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REVIEW

# Activation of mTOR: a culprit of Alzheimer's disease?

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**Abstract:** Alzheimer's disease (AD) is characterized by cognitive impairment in clinical presentation, and by β-amyloid (Aβ) production and the hyper-phosphorylation of tau in basic research. More highlights demonstrate that the activation of the mammalian target of rapamycin (mTOR) enhances Aβ generation and deposition by modulating amyloid precursor protein (APP) metabolism and upregulating β- and γ-secretases. mTOR, an inhibitor of autophagy, decreases Aβ clearance by scissoring autophagy function. mTOR regulates Aβ generation or Aβ clearance by regulating several key signaling pathways, including phosphoinositide 3-kinase (PI3-K)/protein kinase B (Akt), glycogen synthase kinase 3 [GSK-3], AMP-activated protein kinase (AMPK), and insulin/insulin-like growth factor 1 (IGF-1). The activation of mTOR is also a contributor to aberrant hyperphosphorylated tau. Rapamycin, the inhibitor of mTOR, may mitigate cognitive impairment and inhibit the pathologies associated with amyloid plaques and neurofibrillary tangles by promoting autophagy. Furthermore, the upstream and downstream components of mTOR signaling are involved in the pathogenesis and progression of AD. Hence, inhibiting the activation of mTOR may be an important therapeutic target for AD.

**Keywords:** Alzheimer's disease, mammalian target of rapamycin, rapamycin, β-amyloid, neurofibrillary tangles, signaling

## Introduction

Alzheimer's disease (AD), characterized by age-related neurodegenerative disorder, makes clear the progression of cognitive impairment in clinical presentation and the two classical hallmarks of β-amyloid (Aβ) accumulation and aberrant hyperphosphorylated tau in pathology.[1,2] Procedural age is the greatest risk factor for AD since most patients with AD are more than 65 years old.[3,4] Although extensive research in AD has been undertaken over the past few decades, the pathogenesis of AD is still not completely understood. Current therapeutic intervention for AD cannot stop cognitive impairment from progressing in spite of temporarily slowing the worsening of dementia and improving the quality of life. So far, seeking out effective ways to stop the progression of AD and prevent its onset has been a thorny issue.

The mammalian target of rapamycin (mTOR) is a 289-kD serine/threonine multidomain protein with a kinase domain and a FKBP12 binding domain, regulating many physiological processes. mTOR coordinates or interacts with the upstream signal components, including insulin, growth factors, AMPK, PI-3K/Akt, and glycogen synthase kinase 3 (GSK-3).[5–8] More and more studies have found the involvement of the mTOR dysregulation in many diseases, such as aging,[9,10] tumor and cancer,[11,12] diabetes,[12] obesity,[13] cardiovascular disease,[14,15] and neurodegenerative diseases.[16,17] Compelling evidence has shown that the activation of mTOR signaling is a contributor to AD progression and intersects with AD pathology and clinical manifestation.[18,19] mTOR signaling is closely associated with the presence of two hallmarks of the disease (Aβ

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plaques and neurofibrillary tangles [NFTs]) and cognitive impairment in clinical presentation, respectively.[20–22] Therefore, the development of mTOR inhibitors may also be useful for the prevention and treatment of AD.[23]

This review focuses on the roles of mTOR in AD cognitive clinical manifestation and the pathology of amyloid plaques and NFTs. It is also discussed that mTOR inhibitor rapamycin delays cognitive impairment and retards the pathology of amyloid plaques and NFTs. The theoretical basis that inhibiting mTOR induces autophagy enhancement and benefits the treatment of AD is provided here. Finally, whether inhibiting mTOR could be a valid therapeutic means to limit AD pathology is reviewed.

