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REVIEW ARTICLE

Molecular Mechanism of Autophagy: Its Role in the Therapy of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder of progressive dementia that is characterized by the accumulation of beta-amyloid (Aβ)-containing neuritic plaques and intracellular Tau protein tangles. This distinctive pathology indicates that the protein quality control is compromised in AD. Autophagy functions as a "neuronal housekeeper" that eliminates aberrant protein aggregates by wrapping then into autophagosomes and delivering them to lysosomes for degradation. Several studies have suggested that autophagy deficits in autophagy participate in the accumulation and propagation of misfolded proteins (including Aβ and Tau). In this review, we summarize current knowledge of autophagy in the pathogenesis of AD, as well as some pathways targeting the restoration of autophagy. Moreover, we discuss how these aspects can contribute to the development of disease-modifying therapies in AD.

Keywords: Alzheimer's disease, autophagy, amyloid beta, tau, propagation of amyloid beta and tau, mTOR-dependent pathway, mTOR-independent pathway, autophagy-related interventions.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of progressive dementia in the elderly population worldwide. The predominant histological signs of AD are characterized by extracellular amyloid plaques consisting of amyloid-beta (Aβ) and by intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau protein. In particular, oligomerization of Aβ peptide in the brain is an early pathophysiological event that occurs a decade or more before symptom onset [1, 2]. In the healthy brain, the amyloid precursor protein (APP) is generated by α-, β- and γ-secretases through either non-amyloidogenic or amyloidogenic pathways, and is assumed to be in equilibrium. Meanwhile, in AD brain, this balance breaks down and the amyloidogenic pathway is dominant for the cleavage of APP, giving rise to peptide fragments known as Aβ [3, 4]. Once formed, Aβ (and in particular Aβ42) abnormally accumulates, resulting in the formation of Aβ oligomers, cerebral amyloid plaques, neurodegeneration, and ultimately brain atrophy. Tau, is typically localized to axons where it binds and stabilizes microtubules based on its phosphorylation status. In AD, there are high levels of intraneuronal hyperphosphorylated tau and aberrant tau misfolding due to hyperphosphorylation and dissociation from microtubules [5]. This instability of microtubules leads to the severe disruption of axonal transport, which results in neuronal death. Following neuronal death, Tau filaments are aggregated in the extracellular space, and are the major components in the formation of the other types of AD-associated neuropathological lesion, namely, NFTs. Increasing evidence suggest that pathological Tau abnormality is as important as amyloid plaques in AD development [6] (Fig. **1**). Besides aggregation of these two misfolded proteins, Tau and Aβ propagation is responsible for the progression of AD. In 2006, the progressive spread of Aβ deposition was first detected in APP transgenic mice [7]. Soon after, prion-like mechanisms of Tau pathology were verified [8]. Since then, multiple studies suggest that Aβ deposits and Tau assemblies can "seed" the formation of aggregates, followed by their spreading to other cells [9-12].

Autophagy is the key intracellular degradation pathway for eliminating aberrant proteins and promoting survival and suppressing programmed cell death [13]. In case of autophagy, intracellular waste is enwrapped by double-membraned vesicles termed as phagophores and degraded by fusion with lysosomes [14, 15]. Under normal conditions, autophagy is constitutively active and eliminates the cytotoxic effect of damaged proteins and organelles to maintain

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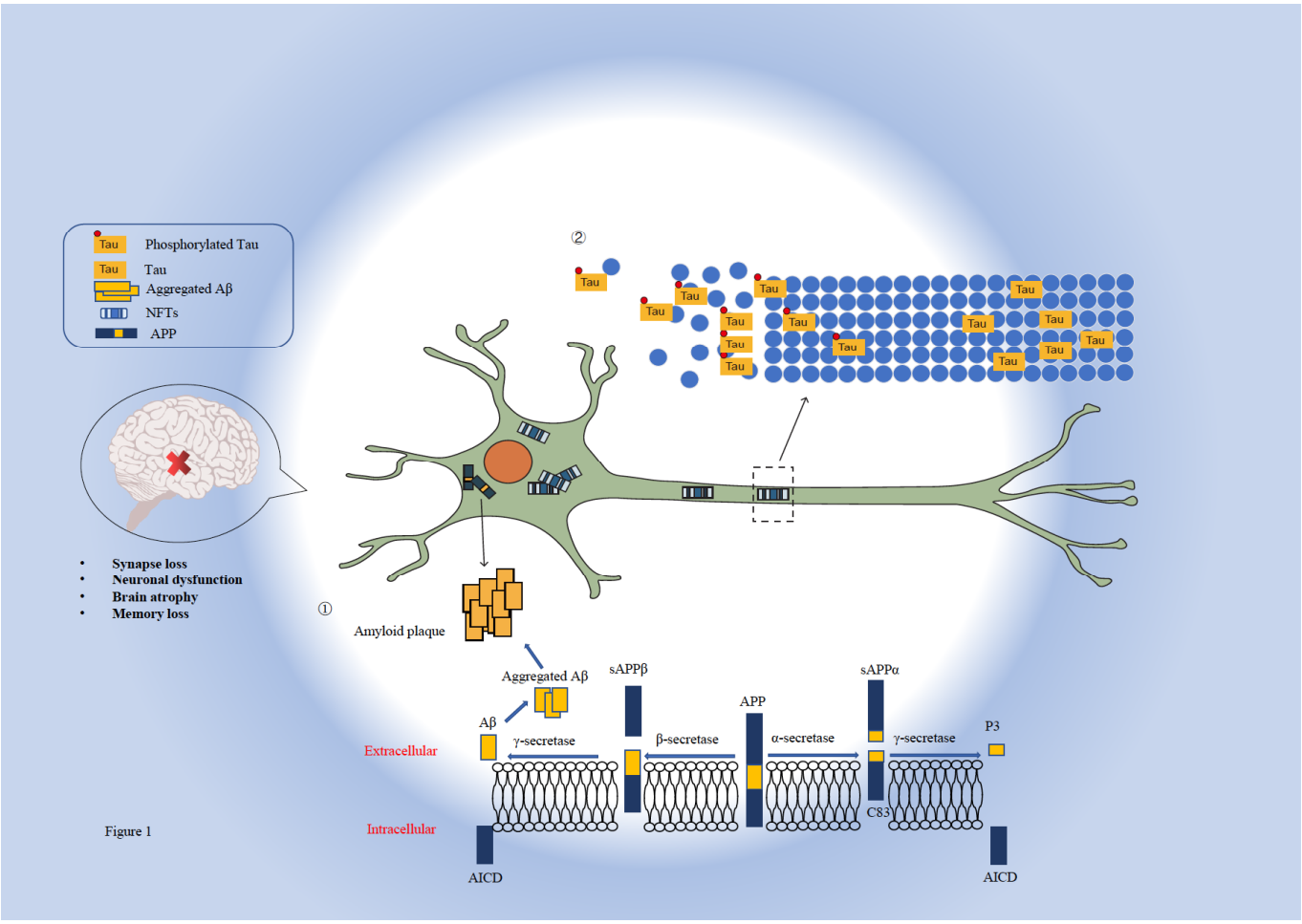

Figure 1

Fig. (1). Amyloid deposits and neurofibrillary tangles (NFTs) are the two main neuropathological lesions described in patients with Alzheimer disease (AD). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

intracellular homeostasis [16, 17]. During the progression of AD, autophagy is aberrant. Dysfunctional autophagy resulting in the accumulation of mutated toxic proteins (*i.e.*, Aβ and Tau), which causes an increase in oxidative stress and neuronal death [18]. Besides, autophagy also interferes with propagation of both misfolded proteins. Exosomes are recognized as the cargo-laden vesicles that help amyloid transmission. During autophagic dysfunction, multivesicular bodies release intraluminal vesicles (ILVs) containing amyloids as exosomes, thereby decreasing the proteotoxic stress in the releasing cells, yet propagating protein aggregates to neighboring cells [19]. Furthermore, the pathological changes of AD also lead to defective autophagy. Persistent accumulation of Aβ-induced aberrant autophagy and decreased autophagosome-lysosome fusion constitute a vicious loop that worsens AD [20].

