorting 34; WIPI, WD-repeat protein interacting with phosphoinositides.

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formed by hyperphosphorylated microtubule associated protein tau (MAPT) (Suh and Checler, 2002). In addition to abnormal protein aggregates, synaptic loss, mitochondrial dysfunction, neuroinflammation activation, and disrupted calcium homeostasis have also been observed in AD patients and rodent models (Querfurth and LaFerla, 2010).

The etiology of AD is extremely complex. It is believed that AD is the consequence of multiple risk factors including age, family history, genetic background, education, and brain injury (Alzheimer's disease facts and figures, 2021). According to the age of onset, AD is usually categorized into early-onset AD (EOAD, onset $<$ 65 years) and late-onset AD (LOAD, onset $\geq$ 65 years). Many of the EOAD are caused by the pathogenic mutations in three genes, i.e., *APP*, *PSEN1* and *PSEN2*, and is inherited in an autosomal dominant manner (Hardy, 2017; Rogaev et al., 1995; Sherrington et al., 1995). Though EOAD is more aggressive, it accounts for less than 3% of all AD cases (Sun et al., 2017). More than 90% of AD cases are LOAD. The genetic components of LOAD are much more complex than those of EOAD. *APOE ε4* is viewed as the strongest LOAD risk gene (Farrer et al., 1997; Saunders et al., 1993). In addition to *APOE*, more than 20 risk genes for LOAD, including *ADAM10, PICALM*, *TREM2*, *CLU*, *SORL1*, *CR1*, *BIN1*, *CD33* and so on, have been identified recently through genome-wide association studies (GWAS) (Jansen et al., 2019; Lambert et al., 2013). These risk genes are involved in multiple signaling pathways, thus providing a greater perspective to understand AD pathogenesis.

In recent years, it has been demonstrated that dysfunctional autophagy is closely linked with AD. Originally, immature autophagosome accumulation and dystrophic neurites were observed in the brains of AD patients via electron microscopy (Nixon et al., 2005). Consistently, accumulated autophagosomes were detected primarily in neuronal dendrites rather than soma in rodent AD models (Yu et al., 2005). It is suggested that defective axonal transportation of autophagosomes from distal axon terminals to the soma is responsible for autophagosome aggregation in dystrophic neurites (Boland et al., 2008; Nixon and Yang, 2011), as immature autophagosomes are normally retrogradely transported to the soma for lysosomal degradation. Interestingly, the abnormal autophagosome gathering is found to occur prior to the formation of amyloid plaques (Yu et al., 2005). Besides, the expression of several autophagy-related proteins was reported to be down-regulated in AD brains (Heckmann et al., 2020a; Lachance et al., 2019; Pickford et al., 2008). These findings strongly suggest that autophagy is defective in AD and compromised autophagy contributes to AD pathogenesis.

2. Overview of autophagy

Autophagy is a conserved catabolic process that degrades defective proteins or organelles in lysosomes and recycles basic components in eukaryotic cells. According to the distinct mechanisms through which autophagic cargos are delivered to lysosomes, autophagy is usually classified into three different types: macroautophagy, chaperon-mediated autophagy (CMA) and microautophagy (Nixon, 2013) (Fig. 1).

2.1. Macroautophagy

Macroautophagy is the dominant and most extensively studied type of autophagy, so it is commonly referred to as "autophagy" for short. Autophagy is a highly dynamic and tightly regulated cellular event in eukaryotic cells (Ohsumi, 2014; Takeshige et al., 1992; Tsukada and Ohsumi, 1993). The basal level of autophagy is low under physiological condition, however, it can be rapidly induced by multiple stimuli such as energy deprivation (Kim et al., 2011), nutrient starvation (Kuma et al., 2004), misfolded proteins (Kraft et al., 2010), damaged organelles (Glick et al., 2010), infection, inflammation (Deretic et al., 2013) and

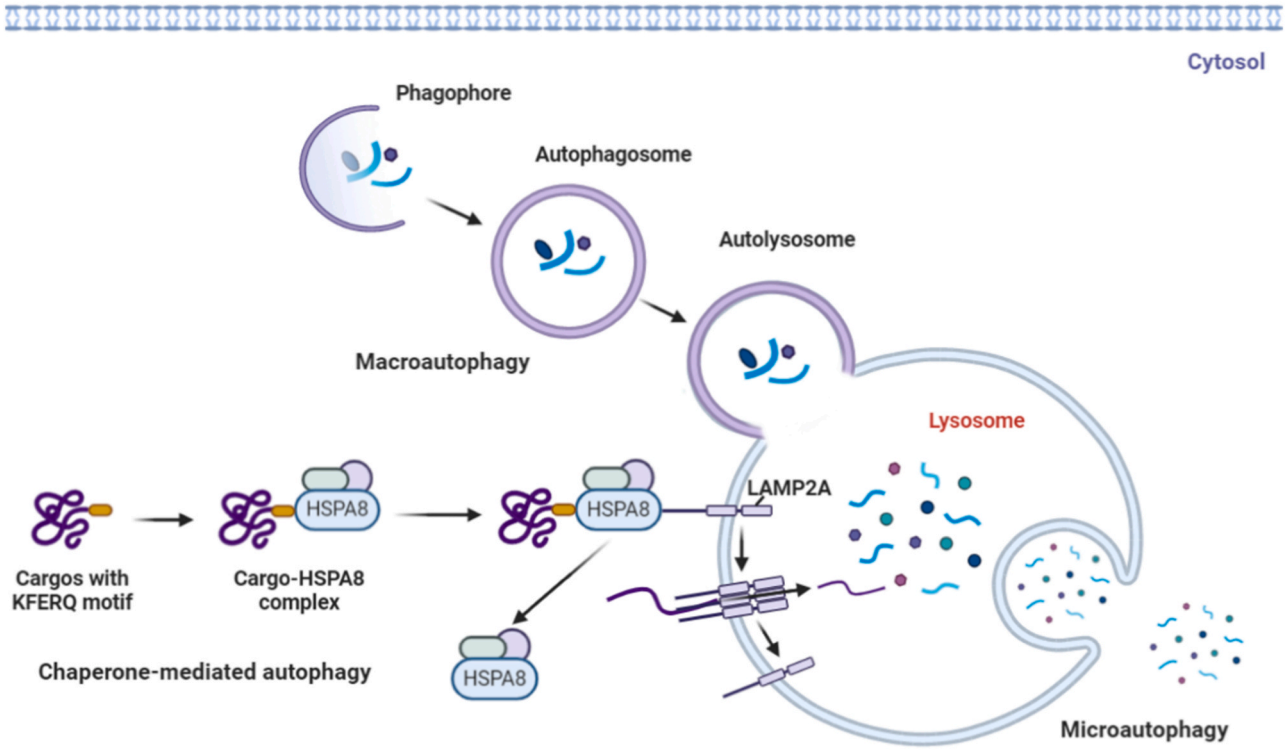

Fig. 1. Schematic illustration of three types of autophagy. The key differences among types are the methodology of lysosomes capturing the substrates. Macroautophagy is characterized by the formation of intermediate double-membrane structures including autophagosomes and autolysosomes. The cargos are engulfed in vesicles and then degraded through fusion with lysosomes. Chaperon-mediated autophagy selectively recognizes substrate proteins containing KFERQ motif. The cargos are delivered into lysosomes mediated by chaperon protein HSPA8 and associated co-chaperons and lysosomal membrane protein LAMP2A, instead of establishing any sealed vesicles. Microautophagy is the simplest type of autophagy in which the cargos are directly engulfed by lysosomes independent of intermediate vesicles or substrate-targeting protein complex.

other stressors (Kroemer and White, 2010). The key event of autophagy is the formation of autophagosome, which is mediated by a variety of proteins called ATGs (autophagy-related genes) (Lamb et al., 2013) (Fig. 2). The whole autophagy process, termed autophagic flux, can be divided into four stages based on autophagosome status: initiation, autophagosome formation, maturation (or fusion) and degradation (Kiriyama and Nochi, 2015). Each step is tightly regulated by multiple molecules.