In this review, we summarize the current knowledge on the relevance of autophagy dysfunction to AD-related pathology. Molecular targets for autophagy modulation and potentially therapeutic drugs mediating autophagic flux disruption in AD will also be reviewed. We hope our work will foster a hopeful therapeutic platform for Alzheimer's disease.

2. AUTOPHAGY MACHINERY

Autophagy is a finely organized phenomenon through which eukaryotic cells can digest overabundant organelles, macromolecules and proteins and recycle their breakdown products [21, 22]. Simply, this degradation pathway is initiated by the fusion of vesicles to form a phagophore, a cup-shaped double-membrane, enveloping small fragments of the cytoplasm and organelles. By elongating, phagophores gradually sequester cargo until they form a double-membrane bound vesicles termed as autophagosomes. By means of cytoskeletal microtubule systems, autophagosomes slide along and fuse with different vesicles, and ultimately with lysosomes. Finally, a single-membraned autolysosome is formed, which allows degradation of the autophagosome contents by lysosomal hydrolases [23, 24].

Autophagy induction is finely regulated by two major complexes: the Unc-51 like autophagy activating kinase (ULK1) complex (consisting of ULK1, autophagy-related protein [ATG]-13, ATG101, and focal adhesion kinase family interacting protein of 200 kDa [FIP200]) and class III phosphatidylinositol 3-kinase (PI3K)/Beclin-1 complex (consisting of vacuolar protein sorting [VPS]-34, VPS15,

ATG6, and ATG14) [24, 25], which are sensors for intracellular homeostasis. The ULK1 complex is mainly regulated by the mammalian target of rapamycin complex 1 (mTORC1) and 5′ AMP-activated protein kinase (AMPK) pathway, which acts as an autophagy blocker and activator [26]. Moreover, p53 is also suggested to transcriptionally regulate ULK1 under oxidative stress conditions [27], as elaborated below. Activated ULK1 recruits PI3K and VPS34, which induces accumulation of phosphatidylinositol-3-phosphate (PI3P) in phagophores and drives autophagosome nucleation [28, 29]. In this step, the Beclin-1 interactome works as a precise regulator. Under normal conditions, Beclin-1 binds to B-cell lymphoma 2 (Bcl-2) to suppress the formation of PI3K complex, leading to the inhibition of autophagy. Meanwhile, under stress conditions, Beclin-1 interacts with VPS34 and triggers the activation of PI3K thus stimulating autophagocytosis [30] (Fig. **2**).

3. BIOLOGICAL MECHANISMS LINKING AUTOPHAGY AND AD

Neurons are characterized by the complex axonal and dendritic structures, which required intense transport and efficient proteostasis to accommodate a dynamic microenvironment [31]. Unlike other eukaryotes, neurons are post-mitotic and are unable to dilute toxic substances by mitosis. Hence, the quality of cytoplasmic and protein/organelles clearance is orchestrated to a large extent by autophagy. However, AD weakens autophagic function, eventually resulting in abnormal accumulation of autophagic substrates and lowering the basal autophagic flux. *Nixon et al.*, [26] examined post-mortem AD brain and found dystrophic neurites to contain immature autophagosomes. Accumulation of autophagosomes is more likely to arise from impaired clearance rather than the induction of autophagy itself. However, autophagy might also regulate AD-related pathology. Nilsson *et al.*, observed that the offspring of autophagy-deficient mice showed greater intracellular aggregation of Aβ together with amyloidosis and memory impairment than mice with functional autophagy [32]. Depleting a key autophagy-related gene, namely *Becn1* (which encodes Beclin-1), suppresses induction of autophagy and leads to AD in the mice model [33]. Moreover, the regulation of autophagy in brain is region- and tissue-specific [24]. In AD, the autophagic mechanism is differentially affected within the cortex, hypothalamus, midbrain, and cerebellum. In addition to these regional differences, neurons are not equally affected within the same region. Hence, because of the inherent reliance on autophagy, specific regions or neurons may be more prone to

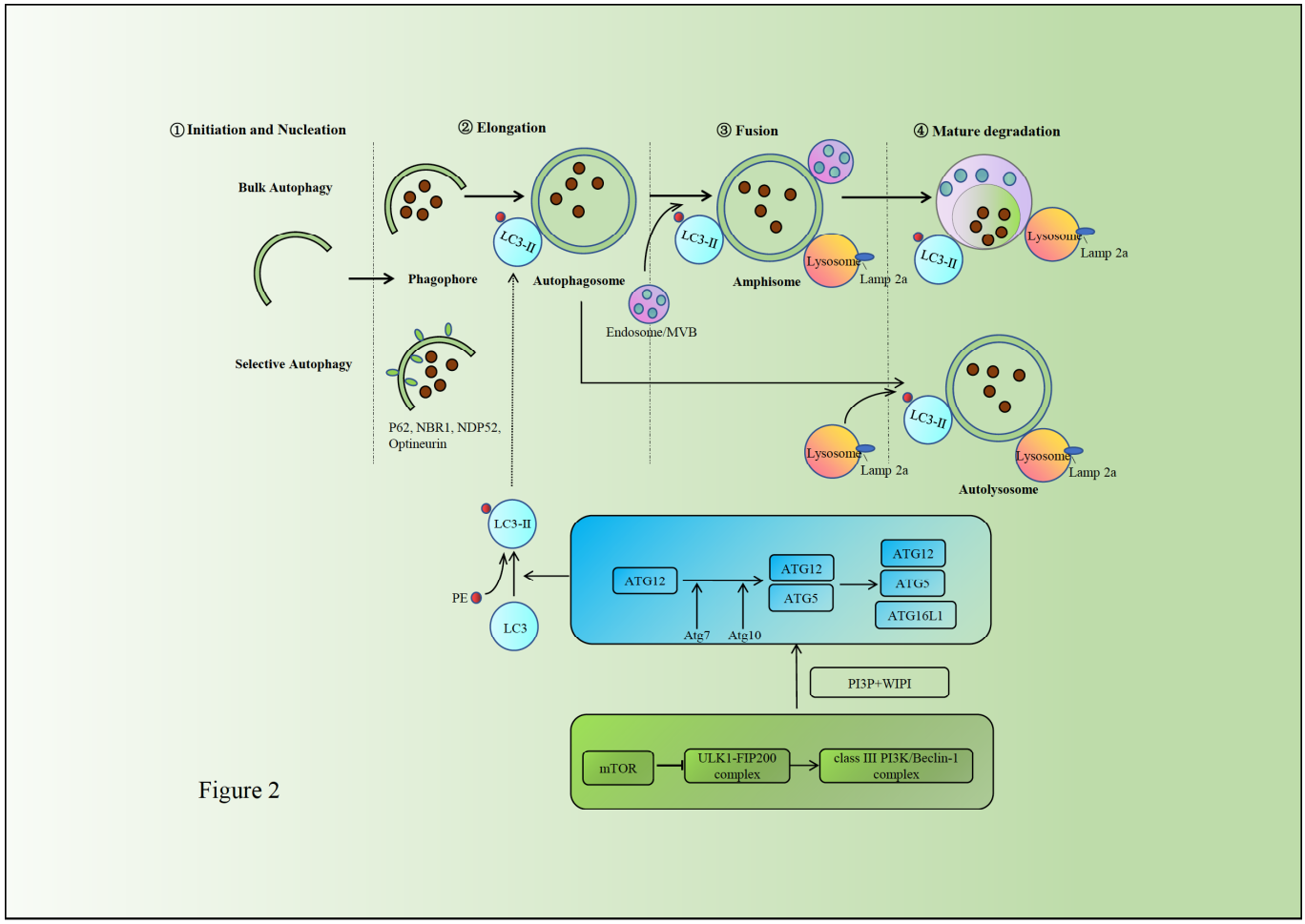

Figure 2

Fig. (2). Schematic overview of the general autophagy pathways. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

protein aggregation, leading to a specific clinical phenotype. Altogether, these findings clearly show that the role of the autophagic system is not only a causative or protective factor but also a consequence of AD.