2.1.1. *Autophagy initiation*

Autophagy initiation is mediated by the ULK complex. ULKs are serine/threonine kinases and include ULK1 (ATG1, homolog in yeast) and ULK2 (ULK1/2). The ULK complex consists of the core component ULK1 or ULK2 and other interacting proteins including ATG13, FIP200 and ATG101 (Fig. 2). In response to autophagy inducers, the ULK complex is activated, thus promotes the activation of its downstream effector, VPS34 complex, which mediates autophagy nucleation (Backer, 2016). The VPS34 complex is comprised of VPS34, Beclin-1 (ATG6 in yeast), VPS15 and ATG14L (Ohashi et al., 2019) in mammals, and is activated through the phosphorylation of ATG14L and/or Beclin-1 by ULK1 (Park et al., 2016a, 2018; Russell et al., 2013). The VPS34 complex acts as a lipid kinase termed class III PI3K, which phosphorylates PtdIns (phosphatidylinositol) to generate PI3P (phosphatidylinositol 3-phosphate). PI3P serves as a scaffold to recruit PI3P-binding molecules such as the PX-BAR protein SNX18 (Knaevelsrud et al., 2013), WIPI (Axe et al., 2008), and FYVE domain-containing proteins including DFCP1 and Alfy (Marat and Haucke, 2016). PI3P and its binding proteins initiate the formation of an isolated pre-autophagosomal structure known as phagophore (Fig. 2). It has been reported that PI3P produced at endoplasmic reticulum (ER) mediates the formation of membrane structures called omegasomes where phagophores begin to be synthesized (Ktistakis and Tooze, 2016). However, in addition to the ER, membranes required for phagophore expansion are likely to originate from multiple sources such as plasma membrane and Golgi apparatus (Lahiri et al., 2019). Recently, two independent groups revealed that RAB11A-positive recycling endosomes contribute to phagophore formation as well in starvation or viral infection induced autophagy (Kuroki et al., 2018; Puri et al., 2018). Moreover, it is proposed that PI3P-WIPI2-RAB11A signaling cascade enables recycling endosomes, instead of the ER, as the primary sources for phagophore initiation (Puri et al., 2018). In summary, autophagy is initiated through the sequential activation of ULK complex, VPS34 complex and the subsequent production of PI3P (Fig. 2).

The initiation stage is sophisticatedly regulated by various molecules. In starvation-induced autophagy, mTORC1 serves as one of the key upstream regulators of the ULK complex (Laplante and Sabatini, 2013). Under nutrient-rich conditions with amino acids and growth factors, mTORC1 is activated through the modulation of two GTPases, i.e., Rheb and Rag (Kim and Guan, 2019). Active mTORC1 phosphorylates ULK1, ULK2 and/or ATG13 to suppress ULK complex activation. Notably, recent studies have demonstrated that ULK1 ubiquitination state is crucial for autophagy initiation. mTOR is found to inhibit ULK1 by impairing the ubiquitin ligase TRAF6-mediated Lys63 (K63)-linked ULK1 polyubiquitination, which is required for ULK1 stability and activity (Nazio et al., 2013). The K63-linked ubiquitin chain of ULK1 can be diminished by the deubiquitinase USP1 (Raimondi et al., 2019). Interestingly, another deubiquitinase USP20 facilitates ULK1 stability by reducing ULK1 ubiquitination (Kim et al., 2018), suggesting that ULK1 is

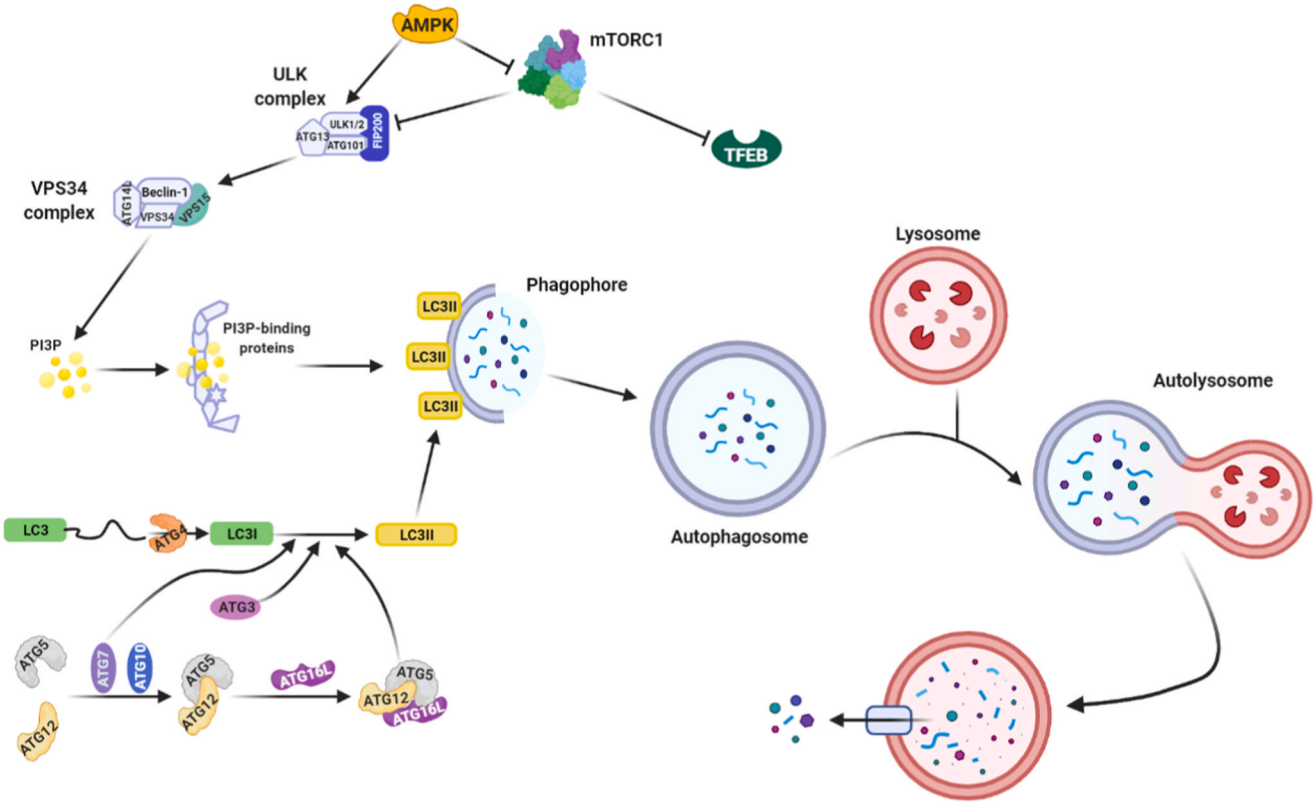

Fig. 2. Schematic diagram of the macroautophagy (autophagy) machinery. Under normal conditions, the active mTORC1 suppresses autophagy initiation. Upon stimulation, mTORC1 is inactivated and AMPK is activated, collectively leading to the activation of ULK complex. Besides, TFEB mediates the transcription of multiple lysosome- and autophagy-related genes. The active ULK complex then activates the VPS34 complex which is responsible for PI3P production. PI3P recruits its binding proteins to form a pre-autophagosomal structure called phagophore. Phagophore elongation and closure is mediated by two ubiquitin-like conjugation systems: ATG5-ATG12-ATG16L complex formation and LC3 lipidation. The sealed phagophore is called autophagosome, and autophagosome is eventually fused with lysosome to form autolysosome. The cargos in autolysosome are degraded by lysosomal enzymes, with the nutrients and metabolites are thus recycled.

modified by more than one type of ubiquitination. In addition to ULK1, TFEB, the master transcription factor of a variety of lysosomal and autophagy related genes, is also suppressed by activated mTORC1 (Martina et al., 2012; Pena-Llopis et al., 2011; Settembre et al., 2012). Taken together, autophagy initiation is thus blocked under nutrient rich conditions. Upon starvation, however, mTORC1 is inactivated followed by the activation of ULK complex through a series of dephosphorylation and phosphorylation (Perluigi et al., 2015), and subsequently autophagy is induced. Another upstream regulatory factor of the ULK complex, AMPK, is a kinase and a well-characterized energy sensor. It can promote autophagy through phosphorylating ULK1. Interestingly, AMPK and mTORC1 are likely to compete on ULK1 phosphorylation, as mTORC1-mediated ULK1 phosphorylation blocks its further phosphorylation by AMPK (Kim et al., 2011). In addition, AMPK is demonstrated to activate autophagy through directly suppressing mTORC1 activity or activating the mTORC1 inhibitor TSC2 (Gwinn et al., 2008; Inoki et al., 2006) (Fig. 2).

Autophagy induction is also tightly modulated via the VPS34 complex. Beclin-1 is the key subunit in the complex, and various molecules regulate autophagy through interacting with Beclin-1. It has been demonstrated that UVRAG (Liang et al., 2006), AMBRA1 (Fimia et al., 2013) and Bif-1 (Takahashi et al., 2007) stimulate VPS34 complex activity and enhance autophagy through association with Beclin-1. Additionally, AMPK is also found to promote autophagy through Beclin-1 phosphorylation at Thr388 (Zhang et al., 2016). For the negative regulators, Bcl-2 (Pattingre et al., 2005) and Bcl-xL (Maiuri et al., 2007) bind to Beclin-1 to suppress VPS34 complex, thus autophagy is compromised. Accordingly, mutations in Bcl-2 (G145A) or Bcl-xL (G138A) that disrupt the interaction with Beclin-1 rescue the suppressed autophagy (Sinha and Levine, 2008). Notably, the small GTPase Rab5 is found to be indispensable for autophagy initiation through modulating VPS34 complex (Jean and Kiger, 2014). Rab5 is viewed as one of the core molecules that mediate endocytosis (Langemeyer et al., 2018). However, it has been demonstrated that Rab5 is required for autophagosome formation through interacting with VPS34 and Beclin-1 in both HD (Huntington's disease) cell and Drosophila models (Ravikumar et al., 2008). Consistently, in growth factor withdrawal induced autophagy, Rab5 was shown to interact with the class IA PI3K subunit p110β, which, in turn, activates Rab5 by enhancing transition from the GDP-bound state (Rab5-GDP) to GTP-bound state (Rab5-GTP). Then VPS34 complex was activated and autophagy was induced (Dou et al., 2013). Similar functions for Rab5 were reported in hepatitis C virus NS4B-induced autophagy (Su et al., 2011).

2.1.2. Autophagosome formation

Autophagosome formation is the key event for the whole autophagic flux, which is mediated by two ubiquitin-like conjugation systems in eukaryotic cells. After autophagy initiation and phagophore synthesis, phagophore then expands and finally seals to form an isolated compartment termed autophagosome. Firstly, ATG7 acts as the E1-like enzyme and ATG10 acts as the E2-like enzyme to catalyze the conjugation of ATG12 to ATG5. ATG16L is then recruited to the ATG5-ATG12 subcomplex to form ATG5-ATG12-ATG16L multimeric protein complex (Mizushima et al., 2003). The other conjugation system is the lipidation of MAP1LC3/LC3 (ATG8 in yeast). Full-length LC3 is firstly cleaved by the protease ATG4 at its carboxyl terminus to generate the cytosolic LC3 type I (LC3I). The cleavage exposes the C-terminal glycine residue where phosphatidylethanolamine (PE) is conjugated to LC3I. This process is known as LC3 lipidation and the lipidated LC3 is called LC3 type II (LC3II) (Tanida et al., 2004). LC3 lipidation is also mediated in a ubiquitin-like conjugation manner, in which ATG7 serves as the E1-like enzyme as well, ATG3 serves as the E2-like enzyme, and the ATG5-ATG12-ATG16L complex serves as the E3-like ligase (Romanov et al., 2012). Thus, LC3II is covalently attached to the phagophore membrane where proteins containing LC3-interacting region (LIR) are recruited. Subsequently, phagophore elongates until it seals at some point to form a vesicle termed autophagosome.

2.1.3. Autophagosome maturation and degradation

Once autophagosome is formed, LC3II bound to the exterior membrane of autophagosome (cytosolic phase) is immediately removed by the ATG4 proteinases (Kauffman et al., 2018). Usually, autophagosomes are subsequently transported to the perinuclear region and fused with proximal lysosome to form autolysosomes (Fig. 2). It has been demonstrated that the fusion step is mediated by several tethering proteins including SNAREs and the HOPS complex (Jiang et al., 2014; Wang et al., 2016b; Zhao et al., 2021). Alternatively, autophagosomes may first fuse with late endosomes to temporarily form amphisomes, which then undergo fusion with lysosomes to produce autolysosomes (Galluzzi et al., 2017). Autophagosomes (or amphisomes), autophagy cargos, and receptors (in selective autophagy) are degraded by lysosomal hydrolases, with the generated products such as amino acids reused. Notably, the acidic lysosomal lumen, which is maintained by the proton pump called v-ATPase (vacuolar-type H^+ ATPase), is required for the activity of resident enzymes (Mauvezin et al., 2015). It has been revealed that AD pathogenic mutations in *PSEN1* suppress autophagic flux through targeting the v-ATPase, which results in defective lysosomal acidification and autophagosome degradation (Lee et al., 2010).

2.1.4. Selective autophagy

Originally, autophagy cargos were thought to be sequestered in non-selective way (bulk autophagy) under the treatment of stimuli such as nutrient deprivation. However, accumulating evidence has demonstrated that autophagosomes selectively recognize specific cargos through adapter proteins under certain circumstances. This form of autophagy is known as selective autophagy (Fig. 3). Selective autophagy can be further classified based on the type of cargos, e.g., aggrephagy involves protein aggregate degradation, mitophagy involves damaged mitochondria degradation, pexophagy involves peroxisome degradation, and xenophagy involves cytosolic pathogen degradation (Gatica et al., 2018; Kirkin and Rogov, 2019) (Fig. 3). Typically, the aberrant proteins are firstly labeled with ubiquitins, and then the ubiquitinated cargos are recognized by the ubiquitin-binding domain (UBD) of adapter proteins such as p62/SQSTM1, NBR1, NDP52, OPTN, TAX1BP1, TOLLIP and RPN10 (Lamark and Johansen, 2021; Menzies et al., 2017). These adapter proteins also contain LIR (LC3-interacting region) motifs through which they associate with LC3, and thus link the ubiquitinated cargos with autophagosomes. Currently, the adapter proteins are referred to as selective autophagy receptors (SARs) (Chu, 2019; Kirkin and Rogov, 2019) (Fig. 3). Selective autophagy has recently gained more attention due to its therapeutic potential for neurodegenerative diseases and ageing. Aggrephagy and mitophagy, for example, have been shown to regulate Aβ metabolism and mitochondrial clearance, respectively (discussed in Section 3).