3.1. Autophagy is a Key Regulator of Aβ Metabolism

First, degradation is considered the first function of autophagy. Indeed, autophagy is considered to be another main Aβ eliminating pathway besides Aβ-degrading enzyme [34], which is especially prevalent in the AD brains. Many studies have shown that autophagy works on reducing extracellular Aβ plaque burden as well as peptide Aβ fragments inside brain cells [32, 35, 36]. Microglia are the resident brain macrophages that constantly survey the neural environment for pathogens and apoptotic cells. In the vicinity of extracellular Aβ plaques, microglia assembled and attempt to clear the pathological deposits of Aβ through phagocytosis. After internalization by microglia, Aβ may leak out of the endolysosomal system into the cytosol, resulting in cellular damage [35]. This phenomenon requires the autophagic machinery for Aβ fibrils degeneration. Moreover, Aβ-induced inflammatory mediators released from microglia damage neurons, and this inflammatory response is controlled by microglial autophagy. In a recent study, Aβ-induced NLRP3 inflammasome activation is aggravated by impaired autophagy [35]. Second, beyond conventional Aβ degradation, a regulation of Aβ secretion and plaque formation is another major function of autophagy in AD [32]. Because Aβ is mainly located on membranes, the presence of Aβ has also been found in autophagic vesicles (aside from the Golgi and endosomes) in patients with AD [37]. This finding indicates that the accumulation of immature autophagic vesicles may be the origin of Aβ production under pathological conditions. In autophagy-deficient mice, Aβ production is decreased by 90%. However, recovery of autophagy reverses Aβ secretion to normal levels [37]. These results do not mean autophagy is an accelerator of AD progress especially for Aβ pathology. On the contrary, this reduction of Aβ plaque load leads to Aβ aberrant intraneuronal accumulation which results in aggravating the damage to neurons [32]. Third, genes essential for autophagy are also implicated in AD pathology. Inhibition of Beclin-1, an adaptor protein that manipulates several autophagy steps, can increase intracellular and extracellular Aβ deposition [38]. Another key regulator of autophagy, presenilin-1 (PS1) participates in the formation of γ-secretase complex. PS1 has been identified as a causative gene for early-onset AD (also known as familial AD) [39]. As described earlier, the role of PS1 in lysosomal-dependent proteolysis is directly relevant to the mechanism by which PS1 mutations contribute to the onset of AD [40]. In addition, the apolipoprotein E gene (*ApoE4*) is also widely accepted as a major risk factor for AD. Studies from Neuro-2a cells and transgenic mice have shown that ApoE4 potentiates lysosomal leakage and apoptosis induced by Aβ peptides [41, 42].

3.2. Autophagy Contributes to the Clearance of Tau

Tau is a microtubule-associated protein (MAPT) that polymerizes tubulin into microtubules, and consequently participates in maintaining the complex neuronal cell microarchitecture, including microtubule assembly and stabilization, particularly in the axons [43]. When tau is monomeric, the ubiquitin proteasome system occupies a dominant position. However, when tau is oligomeric or in aggregate forms, autophagy is depended upon for degradation [40]. In 1996, Bednarski reported for the first time that a lysosomal protease can degrade Tau in cultured hippocampal slices, highlighting autophagy in the pathogenesis of Tau metabolism [44]. Since then, it has been shown that reduction of phosphorylated (p)-tau/NFTs is accompanied by improved neuronal survival and function, which requires lysosomal activity both *in vitro* and *in vivo* [45]. Ammonium chloride is an inhibitor of autophagy processes that delays the clearance of Tau and promotes some high molecular weight Tau formation. Cathepsin D (a lysosomal protease), rapamycin (an autophagy inducer), and trehalose (an activator of autophagy) can also help degrade Tau and reduce the level of Tau aggregates in Drosophila or in the brains of human Tauopathy model mice [46]. Furthermore, various kinases are included in this process *in vivo*. Among them, glycogen synthase kinase-3β (GSK-3β), an autophagy upstream kinase, occupies an important status. GSK- 3β is regarded as the most documented Tau kinase for its upregulation, which modulates abnormal hyperphosphorylation of Tau in AD [47]. Furthermore, as a chaperone protein, clusterin participates in autophagosome biogenesis. In patients with AD, tau levels in cerebrospinal fluid were reportedly dysregulated by the AD-associated clusterin polymorphism, rs11136000 [48].

3.3. Autophagy may Halt the Propagation of Aβ and Tau

Besides gradual accumulation of Aβ and Tau brain pathology, the prion-like spreading of pathological proteins in the central nervous system is also accompanied by progression of AD [49]. Accordingly, studies have demonstrated that exogenous inoculation of Aβ-containing brain extracts spreads Aβ to adjacent regions [7, 50, 51]. Similarly, Tau transmission from microglia to neurons has been verified in cellular and animal models was verified [52]. Currently, exosomes are speculated to be responsible for the propagation of Aβ and Tau. Immunoelectron microscopy of purified exosomes from AD brain sections showed that Aβ localizes to exosomes [53]. Further, inhibition of exosomes synthesis halts neuron-to-neuron Tau transmission [52]. In 2015, *Edward et al*. first identified autolysosomal proteins, such as cathepsin-D and lysosomal-associated membrane protein 1, in neutrally-derived blood exosomes from patients with AD [10, 12], thereby bolstering the interplay between autophagy and exosomal pathways. Furthermore, in primary cortical neurons and Neuro-2a cells, VPS34 inhibition increased secretion of extracellular vesicle-associated APP C-terminal fragments. This supports the hypothesis that endolysosomal dysfunction is the mechanism driving secretion of these fragments from exosomes. Thus, the considerable influence of autophagy in exosomal spread of pathological proteins is crucial for providing new opportunities for perturbing AD progression. However, whether fusion of multivesicular bodies with autophagic vacuoles results in exosome release, or alternatively, exosomes are the production of lysosome degradation or structural differences between autophagic vacuoles and exosomes, still needs further investigation.

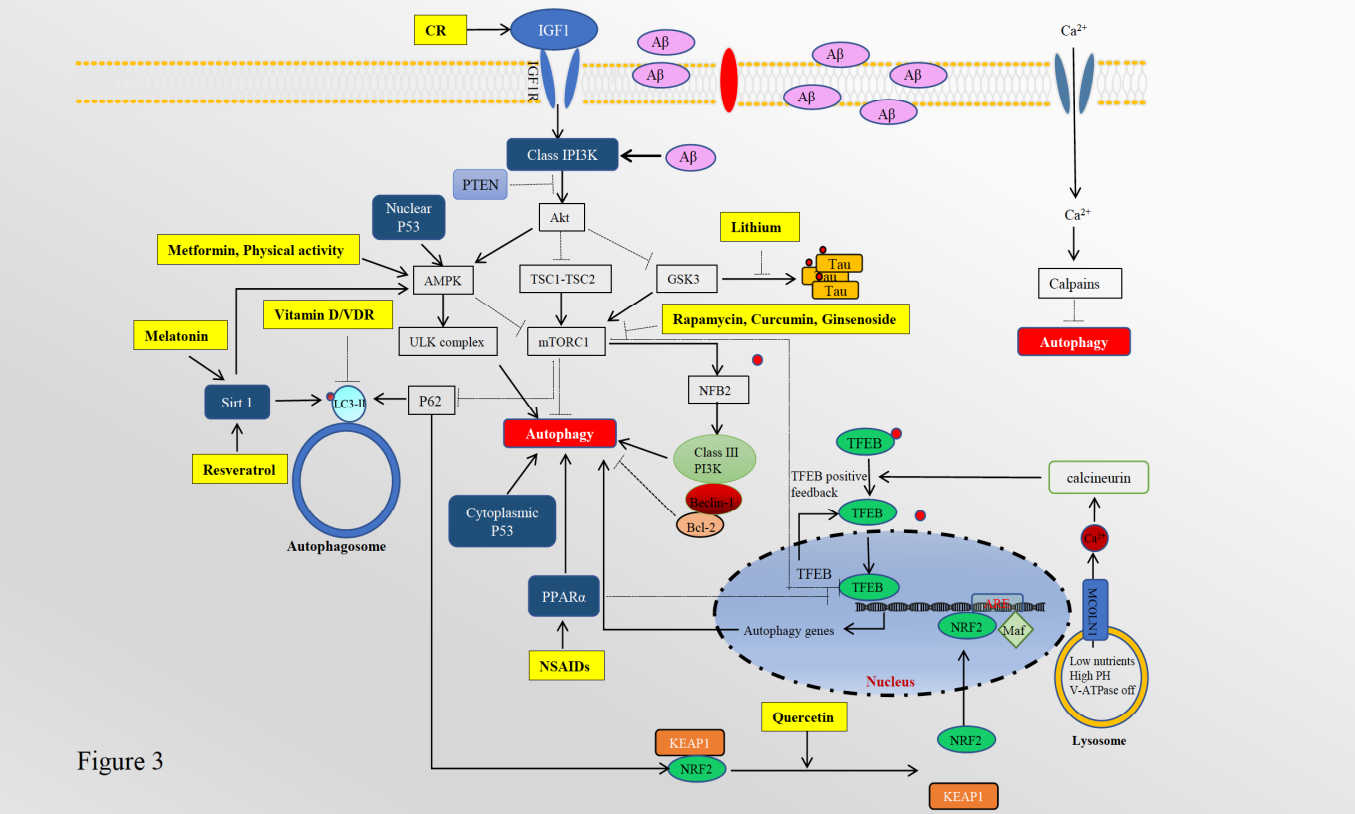

Fig. (3). Overview of the regulation of autophagy and potential drug targets. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. ACTIVATION OF AUTOPHAGY AS A THERAPEUTIC STRATEGY FOR AD

As we discussed above, the activation of autophagy may serve as a therapeutic strategy for AD. Hence, we highlight several possible opportunities for therapeutic intervention, namely, mammalian kinase target of rapamycin (mTOR)-dependent and mTOR-independent. These approaches aim to restore autophagy function and have proven efficacious *in vitro* or *in vivo*, and with potential for translating to clinical application (Fig. **3**).

5. KEY PATHWAYS REGULATING AUTOPHAGY ACTIVITY IN AD

It has been reported that mTOR serves as a brake on autophagy [54], while high mTOR activity was recently described as a new risk factor for AD [55, 56]. Accordingly, suppression of mTOR enhances Aβ clearance, ameliorates tau pathology, and improves cognitive function in cellular and transgenic models of AD [57-60]. Clearly, there is a direct link between AD pathology and the mTOR-dependent autophagy. Further, mTOR coordinates or interacts with the upstream signaling components, including PI3K/AKT, AMPK, GSK-3, and insulin/insulin-like growth factor 1 (IGF-1), and downstream components, including transcription factor EB (TFEB), nuclear receptor binding factor 2 (NRBF2), and p62 [61-64]. Insight into these complex pathways may provide a comprehensive means to counteract AD progression.

5.1. mTOR-dependent Pathway

5.1.1. PI3K/AKT Signaling

During brain development, the PI3K/AKT pathway plays an important role in controlling neurotransmission, establishing neuronal polarity, and in maintaining balance in neuronal survival/death [65, 66]. In the brains of healthy individuals, phosphoinositide 3 kinase (PI3K) activates mTORC1 *via* AKT by phosphorylating the tuberous sclerosis complex (TSC2)-2, which in turn inhibits function of the TSC1/TSC2 complex, negatively regulates conversion of Ras homolog enriched in brain (Rheb) [67]. However, with human aging and AD, the PI3K/AKT pathway is disrupted and consistently activated leading to Aβ aggregation and cognitive decline. In the brain of Down's syndrome patients with AD-like pathology, *Perluigi, et al*., demonstrated a strong association between aberrant activation of PI3K/AKT pathway and decrement in the autophagic flux (low ratio of microtubule-associated protein 1A/1B-light chain 3 [LC3]-II/LC3-I) *via* phosphorylation of the ULK1-ATG13-FIP200 complex [68]. Phosphatase and tensin homolog (PTEN), which downregulates PI3K/AKT signaling pathway, is altered in the brain from patients with AD [69-71]. Upregulation of PTEN can relieve Aβ-induced neurotoxicity [72] and decrease the phosphorylation state of Tau [73].

5.1.2. GSK3 Signaling

Long-term inhibition of GSK3 kinases increases autophagic flux by downregulating mTORC1 *via* phosphory-

lation of both ribosomal protein S6 kinase beta-1 and ULK1, which reduces the interaction between mTORC1 and raptor [74]. In brain samples from individuals with mild cognitive impairment and late-onset AD, p-GSK3 (the active form of GSK3), is demonstrably reduced compared with controls without dementia. This further suggests that abnormal GSK-3 activity is a pathogenic event in both early- and late-stage AD [75]. Early in the amyloid pathology, GSK3 isozymes become activated by increased tyrosine phosphorylation in the hippocampus of old APP transgene mice [76]. Similarly, APP knockout mice show a dramatic decrease in GSK-3 activity [75]. As GSK-3 accelerated Aβ production by escalating the activity of beta-secretase 1(BACE-1) [77], it implies a feedback loop of GSK-3/Aβ generation. GSK3 exists as two isozymes: GSK3α and GSK3β. GSK3β is identified as the major kinase in Tauopathy as well as a major link from amyloid-to-Tau pathology [76]. Activated GSK3β targets hyperphosphorylated Tau protein, which impairs the Tau-microtubule interaction, leading to eventual aggregation into tangles. In hippocampal pyramidal neurons of aged mice, GSK-3 inhibition not only stimulates autophagy activation but also leads to the compromised autophagy resolution. This occurs through GSK3-dependent regulation of lysosomal biogenesis mediated by the TFEB, and in turn, decreases lysosomal proteolysis [78].

5.1.3. AMPK Signaling

As stated earlier, the ULK1-ATG13-ATG101-FIP200 complex is a critical initiator of autophagy and its activity is mainly regulated by the combination of AMPK [79, 80]. Normally, active mTORC1 phosphorylates ULK1 on Ser 757, thereby weakening autophagy [79]. Upon cellular stresses, AMPK interacts with and phosphorylates ULK1 on Ser 317 and Ser 777, leading to the dissociation of the ULK1-mTORC1 complex, translocation of ULK to the pre-autophagosomal membrane and eventually induction of autophagy [79]. Alternatively, AMPK may inhibit mTORC1 activation by directly phosphorylating raptor on two conserved serine residues (Ser722 and Ser792) [81]. Lately, several new findings have suggested that ULk1 provides potential negative feedback for AMPK activity by phosphorylating all three subunits of AMPK (AMPK-α, β and -γ) [25, 82]. Debate on whether activation of AMPK is neuroprotective or neurotoxic is long-lasting. Molecular biological investigations have shown that AMPK is involved in regulation of Aβ levels.Novel synthetic compounds (RSVA series) targeting the activation of AMPK were identified as promising lead molecules facilitating Aβ clearance [83]. However, Vingtdeux *et al.* demonstrated that activated AMPK (p-AMPK) accumulated in AD brain in structures that were similar to NFTs, according to immunohistochemical staining. This supports a role of AMPK in preceding tau aggregation and thus triggering AD progression [84].