2.2. Chaperon-mediated autophagy

In chaperon-mediated autophagy (CMA), the cargos are also selective. Only the substrate proteins containing a KFERQ-like motif can be recognized by chaperon protein complex (Olson et al., 1991) (Fig. 1). In contrast to autophagy, the targeted cargos are delivered to lysosomal surface without the formation of intermediate vesicles such as autophagosome or autolysosome. Instead, the KFERQ-containing substrates are recognized by chaperon protein HSPA8 (also known as Hsc70) together with associated co-chaperons. Subsequently, the cargo-HSPA8 complex is transported to lysosomal membrane where the complex interacts with the cytosolic domain of the lysosomal transmembrane protein LAMP2A (Cuervo and Dice, 1996), an isoform of another lysosomal membrane protein LAMP2. Before the docking of cargo-HSPA8 complex, LAMP2A exists either in monomeric or homodimeric state. Once the substrate complex binds to LAMP2A, HSPA8 is released from the complex and LAMP2A quickly undergoes oligomerization to form a

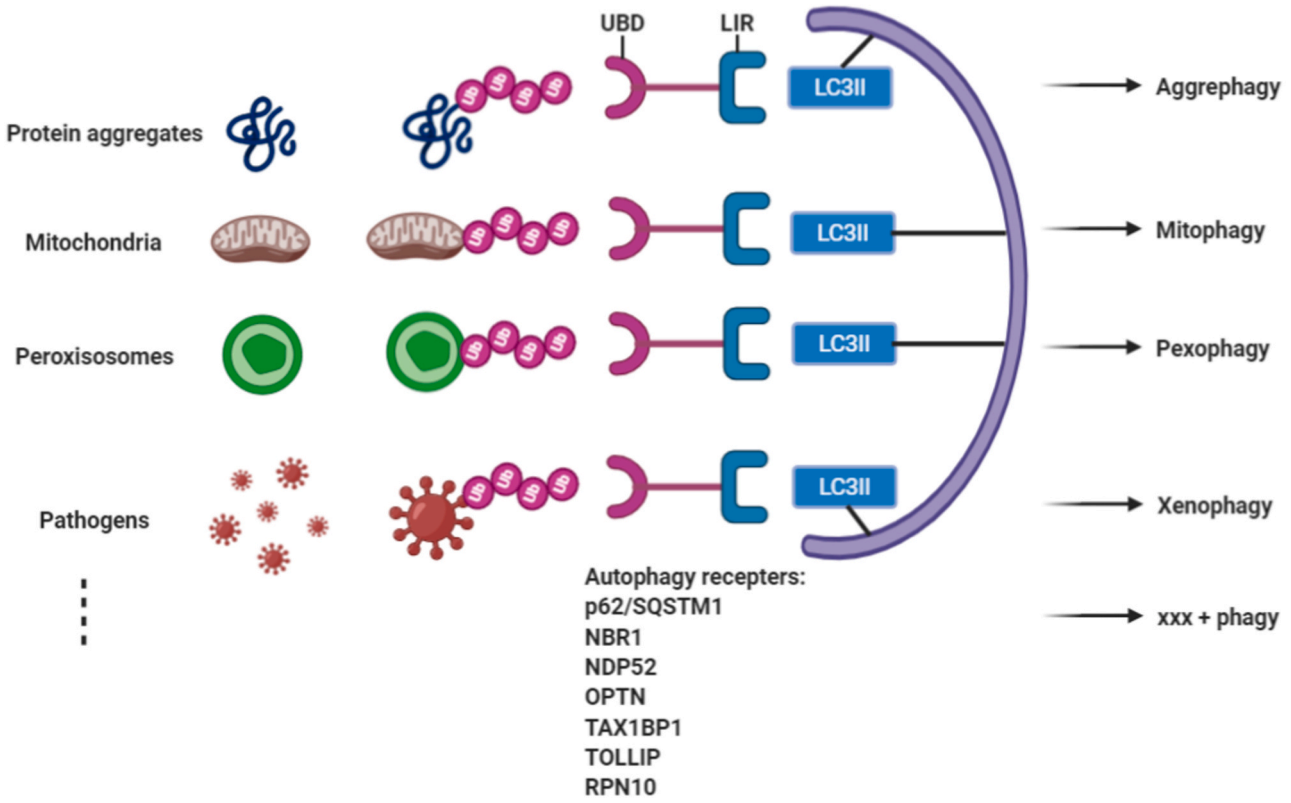

Fig. 3. Schematic representation of selective autophagy. According to the type of cargo for degradation, selective autophagy is termed as "-phagy". For instance, aggrephagy involves the degradation of protein aggregates. Usually, the cargos are initially ubiquitinated and then recognized by selective autophagy receptors (SARs) via the intrinsic ubiquitin-binding domain (UBD). Subsequently, the cargo-SAR complex is directed to autophagosome through the LC3-interacting region (LIR) within SARs, where it is ultimately degraded in lysosome.

pore-like complex. The substrates are firstly unfolded and then translocated into lysosomal lumen where they are degraded. And the LAMP2A oligomer undergoes disassembly to be monomer or dimer for next round of delivery (Bandyopadhyay et al., 2008, 2010) (Fig. 1).

Macroautophagy is believed to be the major type of autophagy in mammals, however, CMA-mediated protein degradation may be largely underestimated. Recent findings suggest that CMA pathway plays a critical role in the pathogenesis of multiple human diseases including cancer, liver diseases and neurodegenerative disorders (Kaushik and Cuervo, 2018). For instance, the processing of AD-related proteins, tau and APP, is modulated by CMA (Park et al., 2016b; Wang et al., 2009). Notably, CMA activity has been found to decline in an age-dependent manner both in human and animal models (Cuervo and Dice, 2000; Rodriguez-Muela et al., 2013; Valdor et al., 2014; Zhang and Cuervo, 2008). Accordingly, recent studies have shown that enhancing CMA improves AD pathologies in mouse models (Bourdenx et al., 2021; Xu et al., 2021), suggesting CMA as a noteworthy drug target.

2.3. *Microautophagy*

Microautophagy is the most straightforward type of autophagy in which the cytoplasmic cargos are directly engulfed by the lysosome or vacuole through membrane invagination. Ultimately, a vesicle surrounding the cargos is formed, then both of the vesicle and cargos are degraded by lysosomal hydrolases (Li et al., 2012) (Fig. 1). Microautophagy can randomly select substrates or specifically degrade certain cargos such as peroxisomes (termed micropexophagy) (Oku and Sakai, 2016).

3. Autophagy in Alzheimer's disease pathogenesis

In addition to aberrant Aβ metabolism and tauopathies, synaptic loss, overactive neuroinflammation, impaired mitochondria, dysfunctional calcium and insulin signaling and so on, are also observed in AD pathologies (Querfurth and LaFerla, 2010). The mammalian nervous system, especially for neurons, depends heavily on autophagy to clear large and insoluble protein aggregates to maintain protein homeostasis (Malampati et al., 2020). In addition, the unique features of neuronal cells confer vulnerability to dysfunctional autophagy. For instance, axonal autophagosomes in neurons have to be transported to the cell body to fuse with lysosomes, because lysosomes are rarely distributed in distal axons (Cheng et al., 2015; Maday et al., 2012).

Accumulating evidence has indicated that impaired autophagy contributes to AD pathogenesis. Initially, it is found that autophagosomes and autolysosomes are accumulated in AD patients' brains through electron microscopy (Nixon et al., 2005). The core subunits of the VPS34 complex, Beclin-1 have been demonstrated to be significantly reduced with AD progression (Lucin et al., 2013; Pickford et al., 2008; Rohn et al., 2011). In line with these findings, PI3P production, which is mediated by the VPS34 complex, was shown to be down-regulated as well in AD patients' brains (Morel et al., 2013). So, it was believed that the accumulation of autophagic structures including autophagosomes and autolysosomes were due to the blockade of autophagic flux (Wolfe et al., 2013). However, Ralph A. Nixon's group recently reported that the expression levels of genes required for autophagosome formation, as well as some lysosomal genes, were up-regulated at both the mRNA and protein levels at early AD stages when they were studying the CA1 neurons in hippocampus from AD patients (Bordi et al., 2016). The findings suggest that the enhanced autophagy at the early stage of AD is protective in response to stress, but autophagic flux is ultimately

compromised with AD progression (Chung et al., 2019). Taken together, growing evidence has indicated that dysfunctional autophagy is closely correlated with AD pathogenesis.