5.1.4. IGF-1 Signaling

IGF belongs to a class of neurotrophic factors that classically regulate neuronal growth and neuronal survival [85]. In 2009, Mona and colleagues observed that IGF-1 regulated autophagy in Purkinje neurons by accelerating basal autophagosome-lysosome fusion rates in an mTOR-dependent manner [86]. Furthermore, in rat embryonic cortical neurons, an inhibitory effect of IGF-1 on autophagy was demonstrated by binding with its receptor, IGF-1R, together with subsequent activation of the PI3K/AKT/mTOR pathway [87, 88]. This also suggests that IGF-1 treatment may decrease Aβ generation by reducing APP phosphorylation and promoting memory deficits. This result is consistent with a previous study showing that subcutaneous administration of IGF-1 to aged rats decreased Aβ levels in brain parenchyma to levels observed in young rats [89]. For Tauopathy, it has been shown that *IGF-1* gene inactivation reduces aberrant tau phosphorylation and potentiates NFT formation [90].

5.1.5. mTOR/TFEB Signaling

TFEB was identified as a positive regulator of autophagy by inducing a broad transcriptional program and controlling autophagosome-lysosome fusion [91]. Inactive TFEB is normally sequestered in the cytoplasm by phosphorylation, while dephosphorylated TFEB translocates to the nucleus and induces activation of transcriptional downstream targets [92, 93]. This event is mediated by binding to the key negative autophagy regulator, MTORC1, which contains coordinated lysosomal expression and regulation (CLEAR) element [94]. However, recently Diego *et al.,* [95]. detected overexpression of calcineurin-induced TFEB nuclear translocation in normally fed cells, providing a novel mTORC1-independent regulator for TFEB. For amyloid pathology, TFEB enhanced lysosomal biogenesis in both astrocytes and neurons, participating in the progression of Aβ clearance and Aβ generation, respectively [96, 97]. Further evidence showed that this effect of TFEB was diminished with inhibition of GSK3β activity in both PS1-deficient mouse models and neural stem cell models [98]. Regarding Tau, exogenous TFEB expression in the rTg4510 mouse brains and T40PL cells (both Tauopathy models) increased misfolded Tau proteins clearance [5]. The authors hypothesized that an AKT-mTOR-TFEB feedback regulatory loop is involved in the p-Tau clearance by inducing autophagy.

5.1.6. mTOR/NRBF2 Signaling

NRBF2 is a novel component of the PtdIns3K complex that is associated with ATG14 in mammalian cells [99]. Ma *et al*. reported that NRBF2 functions as a fine-tuning autophagy regulator. Under normal conditions, NRBF2 is phosphorylated by MTORC1 and preferentially binds a non-autophagic form of PtdIns3K, leading to autophagy inhibition. When MTORC1 is inhibited, NRBF2 becomes unphosphorylated. This form of NRBF2 binds ATG14- Beclin-1, increasing autophagic PtdIns3K complex assembly, stimulating phosphatidylinositol 3-phosphate production, promoting ULK1 association and leading to the activation of autophagy [100]. Recently, it was found that NRBF2 was downregulated in the hippocampus of 5xFAD mice and NRBF2 overexpression reduced $A\beta_{1-42}$ levels by modulating autophagic progression [101].

5.1.7. mTOR/p62 Signaling

The landmark discovery of p62/SQSTM1 as the first mammalian selective autophagy receptor defined a new family of autophagy-related proteins. p62 is a multifunctional protein rich in domains, among which, the LC3-interacting motif (LIR) and ubiquitin-binding domain (UBA) mainly

controlling autophagy uptake. Through its LC3-interacting motif, p62 binds to LC3 to facilitate selective substrate recognition [102, 103]. Through the ubiquitin-binding domain, p62 binds to polyubiquitinated proteins (including Tau), and shuttles them to autophagosomes for degradation [104, 105]. Further, p62 also interferes with the protein interaction between BCL-2 and Beclin-1 during the autophagy process [30]. For mitophagy, p62 balances mitochondrial quality control and recruits damaged mitochondria to the phagophore by connecting with Parkin [106]. By analyzing AD patients' brain, Du *et al*., [107] found that p62 expression is significantly reduced in the frontal cortex. To dissect the role of p62 in reducing Aβ levels, Antonella and colleagues generated APP/PS1 mice with an adeno-associated virus expressing p62. They found better spatial learning performance in APP/PS1–p62 mice compared with APP/PS1-GFP mice. This study also indicated that p62 decreases Aβ levels by facilitating the delivery of Aβ to lysosomes for degradation [108]. Alternatively, p62 knockout mice showed age-dependent accumulation of NFTs and synaptic deficits [109]. Thus, decreased p62 levels directly lead to low autophagy levels, which may accelerate Tau and Aβ protein aggregation resulting in AD progression. Correlation between mTOR activity and p62 is still controversial. It has been reported that p62 acts as a downstream target of mTOR in the cortical neurons [110] and that decreased mTOR precedes or coincides with a decrease in p62 [111]. Contradictorily, studies also revealed that p62 directly binds to mTOR as an indispensable, activating component for mTORC1 [112, 113]. The reason for this discrepancy is still not known and requires further investigation.

5.2. mTOR-independent Pathways

Although the canonical mTOR dependent autophagy pathway has been intensively studied, autophagy can be initiated by mTOR-independent pathways and mediated through non-canonical signaling events as well. Here we will highlight several alternative pathways in AD.

5.2.1. SIRT1

The mammalian silent information regulator 2 homolog-1 (SIRT1) belongs to the family of NAD-dependent protein deacetylases, and has a crucial function in governing longevity [114]. Furthermore, therapeutic upregulation of SIRT1 provides an opportunity for the amelioration of Aβ neuropathology through inhibition of amyloidogenesis [115]. In 2008, Lee *et al*., [116] demonstrated a role for SIRT1 in regulation of autophagy. In particular, transient increased expression of SIRT1 was sufficient to stimulate basal rates of autophagy. SIRT1 governs the formation of autophagic vacuoles by deacetylation of essential autophagy proteins, such as Atg5, Atg7 and LC3 [116]. In addition, SIRT1 also boosted autophagy *via* AMPK activation, and this effect was abolished by the AMPK inhibitor, compound C [117]. In APP/PS1 mice, SIRT1 overexpression reduced Aβ production and Aβ plaques, whereas deleting SIRT1 abolished this protective effect [118]. Another study indicated that incubation of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ fragments with an activator of SIRT1, resveratrol, reduced the length and number of these fibrils [119]. In Tau transgene mice, SIRT1 deletion increased Tau mislocalization postsynaptically and Tau propagation from the injection site to the contralateral hippocampus [120]. Thus, SIRT1 deficiency is now regarded as a causative in cognitive decline [121].

5.2.2. p53

The transcriptional regulator p53 safeguards cells against stress and dysfunction, by controlling cell proliferation and apoptosis. p53 is also cast as a pro-autophagic factor that is directly driven by a specific subcellular localization. Briefly, p53 positively modulates autophagy in the nucleus, whereas cytoplasmic p53 inhibits the induction of autophagy conversely [122]. Many p53 target genes (including PTEN, TSC2 and AMPK) block mTOR signaling, leading to the inhibition of autophagy [123]. Involvement of p53 in the control of mitophagy has also been reported [124]. In AD, increased p53 levels were detected in various regions of patient brains compared with healthy individuals [125, 126]. Likewise, γ-secretase complex (composed of PS1 or PS2, nicastrin, gamma-secretase subunit Aph-1, and presenilin enhancer 2)-mediated p53-dependent neuronal death. In turn, p53 may enhance expression of PS-1 and PS-2, which results in cross-talk between p53 and Aβ production [127]. For Tauopathy, studies revealed that sustained expression of p53 promoted Tau phosphorylation which precipitates formation of NFTs [128].

5.2.3. Beclin-1

Whereas mTOR negatively regulates initial autophagosome formation, Beclin-1 regulates both autophagosome formation and autolysosome fusion. By binding with VPS34, Beclin-1 triggers formation of endosomes and autophagosomes, which stimulates the onset of autophagy. Upon binding with BCL-2, Beclin-1 dissociates from Vps34 and inhibits autophagic cell death [129]. Beclin-1 also interacts with PTEN-induced kinase 1 (PINK1) in mitochondria, which can stimulate the clearance of defective mitochondria [130]. With a key role in modulating autophagy, the Beclin-1 interactome is an important regulator of AD pathology. Patients with AD express lower levels of Beclin-1 than age-matched controls [38]. *Pickford et al.,* [38] cross-bred Beclin-$1^{-/-}$ mice with APP transgenic mice, and demonstrated robust deposition of Aβ aggregates. Subsequently, Altea *et al*., showed that genetically disrupting Beclin-1/BCL-2 binding in 5xFAD mice hyperactivates autophagy and leads to sequestration of amyloid oligomers [33]. Beclin-1 is also reportedly present in tau-positive dystrophic neurites, where it interacts with the PINK/Parkin pathway to facilitate autophagosome maturation and enhance tau degradation [131].

5.2.4. PPARα

The nuclear receptor, peroxisome proliferator-activated receptor alpha (PPARα) is characterized as a pivotal regulator of energy metabolism and peroxisomal function [132]. In response to PPARα activation, normal suppression of autophagy is reversed and the autophagic lipid degradation is induced. Specifically, levels of LC3-II and other indicators of autophagy are upregulated and associated with decrease in inhibitory phosphorylation of ULK1 [79, 133]. Further, activation of PPARα also leads to the increased transcription of

TFEB and stimulates lysosomal biogenesis in brain cells [134]. Recently, *Luo et al*., demonstrated that enhanced PPARα expression protects against amyloid pathology and cognitive decline though its role in activating autophagy and lysosomal pathway [135]. In accordance with this, Chandra S *et al*., [136] further delineated that cerebral Aβ plaques ware markedly reduced in 5xFAD mice *via* upregulation of TFEB in a PPARα-dependent fashion.

5.2.5. NRF2

Next to the TFEB and FOXO family of transcription factors, nuclear factor erythroid-2 related factor 2 (NRF2) also participates in the regulation of autophagy-related genes, including ULK, ATG7, and ATG5 [137]. Once activated, NRF2 dissociates from Kelch-like ECH-associated protein 1 (KEAP1) and translocates from cytoplasm to the nucleus, where it coordinates a battery of antioxidant response element (ARE) dependent genes [138]. Dissociated KEAP1 interacts with both LC3-II and p62, facilitating the formation of autophagosomes and relieving NRF2 from inhibition. In aged APP/PS1 mice, NRF2 expression significantly improved learning and memory retention [139]. To further determine the relevance of NRF2 and amyloidopathy, a mouse model (namely AT-NRF2-KO) was generated lacking an obvious amyloid load and NRF2-expression. As early as 6 months, the AT-NRF2 KO mice precede the aggregation of Aβ and Tau filaments with reduced hippocampal long-term potentiation [140]. In human neurons suffering from proteotoxic APP/Aβ insults, an increased nuclear NRF2 expression and the upregulation of the autophagy proteins P62 and ATG7 indicated that NRF2 precludes Aβ formation by activating an autophagy defensive program [137]. Another autophagic receptor, nuclear domain 10 protein (NDP52), also appears to be induced by NRF2 and directly degrades phosphorylated Tau due to increased autophagic clearance [141, 142].

5.2.6. Lysosomal Calcium Signaling

Transient receptor potential mucolipin-1 (TRPML1; also named MCOLN1) is a cation-permeable channel predominantly localized to late endosomal/lysosomal membranes, which regulates lysosomal calcium release during lysosomal fusion with other membranes [143]. Beyond the role of TRPML1 in endolysosomal trafficking, new findings show that TRPML1 facilitated nuclear translocation of TFEB and stimulated transcription of its target genes. In cells silenced for TRPML1, the number of PI(3)P-positive vesicles and the levels of autophagic markers (LC3, P62 and Beclin-1) is reduced indicating the impairment of autophagosome formation [24, 95]. Moreover, TRPML1 also inhibits inhibit AD progression. For example, in primary neurons, activation of TRPML1 promotes the clearance of intraneuronal Aβ from lysosomal compartments [144]. The mucolipidosis IV mouse model (*i.e*., TRPML1$^{-/-}$ mice) display progressive behavioral and locomotor deficits and cognitive impairment [145]. In APP/PS1 transgenes mice, TRPML1 overexpression markedly improved the recognition index with a significant increase of autophagic markers (LC3, P62 and Beclin-1) and concurrent with the inhibition of AMPK/mTOR pathway, indicating TRPML1 decreases protein aggregates by regulating endosomal–lysosomal pathway [146].

5.3. PINK1/Parkin-dependent Mitophagy

Accumulation of damaged mitochondria in axons and at synapses is a hallmark of age-related diseases, including AD. Electron microscopy images of postmortem human hippocampus samples from patients with AD showed altered mitochondrial morphology, while Basal levels of mitophagy being 30%-50% lower than normal controls [147]. Parkin mediates the removal of damaged mitochondria [148], and PINK-Parkin pathway has emerged as a key regulatory pathway of mitophagy [149]. Under physiological conditions, PINK1 is continuously imported into mitochondria for cleavage and degradation [150, 151]. However, in AD, PINK1 accumulates on the outer membrane of mitochondrial and phosphorylates Parkin at Ser65 (which is necessary for its activation) [152-154]. Thus, PINK1 can act as a tag for mitochondrial injury. Activated Parkin prevents damaged mitochondria from integrating with other healthy mitochondria by ubiquitinating mitofusin-2 protein present in the mitochondrial membrane. Consequently, the damaged mitochondria are eventually degraded in the autophagic pathway *via* binding to LC3 through P62 [155]. In accordance with these findings, PINK1 overexpression attenuated Aβ accumulation by inducing more abundant expression of autophagy proteins, such as LC3 and NDP52, in APP/PINK1 mice [156]. Moreover, Parkin was selectively recruited to the depolarized mitochondria, which led to elevated levels of LC3-II and p62, resulting in increased post-translational APP expression [157, 158]. All this suggests that enhancement of PINK1-Parkin pathway can improve the outcome of AD progression by facilitating mitophagy functions. Recently, Fang *et al.* [147] systematically demonstrated activation of mitophagy improving memory functions, ameliorating Aβ pathology, and promoting phagocytic activity of microglia in transgene AD mice. This group also showed restoration of mitophagy by PINK1 overexpression lowered intraneuronal tau levels and mitigated NLRP3/caspase-1-dependent neuroinflammation.

6. AUTOPHAGY-RELATED INTERVENTIONS

Based on the aforementioned information, the most effective way to treat AD is to prevent the aggregation of Aβ and Tau proteins. Autophagy is a well-recognized scavenger that can degrade these aged and malfunctioning proteins. Thus, autophagy-stimulating interventions may have promising therapeutic targets for AD treatment in clinical trials. Here, we shortly discuss interventions under investigation (Table **1**).

6.1. Autophagy Modulating Drugs

6.1.1. Rapamycin

Rapamycin (also known as Sirolimus) is an mTOR inhibitor, and was the first drug that has been experimentally proven to slow down the progress of aging [159]. This anti-aging ability of rapamycin is ascribed to its suppression of the activation of mTOR-dependent autophagy flux. In neuronal cultures, toxicity of different amyloidogenic peptides can be counteracted by rapamycin [61, 160]. In transgenic mouse models of AD, rapamycin prevented learning and memory deficits and reduced amyloid plaque burden [161]. However, a previous publication suggested that rapamycin is

Table 1. Autophagy-stimulating compounds and life style interventions which are currently under-study for AD treatment.