3.1. Autophagy in Aβ metabolism

Autophagy is involved in Aβ metabolism likely via regulation of its generation and clearance. Aβ originates from the processing of its precursor protein APP, which is sequentially cleaved by β-secretase (BACE1) and γ-secretase (Selkoe and Hardy, 2016). It has been demonstrated that a compound induced, ATG5-dependent autophagy enhances the degradation of APP itself (Cavieres et al., 2015). In addition, APP and the four subunits of γ-secretase complex were observed residing in autophagosomes, suggesting that at least some Aβ peptides are produced through autophagic pathway (Di Meco et al., 2020). Moreover, it has been revealed that autophagy is required not only for Aβ production, but also Aβ secretion. As mentioned before, ATG7 acts as the E1-like enzyme for the ubiquitin-like conjugation in autophagosome formation. Nilsson et al. established the ATG7 KO mouse strain and crossed with an AD mouse model (Nilsson et al., 2013, 2015). It is shown that extracellular Aβ plaque formation was drastically decreased in ATG7 KO, autophagy-deficient AD mice. However, intraneuronal Aβ was markedly accumulated, indicating that Aβ secretion was compromised after autophagy is impaired (Nilsson et al., 2013, 2015). In particular, a recent clinical study reported that people carrying harmful ATG7 variants display various neurodevelopmental abnormalities (Collier et al., 2021). The variants cause significant decline or complete loss of ATG7 protein and autophagy is severely compromised. Strikingly, the learning ability of two variant carriers aged less than 30 years was observed to be defective (Collier et al., 2021), suggesting the potential correlation between dysfunctional autophagy and impaired cognition.

Autophagy is also found to modulate Aβ clearance. Previous research has shown that when AD model mice were treated with rapamycin (a specific inhibitor of mTOR), autophagy was thus enhanced. It is observed that both intracellular Aβ and extracellular amyloid deposition in brains were markedly reduced, and the animals' cognition was significantly improved as well (Caccamo et al., 2010; Majumder et al., 2011). The removal of extracellular Aβ is believed to be mediated by microglial endocytosis (Heckmann et al., 2020b; Huang et al., 2021; Zhang et al., 2015). In addition to chemical agents, consistent results were obtained in genetically engineered animal models. For example, in mice, knock-in of a point mutation (F121A) in the gene encoding Beclin-1 disrupts Beclin-1 and Bcl-2 interaction, resulting in the stimulation of basal autophagy. It is demonstrated that amyloid plaques were significantly decreased and cognitive impairment was prevented in AD model mice carrying the Beclin-1 F121A mutation (Rocchi et al., 2017). In line with this study, in Beclin-1 knock out (KO) AD mice, both intraneuronal Aβ and extracellular Aβ aggregation were accumulated compared to the control mice (Pickford et al., 2008). Autophagy seems to affect Aβ clearance at multiple stages. Cathepsin B is a critical lysosomal protease required for the degradation of autophagic substrates. It has been shown that genetic ablation of cathepsin B worsened AD pathologies in AD model mice, including increased Aβ42 abundance and amyloid deposition. Conversely, when cathepsin B was overexpressed through lentiviral transduction, amyloid plaques were reduced even in the aged AD mice (Mueller-Steiner et al., 2006). These results suggest that facilitated autophagic flux, at any stage, is beneficial for mitigating AD progression.

In addition to bulk autophagy, selective autophagy is also found to function in Aβ metabolism. As discussed earlier, selective autophagy that degrades aggregated proteins is called aggrephagy (Kirkin and Rogov, 2019). Previous research has identified several selective autophagy receptors specific for aggrephagy, including p62/SQSTM1, NBR1 and OPTN (Malampati et al., 2020). Normally, Aβ binds to ubiquitin to form a complex that is not prone to aggregate into insoluble fibrils (Bellia et al., 2019). The complex probably undergoes degradation by the ubiquitin-proteasome system (UPS) (Hong et al., 2014). If Aβ is polyubiquitinated, however, it is likely to generate insoluble fibrils (Morimoto et al., 2015), which are resistant to UPS-mediated degradation (Verhoef et al., 2002). Alternatively, the fibrils would presumably be recognized by autophagy receptors and degraded by aggrephagy (Malampati et al., 2020; Morimoto et al., 2015).

3.2. Autophagy in tauopathies

Autophagy also plays a critical role in tau pathology other than Aβ metabolism. Initially, in vitro data showed that once autophagic flux was blocked, tau clearance was compromised and insoluble tau aggregates were significantly accumulated (Hamano et al., 2008). In the brains of familial AD patients, it is found that hyperphosphorylated tau is colocalized with the autophagosome marker LC3 and the autophagy receptor p62/SQSTM1, while the overlap was not observed in control subjects without neurodegenerative diseases (Piras et al., 2016). Consistently, LC3 and p62/SQSTM1 immunoreactivity was associated with tau aggregates in a tau model cell line (Guo et al., 2016). These studies indicate that tauopathies are likely to be altered by autophagy as well. Indeed, in ATG7 conditional KO (cKO) mice, the phosphorylation of tau was markedly up-regulated, which is possibly due to the accumulation of GSK3β, one of the major tau kinases, in brains of ATG7 cKO mice (Inoue et al., 2012).

In line with its role in Aβ metabolism, autophagy induction is shown to alleviate tauopathies. The mouse model carrying tau mutant treated with mTOR inhibitor rapamycin shows significantly reduced phosphorylated tau. Conversely, TSC2 (a mTOR negative regulator) KO mice, in which mTOR signaling was constitutively activated, displayed elevated tau levels as well as tau phosphorylation (Caccamo et al., 2013). Most recently, a study identified several mTOR inhibitors that are more potent than rapamycin, and these compounds were used to treat neurons differentiated from human neural progenitor cells (NPCs) with tau mutant. The results showed that these identified compounds drastically reduced tau phosphorylation and insoluble tau (Silva et al., 2020), thus providing more evidence that stimulated autophagy ameliorates tauopathies. mTOR is not the only molecule in autophagic pathway targeting tau related pathology. It has been observed that, as well as p62/SQSTM1, the autophagy receptor NDP52 recognizes phosphorylated tau in brains of AD model mice (Kim et al., 2014). And when NDP52 was up-regulated by a compound from tea extract, the clearance of phosphorylated tau by autophagy was demonstrated to be enhanced in cultured neurons (Chesser et al., 2016). Likewise, elevated expression of NDP52 by its upstream transcription factor Nrf2 was shown to promote the degradation of phosphorylated tau (Jo et al., 2014; Malampati et al., 2020). In addition to mTOR and autophagy receptors, TFEB, one of the core regulators in autophagy, is also viewed as a critical factor in tau pathologies. Several studies have demonstrated that up-regulation of TFEB in tau mouse models markedly reduced soluble phosphorylated tau and insoluble tau aggregates, and cognitive functions were improved (Polito et al., 2014; Wang et al., 2016a). Recent evidence indicates that TFEB mediates tau clearance by modulating lysosomal exocytosis of tau. Conditional knock out (cKO) of TFEB in tau P301S transgenic mice leads to reduced tau abundance in interstitial fluid but elevated intraneuronal tau phosphorylation and enhanced tau spreading (Xu et al., 2020).

Chaperon-mediated autophagy (CMA) is involved in tauopathies as well. Tau contains two motifs in its C-terminus that can be recognized as a CMA substrate. In contrast, tau mutants are still targeted to lysosomes via LAMP2A oligomerization, but cannot be completely transported into the lumen (Wang et al., 2009). Instead, the entry of mutant tau proteins into lysosomal lumen stops midway. The lumen parts are then degraded, while the smaller remaining fragments oligomerize on lysosome membrane and block CMA (Wang et al., 2009). In addition to mutated tau, a recent study demonstrated that tau acetylation is resistant to CMA-mediated degradation and tauopathies are aggravated when CMA is inhibited in a mouse model (Caballero et al., 2021). Concomitantly,

the same group found that loss of CMA accelerates tau aggregation and promotes disease progression, and elevation of CMA activity using small molecules significantly mitigates AD pathology in two different AD mouse models (Bourdenx et al., 2021). This evidence indicates that both macroautophagy and CMA are indispensable regulators in light of tauopathies.