Compound	Therapeutic Class	Mechanism of Autophagy	Refs.
Rapamycin	Immunosuppressant	Inhibition of mTORC1	[61, 160, 161, 163]
Ibuprofen	Nonsteroidal anti-inflammatory drug	inhibition of GSK3β	[166]
Aspirin	Nonsteroidal anti-inflammatory drug	• PPAR-mediated upregulation of TFEB • Regulation of mitophagy	[167] [168]
Lithium	Anti-psychiatric	Inhibition of GSK-3β	[171, 172]
Memantine	Non-competitive NMDA receptor antagonist	• Promotion of mitophagy • Inhibition PI3K/Akt/mTOR pathway	[174] [175]
Melatonin	Neurohormone	• Activation of SIRT1	[178, 179]
Metformin	Antidiabetic	• Activation of AMPK • Activation of SIRT1 • Facilitating Parkin-mediated mitophagy	[186] [181] [183]
Vitamin D	Essential Vitamin	• Activation of AMPK • Calcium signaling • Disruption of Beclin-1	[194] [194] [193]
Trehalose	Natural disaccharide	Unknown	[195, 196, 197]
Resveratrol	Neutraceutical	• Activation of SIRT1 • Activation of AMPK • Inhibition of mTORC1	[118, 119, 179] [199] [198]
Quercetin	Neutraceutical	• Activation of Nrf2 • Inhibition of GSK3β	[204] [205]
Ginsenosides	Neutraceutical	• Activation of Nrf2 • Inhibition of mTOR • Inhibition of GSK3β	[208] [207, 209] [210]
Curcumin	Neutraceutical	• inhibition of PI3K/Akt • mTOR-independent upregulation of TFEB	[213] [215]
Calorie restriction/Fasting	Lifestyle interventions	• Activation of SIRT1 • Activation of IGF-1	[115, 224] [223]
Physical Activity	Lifestyle interventions	• Activation of AMPK • Upregulation of p62 • Upregulation of BECN1	[230] [228] [229]

only useful for patients in the very early stages of AD [162]. Intervention with rapamycin at later points would add "fuel to this fire" by exacerbating existing lysosomal problems. Although treatment with rapamycin increased the generation rate of lysosomal-system cargo, during the last period of AD, this would result in accumulation of lysosomal vesicles and further promotion of transcellular seeding of Aβ and Tau by exosomes. In addition, clinical application of rapamycin should also consider adverse effects due to mTOR inhibition because cellular functions besides autophagy are potentially disturbed [163]. Common adverse reactions of rapamycin include respiratory and urinary tract infections, gastrointestinal pain, thrombocytopenia, and dyslipidemia. Temsirolimus is an esterified rapamycin derivative. Because of its tolerable side-effects compared with rapamycin, temsirolimus is under investigation as a potential therapeutic extension to long-term treatment of AD by enhancing autophagy activity [164].

6.1.2. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Based on a large health care database, scientists found that participants with a long-term use of NSAIDs were at lower-than-expected risk of AD of >5 years due to suppressed formation of $A\beta_{1-42}$ [165]. Among individual NSAIDs, ibuprofen and aspirin showed the most marked neuroprotective effect. Ibuprofen reduced Tau pathology by inhibiting of the GSK3β pathway [166]. Meanwhile, aspirin exhibited amyloid-lowering effects by stimulating lysosomal biogenesis *via* PPAR-mediated upregulation of TFEB [167]. Acetylation is a key mechanism for regulating mitophagy. Appropriately, aspirin inhibited oligomerization of amyloid peptides and subsequent formation of insoluble aggregates by disrupting mitochondrial protein acetylation, and further strengthening the potential therapeutic role of aspirin in AD [168].

6.1.3. Lithium

Lithium (Li^+) has been shown to significantly decrease cognitive decline in patients with AD without showing any significant adverse effects [169]. In another study of participants with amnestic mild cognitive impairment, long-term lithium treatment reduced p-tau concentration in cerebrospinal fluid and improved performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale [170]. Recent studies address the effects of lithium leading to cognitive enhancements may due to the induction of autophagy [171, 172]. By inhibitingGSK-3β activity, lithium triggered an autophagic response and modified biological cascades pertaining to the pathophysiology of AD.

6.1.4. Memantine

Memantine is a non-competitive NMDA receptor antagonist, which has been approved for the treatment of moderate-to-severe AD [173]. Recently, from a screening of 796 chemicals, memantine was identified as a novel autophagy inducer with better tolerance and much safer effects. The group found memantine to enhance clearance of damaged mitochondria *via* the upregulation of autophagy in SH-SY5Y cells illuminating the possible neuroprotective mechanism of memantine [174]. Memantine also demonstrated neuroprotective effects by inducing autophagy *via* inhibition of the survival PI3K/AKT/mTOR pathway in an *in vitro* study [175].

6.1.5. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone and secreted principally by the pineal gland. Production of melatonin declines during aging, with levels extremely decreased (to below 5%) in AD [176, 177]. Based on these observations, melatonin has been proposed as a potential biomarker for AD. Earlier investigations identified SIRT1 as a critical downstream effector of melatonin in promoting cognitive functions from autophagy [178, 179]. In a recent trial, melatonin supplementation (using much higher concentrations than physiological concentrations) prevented cognitive decline, decreased Tau hyperphosphorylation, and recovered the impaired autophagy flux in the rat and human Tauopathy models [180].

6.1.6. Metformin

Metformin is the first-line oral anti-diabetic drug for type II diabetes. By disturbing complex I of the electron transport chain, metformin induces expression of AMPK and SIRT1, which is thought to be the related to its mechanism of action [181, 182]. The AMPK–mTOR and SIRT1 pathways are the traditional regulatory pathways for autophagy. Metformin also decreases the inhibitory interaction with cytosolic p53 by facilitating Parkin-mediated mitophagy [183]. Consistently, metformin may be a novel activator of autophagy. Recently, a clinical trial showed that long-term treatment of metformin in type II diabetes significantly lowered the incidence of dementia [184, 185]. Chen *et al.*, [186]. further claimed that metformin reduced Tauopathy and improved cognitive impairment by activating AMPK-dependent autophagy. Although a protective effect of metformin in AD has been shown *in vivo* and *in vitro*, several studies have demonstrated the opposite viewpoint, and shown that metformin may exacerbate AD progression [187, 188]. Thus, there are still confounding issues at present before a definitive relationship between metformin and AD can be established. Further investigation is required to solidify or refute this relationship

6.1.7. Vitamin D and VDR

Epidemiological data show that serum vitamin D concentrations correlated negatively with the severity of AD. Further, vitamin D deficiency is surfaced to be a risk factor for cognitive decline [189]. Vitamin D modulates its biological effects by hydroxylation, resulting in its biologically active form, 1,25-dyhydroxyvitamin D3(1,25(OH)2D3), which signals through its receptor (VDR) [190]. It has been reported that 1,25(OH)2D3 increased $A\beta_{1-40}$ vectorial transport across the blood-brain barrier, which reinforced the systemic clearance of $A\beta_{1-40}$ [39, 191]. Additionally, long-term treatment of mice with 1,25(OH)2D3 during a period of plaque formation reduced soluble and insoluble Aβ, particularly in the hippocampus, in which VDR are abundant. This additionally led to improvements in conditioned fear memory [192]. Recently, vitamin D was reported as a potent inducer of autophagy and indeed may suppress Aβ-induced toxicity in this way. Mechanistically, VDR constitutively represses autophagy. Specifically, upon 1,25(OH)2D3 stimulation, basal levels of autophagy increased by the de-repression of the key autophagy genes, namely, LC3-II and Beclin-1 [193]. The mechanism of 1,25(OH)2D3-induced autophagy also involved AMPK pathway which was triggered by calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) activation [194].

6.1.8. Trehalose

Trehalose is a natural disaccharide derived by condensation of two glucose molecules. The beneficial effects of trehalose are related to autophagy induction in an mTOR-independent pathway [195]. In APP/PS1 transgenic mice, trehalose interferes with the formation of Aβ peptide, which significantly reduced the number of amyloid deposits and inhibited the neurotoxicity of Aβ [196]. Besides the selective targeting to Aβ peptides, long-term treatment of trehalose also decreased Tau inclusions in neurons, with a concomitant reduction in p62 levels, suggesting the relevance of autophagy in modulating Tau pathology [197]. Given that trehalose is a safe food ingredient for human use and is Food and Drug Administration "GRAS" (Generally Recognized As Safe), we believe trehalose is a promising agent for further pharmacological investigation in patients with AD.