3.3. Autophagy in synaptic function

In addition to Aβ deposition and tau aggregation, synaptic dysfunction is another characteristic feature of AD pathology. Synapses are neuron-specific structures that serve as the basic units for communication from presynaptic to postsynaptic neurons. It has been observed that the number of synapse is reduced at the early stage of AD pathogenesis (Chen et al., 2019). Recently, accumulating evidence proposes that functional autophagy is required for synaptic functions including neurotransmission and synaptic plasticity (Lieberman and Sulzer, 2020). Synaptojanin-1 is a presynaptic lipid phosphatase involved in the endocytosis of synaptic vesicles. Research has shown that late endosomes and autophagosomes are accumulated in zebrafish cone photoreceptors following genetic ablation of Synaptojanin-1 (George et al., 2016), suggesting that Synaptojanin-1 is indispensable to maintain normal autophagy at synapses. Likewise, the Synaptojanin-1 interacting protein, Endophilin (also known as Bif-1) is demonstrated to associate with Beclin-1 to modulate autophagy initiation through regulating the VPS34 complex activity (Takahashi et al., 2007). Additionally, autophagy has been proven to be involved in presynaptic release of dopamine. Elevated dopamine release is reported in ATG7 cKO dopaminergic neurons, which can be rescued by the treatment with the mTOR inhibitor rapamycin (Hernandez et al., 2012). Subsequent studies revealed that the association of Rab26 and ATG16 (Binotti et al., 2015), Bassoon and ATG5 (Nikoletopoulou and Tavernarakis, 2018), are also important players for synaptic vesicle release. Studies on autophagy in postsynaptic loci remain relatively limited. The role of autophagy appears to involve degradation of the neurotransmitter receptors including $GABA_A$ and AMPA receptors (Lieberman and Sulzer, 2020).

Autophagy is also necessary for synaptic plasticity, i.e., synaptic features that change in structure, number and function to strengthen or weaken the contact. It is believed that synaptic plasticity is essential for cognitive functions such as learning and memory. At the cellular level, there are two forms of synaptic plasticity related to learning and memory, i.e., long-term potentiation (LTP) and long-term depression (LTD). Initially, it is reported that BDNF (brain-derived neurotrophic factor) deficiency can up-regulate LC3II and promote autophagosome accumulation but compromise LTP; in contrast, impaired LTP due to BDNF ablation can be rescued after autophagy is suppressed (Nikoletopoulou et al., 2017), suggesting that autophagy induction impairs LTP. However, a recent study demonstrated that autophagy stimulation in mouse hippocampus was required for new memory formation and LTP was blocked after pharmacological inhibition of autophagy (Glatigny et al., 2019). Despite the inconsistencies between the two studies, it should be noticed that the former study focuses on the function of BDNF on synaptic plasticity, and it is widely accepted that BDNF is a multifunctional secretory protein. Thus, unpredictable side effects might be caused due to the ablation of BDNF.

3.4. Autophagy in mitochondrial dysfunction

Mitochondria are the organelles of energy production. Functional mitochondria are essential for neurons to maintain calcium homeostasis, synaptic plasticity and cellular survival (Mattson et al., 2008). However, in the process of energy production, reactive oxygen species (ROS) are generated as by-products and the accumulation of ROS is damaging to mitochondria. Multiple quality control strategies have been identified to maintain mitochondrial function and homeostasis (Pickles et al., 2018; Scheibye-Knudsen et al., 2015). In AD pathogenesis, accumulated Aβ potently generates excessive ROS and causes abundant damage to mitochondria (Querfurth and LaFerla, 2010). Mitophagy is the dominant approach to eliminate damaged mitochondria (Fang et al., 2014; Gatica et al., 2018; Kerr et al., 2017). In mammals, except for rare cases involving sperm mitochondria in fertilized eggs and differentiating red blood cells (Sutovsky et al., 2000), mitophagy is canonically induced by the collapse of mitochondrial membrane potential (MMP) caused by ROS overload. The PINK1-Parkin pathway is a well-studied pathway mediating MMP-dependent mitophagy (Chu, 2019). PINK1 is a serine/threonine protein kinase in cytoplasm, and it is translocated into mitochondrial matrix in normal functional mitochondria. In damaged mitochondria, however, the compromised MMP blocks PINK1 import and keep it on the outer mitochondrial membrane (OMM) where PINK1 is activated through autophosphorylation (Aerts et al., 2015; Kondapalli et al., 2012; Narendra et al., 2010). Activated PINK1 phosphorylates and activates Parkin, and simultaneously PINK1 phosphorylates ubiquitin on OMM as well to generate phospho-ubiquitin (Kane et al., 2014; Koyano et al., 2014). As an E3 ligase, Parkin recognizes the phospho-ubiquitin on OMM, leading to additional Parkin recruitment (Trempe et al., 2013). Typically, ubiquitinated mitochondria are recognized by autophagy receptors p62/SQSTM1 and OPTN, and then undergo autophagic degradation (Chu, 2019; Geisler et al., 2010). Alternatively, Parkin is demonstrated to be dispensable and phosphorylated ubiquitin by PINK1 itself is potent enough for autophagy receptor NDP52 and OPTN recognition (Lazarou et al., 2015). Recently, an important study identified PTEN-L, a novel isoform of PTEN, as a pivotal negative regulator of PINK1-Parkin mediated mitophagy. Specifically, PTEN-L is found to stop mitophagy by dephosphorylation of Parkin and ubiquitin via its intrinsic phosphatase activity (Wang et al., 2018). In addition to PINK1-Parkin-mediated mitophagy, multiple other forms of mitophagy have been reported (Chu, 2019; Gatica et al., 2018; Pickles et al., 2018), indicating the complexity of mitochondrial homeostasis maintenance.

Mitochondrial dysfunction is a common characteristic of AD. Postmortem studies have demonstrated that hippocampal mitophagy was markedly reduced in AD patients. Moreover, as mitochondrial dysfunction is an early pathological feature of AD and entorhinal cortex (EC) is the region firstly affected by AD, it has been proposed that defective mitophagy in EC may be an initial hallmark of AD pathology (Kobro-Flatmoen et al., 2021). Similar phenotype was observed in AD mouse models and neurons derived from induced pluripotent stem cell (iPSC) of AD affected individuals (Fang et al., 2019; Lou et al., 2020), suggesting that mitophagy induction may ameliorate AD pathogenesis. Indeed, a recent study applied pharmacological agonizts of mitophagy to treat AD model cells and organisms. The results demonstrated that enhanced mitophagy alleviated both Aβ and tau pathologies, and improved the cognitive functions of AD *C. elegans* and mouse models (Fang et al., 2019). Although the relationship between mitophagy and AD pathogenesis requires further investigation, mitophagy mediated clearance of dysfunctional mitochondria displays therapeutic potential for AD intervention.

4. Current therapeutics for AD

AD is an extremely complex disease, and there are still no effective medications to slow or prevent AD progression. Only four drugs (rivastigmine, galantamine, donepezil and memantine) are presently approved by US FDA for AD treatment, three of which (rivastigmine, galantamine and donepezil) are cholinesterase inhibitors and memantine targets NMDA receptor (Long and Holtzman, 2019). The efficacy of these drugs is very limited and varies with different individuals (Knight et al., 2018). Notably, US FDA recently announced to approve Aducanumab (trade name Aduhelm), a monoclonal antibody targeting aggregated Aβ, as a new agent for AD treatment. But more clinical trials are still required to examine its clinical benefit.

To date, over 100 double-blind clinical trials have failed, in which more than 20 compounds showed no effect after completion of phase 3

trials (Cummings et al., 2021; Long and Holtzman, 2019). Currently, there are 126 agents are undergoing clinical trials, most of which are targeting Aβ metabolism, tau, inflammation, neurotransmitter receptors, synaptic plasticity and so on. Notably, among these interventions, more and more agents are designed from perspectives other than amyloid and tau pathologies (Cummings et al., 2020). For instance, the National Medical Product Administration (NMPA) of China approved GV-971 in 2019 for the treatment of AD at mild-to-moderate stage (Wang et al., 2019). GV-971 is an oligomannate extracted from brown algae, and it is believed to be a multitargeted compound crucial for the balance of gut microbiota. GV-971 administration is reported to significantly prevented AD progression by modulating dysbiosis of the gut microbiome induced excessive inflammation in brain (Wang et al., 2019). As GV-971 has exhibited high safety in clinical trials and its mechanisms of action are distinct, researchers are cautiously optimistic for its commercial application. Additionally, some other agents attempt to suppress AD pathogenesis indirectly via regulating signaling pathways involved in metabolism, epigenetic changes, vascular system, neurogenesis as well as protein homeostasis (Cummings et al., 2021; Hara et al., 2019). The novel perspectives represent potential approaches for future AD treatment.

5. Autophagy-stimulating strategies for AD therapeutics

Due to the massive failure of compounds targeting amyloid and tau, researchers are considering other therapeutic strategies for AD (Long and Holtzman, 2019). A consensus is being reached on autophagy-related interventions. Accumulating evidence indicates that enhanced degradation of misfolded proteins and impaired organelles through autophagy induction might be ideal for AD therapy. As autophagy is a conserved, highly dynamic and sophisticatedly-regulated cellular event, it could theoretically be stimulated at multiple levels, thus providing various pharmacological targets to develop agonizts or antagonists accordingly.

Although immunotherapy and other therapies like gene therapy are intriguing options for AD intervention, small molecules are still preferable, as they can easily cross the blood-brain barrier (BBB). Hundreds of compounds have been clinically tested against AD in recent years (Cummings et al., 2020, 2021). Here, we select a list of autophagy-stimulating agents that have been investigated in AD animal models and/or proven to be safe in various phases of clinical trials, even though some of them were not originally designed for AD treatment (Table 1). Next, we discuss the underlying mechanisms of these compounds in autophagy and their performance in animal models and clinical trials.

5.1. Compounds targeting bulk autophagy

Most of the selected agents induce autophagy through inhibiting mTOR and/or activating AMPK (Table 1). Rapamycin and its derivatives are macrolide compounds and well-characterized mTOR inhibitors. The administration of rapamycin in AD model mice has been demonstrated to alleviate Aβ aggregation, tauopathies and improve cognitive functions (Lin et al., 2013; Ozcelik et al., 2013; Spilman et al., 2010). Although clinical data regarding rapamycin administration in AD patients are not available, low-dose rapamycin improve some ageing related markers, suggesting its potential function in slowing ageing (Selvarani et al., 2021; Singh et al., 2016). Rapamycin and its analogs (rapalogs) display side effects in humans, including mucositis and rash, stomatitis, hyperglycemia, hyperlipidemia and hypophosphatemia (Li et al., 2019; Mita et al., 2008; Soefje et al., 2011). However, the mild toxicity of rapalogs appears to be tolerated in view of their remarkable potential in the treatment of age-related diseases, including AD (Dumas and Lamming, 2020; Selvarani et al., 2021). Curcumin is a natural product from *Curcuma longa* plants, which potently suppresses PI3K-Akt-mTOR signaling pathway. In AD model mice, the treatment of

Table 1
Autophagy-inducing compounds with therapeutic potential for AD treatment.

Compound	Mechanism of action	Animal model data	Clinical trial data
Rapamycin (and its derivatives)	mTOR inhibition	Reduces amyloid plaques, tauopathies, and improves cognition (Lin et al., 2013; Ozcelik et al., 2013; Spilman et al., 2010)	Down-regulates some senescence markers, and improves senescence-related physical performance (Singh et al., 2016)
Lithium	AMPK activation	Reduces tauopathies (Caccamo et al., 2007)	Improves cognition (Matsunaga et al., 2015)
Curcumin	mTOR inhibition	Reduces amyloid plaques, and improves cognition (Wang et al., 2014)	Reduces inflammation (Salehi et al., 2019)
Resveratrol	AMPK activation	Reduces amyloid plaques (Vingtdeux et al., 2010)	Improves cognition (Kou and Chen, 2017; Turner et al., 2015)
Glucosamine	AMPK activation, mTOR inhibition	Not applied to AD animal models yet	Improves osteoarthritis (Zeng et al., 2015; Zhu et al., 2018)
Metformin	AMPK activation, mTOR inhibition CMA activation	Reduces amyloid plaques, tauopathies and improves cognition (DiTacchio et al., 2015; Farr et al., 2019; Lu et al., 2020; Xu et al., 2021)	Improves cognition (Koenig et al., 2017)
Oleuropein	AMPK activation, mTOR inhibition	Reduces amyloid plaques and improves cognition (Grossi et al., 2013)	Improves glucose homeostasis (Nediani et al., 2019)
Memantine	Activation of autophagy in an mTOR-dependent or -independent manner	Reduces amyloid plaques, tauopathies, and improves synaptic plasticity and cognition (Martinez-Coria et al., 2010)	FDA approved for AD treatment
Carbamazepine	Activation of autophagy in an mTOR-dependent or -independent manner	Reduces amyloid plaques and improves cognition (Li et al., 2013; Zhang et al., 2017)	FDA approved for the treatment of epilepsy, trigeminal neuralgia and so on
Nilotinib	mTOR inhibition, Elevation of VPS34 complex formation	Reduces amyloid plaques and improves cognition (Lonskaya et al., 2013)	Reduces amyloid accumulation and CSF Aβ (Turner et al., 2020)
Spermidine	Activation of autophagy via	Not applied to AD animal models yet	Reduces blood pressure and

(*continued on next page*)

Table 1 (*continued*)

Compound	Mechanism of action	Animal model data	Clinical trial data
	modulating Beclin-1		cardiovascular disease risk (Eisenberg et al., 2016)
Trehalose	TFEB activation	Reduces amyloid plaques, tauopathies, and improves cognition (Du et al., 2013; Portbury et al., 2017; Schaeffer et al., 2012)	Improves swallowing and muscle power in Oculopharyngeal Muscular Dystrophy (Khalifeh et al., 2019)
Nicotinamide riboside (NR)	Mitophagy activation	Reduces amyloid plaques, tauopathies, and improves cognition (Fang, 2019; Fang et al., 2019, 2014; Gong et al., 2013; Green et al., 2008; Lautrup et al., 2019a; Liu et al., 2013)	Limitedly improves cognition (Di Meco et al., 2020). NR-based clinical trials on PD and ALS are ongoing (Lautrup et al., 2019b).

curcumin has significantly reduced amyloid aggregation and inhibited memory decline (Wang et al., 2014). Clinical results indicate that curcumin functions in suppressing inflammation (Salehi et al., 2019). Considering the damage of neuroinflammation in AD, curcumin is an attractive agent targeting AD treatment.

The anti-psychiatric drug lithium is demonstrated to promote autophagy through activating AMPK (Bao et al., 2019). Lithium is reported to markedly ameliorate tauopathies in 3xTg AD model mice (Caccamo et al., 2007), but shows no significant effects on tau phosphorylation in clinical trials (Hampel et al., 2009). In addition, lithium administration considerably improved cognition of AD patients and individuals with MCI (mild cognitive impairment) (Matsunaga et al., 2015). Resveratrol is also reported to stimulate autophagy in an AMPK-dependent manner, resulting in AD pathology attenuation in animal models (Vingtdeux et al., 2010). However, resveratrol is a multitargeted compound, and it is also found to enhance autophagy via sirtuin1-mediated signaling pathway (Uddin et al., 2019). As resveratrol is a grape-derived polyphenol, it is very safe in clinical trial. Although it shows some protective effects in AD patients, inconsistent results have also been observed (Kou and Chen, 2017; Turner et al., 2015). Interestingly, a recent study based on a machine learning framework also recognizes resveratrol as a candidate drug for AD (Rodriguez et al., 2021).