6.2. Natural Extracts

6.2.1. Resveratrol

Resveratrol(trans-3,4′,5-trihydroxystilbene) displays neuroprotective effects by enhancing autophagy *via* controlling SIRT1-mediated transcriptional regulation *in vivo* [118, 119, 179]. Resveratrol also mediates AMPK-dependent or mTOR-dependent autophagy in mice, and thus is associated with anti-amyloidogenicity [198, 199]. In Tau transgenic mice, resveratrol exhibited a strong tendency to decrease tangle deposition along with the reduction of Tau hyperphosphorylation [200]. Although resveratrol is very safe, there are problems related to its clinical use. One is its short

half-life in serum, with another being its low oral bioavailability. Recently, long-term use with adequate dosages appears to be an effective way of improving its bioavailability. Nonetheless, further work is still needed to find out how to prolong the short half-life of resveratrol.

6.2.2. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) has been shown to promote learning and memory performance [201] and inhibit the formation of Aβ peptides by regulating BACE-1 activity in AD rats [202]. A recent report showed that the anti-amyloidogenic effect of quercetin is associated with autophagy activation [203]. The NRF2 pathway is the major signaling component in mediating the neuroprotective effect of quercetin. *Li et al*., demonstrated that quercetin improved cognitive memory by reducing $A\beta_{1-42}$ levels and increasing expression of NRF2/ heme oxygenase-1 in rat brain [204]. For tau pathology, quercetin reduced hyperphosphorylation of Tau protein by inhibiting GSK3β activity [205]. Consistently, quercetin may be a novel therapeutic agent for AD. As a caveat, low efficiency through the blood-brain barrier and easy metabolism have limited its clinical application. To overcome these limitations, a quercetin modified polysorbate 80-coated gold and palladium core-shell structured nanoparticle has been synthesized. This quercetin modified nanoparticle activated autophagy, accelerated Aβ clearance, and diminished Aβ-mediated cytotoxicity more efficiently than quercetin alone [206].

6.2.3. Ginsenosides

In AD mice, ginsenoside Rb1 improved learning ability and reduced $A\beta_{1-42}$ in the cortex and hippocampus. Using laser scanning confocal microscopy, Guo *et al*., [207]. observed LC3 dispersed throughout the cell and at the membrane of autophagosomes after ginsenoside administration. This indicates that autophagy activation is involved in the Aβ-scavenging effects of ginsenosides. mTOR and NRF2 are recognized as the dominant signaling pathways mediating the neuroprotective role of ginsenosides in attenuating Aβ formation [207, 208]. A study further demonstrated that mTOR-dependent TFEB-mediated autophagy maybe another key pathway facilitating the anti-amyloidogenic effect of ginsenoside K [209]. Ginsenoside Rg1 administration also reduced tau accumulation in a rat model by decreasing GSK3β pathway activation [210].

6.2.4. Curcumin

Curcumin (*bis*-α, β-unsaturated β-diketone) is a natural compound traditionally used for its anti-tumorigenic and anti-hyperlipidemic properties. The therapeutic function of curcumin in promoting Aβ clearance and ameliorating symptoms of AD *in vivo* and *in vitro* has received wide attention [211, 212]. In APP/PS1 transgenic mice, curcumin reduced Aβ generation, induced autophagy, and upregulated expression of Beclin-1 and LC3 I/II [213]. The neuroprotective effect of curcumin is associated with inhibition of the PI3K/AKT/mTOR pathway [213]. Even although the therapeutic function of curcumin has been demonstrated, its poor absorption and low bioavailability have curtailed its clinical application [214]. Compound C1, a monocarbonyl analog of curcumin with a stable structure and good blood–brain barrier permeability, can potently induce nuclear translocation of endogenous TFEB and enhance autophagy in Neuro-2a cells, without inhibiting mTOR activity. Consequently, this may be a novel drug candidate for AD [215].

6.3. Lifestyle Interventions

6.3.1. Calorie Restriction and Fasting

Calorie restriction (CR) (consuming calories 10%–40% less than an *ad libitum* animal, yet maintaining proper nutrient intake) is generally known as one of the best interventions for slowing aging and increasing lifespan [216]. However, as CR is difficult to perform in practice and easy to cause malnutrition, intermittent fasting (IF) is considered an optimal intervention [217, 218]. Both CR and IF interventions can ameliorate behavioral deficits in 3×TgAD mice. Although only CR affected $A\beta_{1-42}$ and tau levels in the hippocampus, IF also showed neuroprotective effects against excitotoxic insults and promoted synaptic plasticity [219]. Because inhibition of autophagy attenuates the anti-aging effect of CR and IF, it has been hypothesized that autophagy plays a central role in CR/IF-mediated longevity [220]. In 5×FAD mice, time-lapse live imaging showed a marked increase in levels of EGFP-LC3 vesicles after fasting treatment, which implies that autophagy is activated under starvation. Moreover, starvation-induced autophagy also reduced extracellular Aβ and increased intracellular Aβ degradation [221]. Further, it has been shown that CR ameliorated memory deficits and prevented impairment of adult neurogenesis by restoring autophagic flux in transgenic mice [222]. The IGF-1 and SIRT1 pathways are two widely accepted theories to explain the mechanisms underlying the protective effects of CR. Upon CR intervention, mRNA levels of *IGF-1* in the hippocampus are elevated [223]. Similarly, CR also promoted the non-amyloidogenic pathway of APP and attenuated Aβ generation by reducing SIRT1 expression in Tg2576 mice, another mouse model of AD [115, 224].

6.3.2. Physical Activity

Regular physical activity can enhance brain vitality and provides cognitive and psychological benefits [225]. A large prospective study found that exercise improved cognitive and physical performance in patients with AD, with possible additional benefits of reducing neuropsychiatric symptoms [226]. Furthermore, *APOE*4 allele carriers benefited from exercise intervention on cognitive tasks [227]. Many studies suggest the therapeutic role of physical activity is mediated through autophagy. Swimming training improved learning and memory impairments by downregulating autophagy-related proteins including LC3, Beclin-1, and ATG7, and upregulating p62 in aging rats [228]. Late running reduced Aβ plaque burden with upregulation of autophagy markers (Beclin-1 and syntaxin 17) in the neocortex and hippocampus of AD mice [229]. Regular aerobic exercise delayed the progress of aging and upregulated striatal autophagy *via* the AMPK/SIRT2 pathway [230]. Although exercise benefited neurocognition in aging models, it is important to note that the duration or intensity of exercise did not matter for the beneficial effects [231]. The best exercise for elderly is in accordance with their cardiorespiratory function.

CONCLUSION AND PERSPECTIVE

In this review, we have summarized the key role of autophagy in the pathogenesis of AD and discussed potential therapeutic strategies to delay cognitive decline by restoring autophagy. However, applying this strategy in clinical treatment is still some time away. First, long-term or overly activated autophagy may be harmful for cells and may result in cell death. A compound that efficiently activates autophagy but is also safe with long-term use is highly desirable. Second, obstacles of a pharmacological, technical or experimental nature have hampered the straightforward implementation of autophagy modulators in the clinic. One major challenge is that several pro-autophagic drugs not only independently activate autophagy but also potentially disturb other cellular functions, resulting in adverse effects. Third, it is difficult to monitor autophagic flux feasibility and assess therapeutic efficiency of autophagy modulation. To date, immunohistochemical staining against autophagy-specific biomarkers and transmission electron microscopy is a frequently used method to monitor autophagy. However, neither can interpret the results *in vivo* in a real-time manner. To be applied in a clinical setting, a biomarker or an autophagy-specific surrogate is needed to efficiently assess autophagy modulation. Fourth, how to precisely target the autophagic machinery in the correct tissue and avoid adverse effects associated with systemic autophagy is another big challenge. Nanomedicine maybe a feasible approach, delivering drugs to the targeted sites with a low dose. Nanocarriers can also penetrate through the blood-brain barrier thereby improving bioavailability of the drugs in the brain tissue. Thus, although tremendous advances have been made in our understanding of autophagy, many unanswered questions remain. Much work is needed before we can hope to harness the full therapeutic potential of autophagy modulators.

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