Other agents are reported to elevate autophagy through both AMPK activation and mTOR inhibition. Glucosamine is an essential component in cartilage, and it is usually used as a supplement to improve the pain caused by loss of cartilage (osteoarthritis). Recent research indicates that glucosamine is an autophagy agonist that acts by suppressing mTOR and activating AMPK both in vitro and in vivo (Carames et al., 2013; Chen et al., 2018). At present, there are no reports regarding the effects of glucosamine administration on AD animal models. However, glucosamine has been shown to enhance longevity in worms and old mice (Weimer et al., 2014). As age is a major risk factor for AD, glucosamine may have protective effects against AD through facilitating healthy ageing. Metformin is a biguanide compound that is widely used for the patients with type 2 diabetes. It activates AMPK and/or inhibits mTORC1 to induce autophagy (Kalender et al., 2010; Onken and Driscoll, 2010). Importantly, metformin has recently been identified as a novel CMA activator through phosphorylating Hsc70 (also known as HSPA8) mediated by TAK1-IKKα/β signaling (Xu et al., 2021). The mechanism of action may be controversial, but metformin consistently and potently reduces AD-like pathologies and improves cognition in AD mouse models (Table 1). Moreover, metformin displays promising results in improving certain cognitive functions in clinical trials (Koenig et al., 2017). Oleuropein is extracted from green olive and it stimulates autophagy by inhibiting mTOR and/or activating AMPK as well (Rigacci et al., 2015). Oleuropein has been demonstrated to markedly reduce Aβ plaques and ameliorate synaptic plasticity in a well-established AD mouse model TgCRND8 (Grossi et al., 2013; Luccarini et al., 2015). Clinical studies have demonstrated that oleuropein has some beneficial effects on several human chronic non-communicable diseases including cardiovascular diseases and diabetes (Nediani et al., 2019). As these chronic disorders are closely correlated with AD development, further investigations on the efficacy of oleuropein in AD prevention should be considered.

Both mTOR and AMPK are dispensable targets to induce autophagy. The FDA approved agent for AD treatment, memantine, is shown to enhance autophagy either mTOR dependently or independently (Song et al., 2015). Similarly, the FDA approved antiepileptic drug carbamazepine can also induce autophagy in mTOR-dependent or -independent way. Carbamazepine shows intriguing therapeutic potential for AD due to its benefits in amyloid aggregate reduction and cognition improvement in 3xTg AD model mice (Li et al., 2013; Zhang et al., 2017). Nilotinib is a tyrosine kinase inhibitor, which is usually applied for the treatment of chronic myeloid leukemia (CML). A recent study showed that nilotinib stimulates autophagy through c-ABL-mediated mTOR inhibition (Hussain et al., 2019). Although nilotinib is likely to target multiple factors involved in the autophagic process (e.g., VPS34 complex) (Yu et al., 2020), its efficacy on autophagy induction is consistent. In addition, in vivo studies and clinical trial results have demonstrated that nilotinib decreases amyloid deposition (Table 1). Notably, nilotinib has also been identified to be a potential drug against AD using artificial intelligence (Rodriguez et al., 2021), making it an appealing candidate for AD therapeutics. Spermidine is a natural polyamine existing in all eukaryotic cells and is required for cell proliferation, differentiation and apoptosis (Pegg, 2016). Recent studies have revealed that spermidine elevates autophagy in vitro through up-regulating the acetyltransferase EP300, a Beclin-1 and LC3 binding protein (Sacitharan et al., 2018). Although spermidine has not been applied in AD animal models, it displays consistent effects against ageing in multiple model organisms, including yeast, *C. elegans*, *Drosophila* and mice (Eisenberg et al., 2016, 2009; Yue et al., 2017). As such, spermidine may have the potential to treat age-related neurodegenerative disorders such as AD. Trehalose is a natural disaccharide. In contrast to other autophagy inducers mostly targeting mTOR, AMPK or VPS34 complex, trehalose activates autophagy via the transcription factor TFEB. Studies demonstrated that the administration of trehalose promotes TFEB dephosphorylation, resulting in TFEB nuclear translocation and the up-regulation of multiple TFEB downstream effectors required for autophagy in an mTOR independent manner (Rusmini et al., 2019). Amyloid and tau pathologies in AD mouse models treated by trehalose show significant improvement (Table 1), indicating that trehalose is worth consideration for AD therapy.

5.2. Compounds targeting mitophagy

In addition to bulk autophagy, researchers have also investigated selective autophagy to identify potential drug targets for neurodegenerative diseases in recent years. Considerable efforts have been expended on screening compounds that may enhance aggrephagy and mitophagy. Small molecules targeting aggrephagy have recently been reviewed (Malampati et al., 2020). Here, we discuss the anti-ageing compound, nicotinamide, which has been proven to stimulate mitophagy. Nicotinamide is an active form of vitamin B3. It serves as the precursor of oxidized nicotinamide adenine dinucleotide (NAD^+) which is a critical coenzyme in the catalysis of a broad range of intracellular metabolic events. Extensive studies have demonstrated that

nicotinamide and its derivatives, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), induce mitophagy and are protective against ageing (de Picciotto et al., 2016; Mills et al., 2016; Yoshino et al., 2018). Recent evidence indicates that nicotinamide replenishment markedly ameliorates amyloidosis, tauopathies and cognitive impairment in AD mouse models (Table 1). Even though clinical trial of nicotinamide in AD patients are not inspiring, nicotinamide exhibits excellent safety even under high dose treatment (Di Meco et al., 2020). These mitophagy enhancers, including nicotinamide, NR and NMN, are safe and natural molecules that have already been commercially produced. Therefore, their effects on AD are worth further exploration.

6. Concluding remarks and future perspectives

AD and other neurodegenerative disorders are proteinopathies characterized by formation of abnormal and insoluble protein aggregates. Tremendous effort has been made to develop interventions targeting amyloidosis and tauopathies. However, effective disease-modifying medications are still absent and numerous amyloid- and tau-directed compounds have failed at clinical trials.

In recent years, increasing evidence has demonstrated that dysfunctional autophagy is not just correlated with AD pathologies, but is likely to be a causative factor for AD development. Multiple AD risk genes, including *PSEN1*, *PICALM*, *CLU*, *TREM2*, etc. have been found or suggested to modulate autophagic flux. Thus, stimulating autophagy to enhance the elimination of misfolded proteins is proposed to be an option for AD therapy. Indeed, a variety of autophagy enhancers have been identified to slow AD progression and improve cognition, at least in AD animal models. However, the beneficial effects of autophagy stimulators in AD patients have not been observed or are limited. Clinical trials have identified some candidates that are highly safe and/or already approved by FDA to treat diseases other than AD. Hence, it should be possible to perform clinical trials with larger sample sizes and determine the efficacy of candidate interventions in distinct subgroups of enrolled subjects in different stages of AD and MCI. In addition, considering the complexity of AD, single agent may not be effective to alleviate AD symptoms. Therefore, combining more than one autophagy activator should be considered in future clinical trials. Furthermore, as the pathological changes of AD accumulate in the brain for years or even decades before clinical diagnosis, administration of potential interventions (not just autophagy-stimulating compounds but also Aβ-, tau-, and APOE-directed agents) at the preclinical stage should be employed to evaluate the efficacy.

Autophagy is particularly conserved in eukaryotic organisms. Despite the huge advances in elucidating autophagic process, more effort is required to understand the mechanisms of the sophisticatedly regulated, highly dynamic cellular event. Recent studies have shown that some forms of autophagy selectively degrade specific substrates through autophagy receptors, termed selective autophagy. Unraveling the molecular basis of cargo selection and recognition would be helpful to precisely activate certain autophagy pathway. Mitophagy is gaining more attention lately, as impaired mitophagy might be the earliest AD pathological sign in the entorhinal cortex. In addition, defective CMA is also found to contribute to AD development. AD is a complex multifactorial disease and researchers have encountered many frustrating challenges in the development of AD therapeutics. Autophagy-directed strategies may provide a new and promising alternative for developing anti-AD medications.

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