## Mammalian target of rapamycin

mTOR, also known as the mechanistic target of rapamycin or FK506 binding protein 12-rapamycin associated protein 1 (FRAP1), is a 289-kD serine/threonine protein kinase that is closely related to the regulation of many physiological processes such as maintaining cell growth, proliferation and survival, and regulating protein synthesis and transcription via a wide variety of cellular signals.[24,25] mTOR is present in two main types of molecular complex: mTOR complexes 1 and 2 (mTORC1 and mTORC2).[26]

mTOR signaling has been regulated by its upstream components, including insulin, growth factors (such as IGF-1), LKB1/AMPK, PI3K/Akt, GSK-3β, IKKβ, MAPK, and p53.[27–31] Activated mTORC1 also has a number of downstream biological effects including translation of mRNA via the phosphorylation of downstream targets (4E-BP1 and p70S6 Kinase), suppression of autophagy (Atg13, ULK1), ribosome biogenesis, and activation of transcription leading to mitochondrial metabolism or adipogenesis. mTORC2 regulates ion transport and growth via SGK1 phosphorylation and controls cytoskeletal dynamics via activating (PKC) protein kinase C.

Therefore, aberrant mTOR signaling is closely related to many disease states.[32,33] mTOR signaling intersects with AD pathology in several respects, suggesting its potential role as a contributor to the neurodegenerative process. Scientific evidence has supported that the activation of mTOR signaling plays a critical role in the pathogenesis of AD while the activation of mTOR signaling contributes to Aβ generation and the formation of NFTs.[20]

## The activation of mTOR: a trigger for Aβ generation and failure of Aβ clearance?

The most striking pathogenic hallmark recognized by the scientific community for AD is the production and deposition of Aβ.[34,35] Genetic evidence indicates that the main factor of Aβ generation is based on mutations either in the precursor protein for Aβ (β-amyloid precursor protein [APP]) or in presenilin-1 (PS1) or presenilin-2 (PS2).[36,37] It is well accepted that the production of Aβ is the enzymatic processes responsible for the metabolism of APP, sequentially cleaved by two membrane-bound endoproteases: β- and γ-secretase.[38,39] β-secretase is considered to be the rate-limiting enzyme in Aβ generation, while γ-secretase, a multisubunit enzyme composed of the proteins APH1, PEN2, nicastrin, and presenilin (PS1 or PS2), is the final endoprotease that generates the peptide Aβ.[40,41]

Increasing evidence highlights that the activation of mTOR is an enhancer of Aβ generation and deposition (Figure 1).[20,42] mTOR, an inhibitor of autophagy, decreases the Aβ clearance of the autophagy/lysosome system which accounts for the clearance of abnormal proteins.[20,43] mTOR also modulates the metabolism of APP by regulating β- and γ-secretase.[23,44] In addition, mTOR may interact with several key signaling pathways and regulate Aβ generation or Aβ clearance, including PI3-K/Akt,[45,46] GSK-3,[32] AMPK,[47] and insulin/IGF-1.[43]

### Activation of mTOR induces the failure of Aβ clearance

A variety of research studies have proved that the activation of mTOR leads to the failure of Aβ removal from the brain since the dysfunction of autophagy triggered by mTOR facilitates the process of Aβ generation and weakens its clearance.[22,44,48]

Autophagy, the molecular machinery for self-digestion, is an essential catabolic process in response to a multitude of physiological and pathological situations.[49,50] It is well known that autophagy is an intracellular degradation system that delivers cytoplasmic components to lysosome and degrades cellular components through autophagy/lysosomal pathway to alternatively remove unnecessary cellular constituents.[50,51] In the normal physiological function of cell metabolism, autophagy upholds the balance between the synthesis, degradation, and subsequent recycling of cellular products, playing an important role in maintaining cellular homeostasis, cell survival, differentiation, and development.[52,53] Although numerous studies have revealed the nature and role of autophagy since the 1960s, many questions about the actual processes and mechanisms still remain. In particular, its role in some diseases still stays in the exploratory or research stage status. Yet it has been well recognized that autophagy plays a crucial role in many

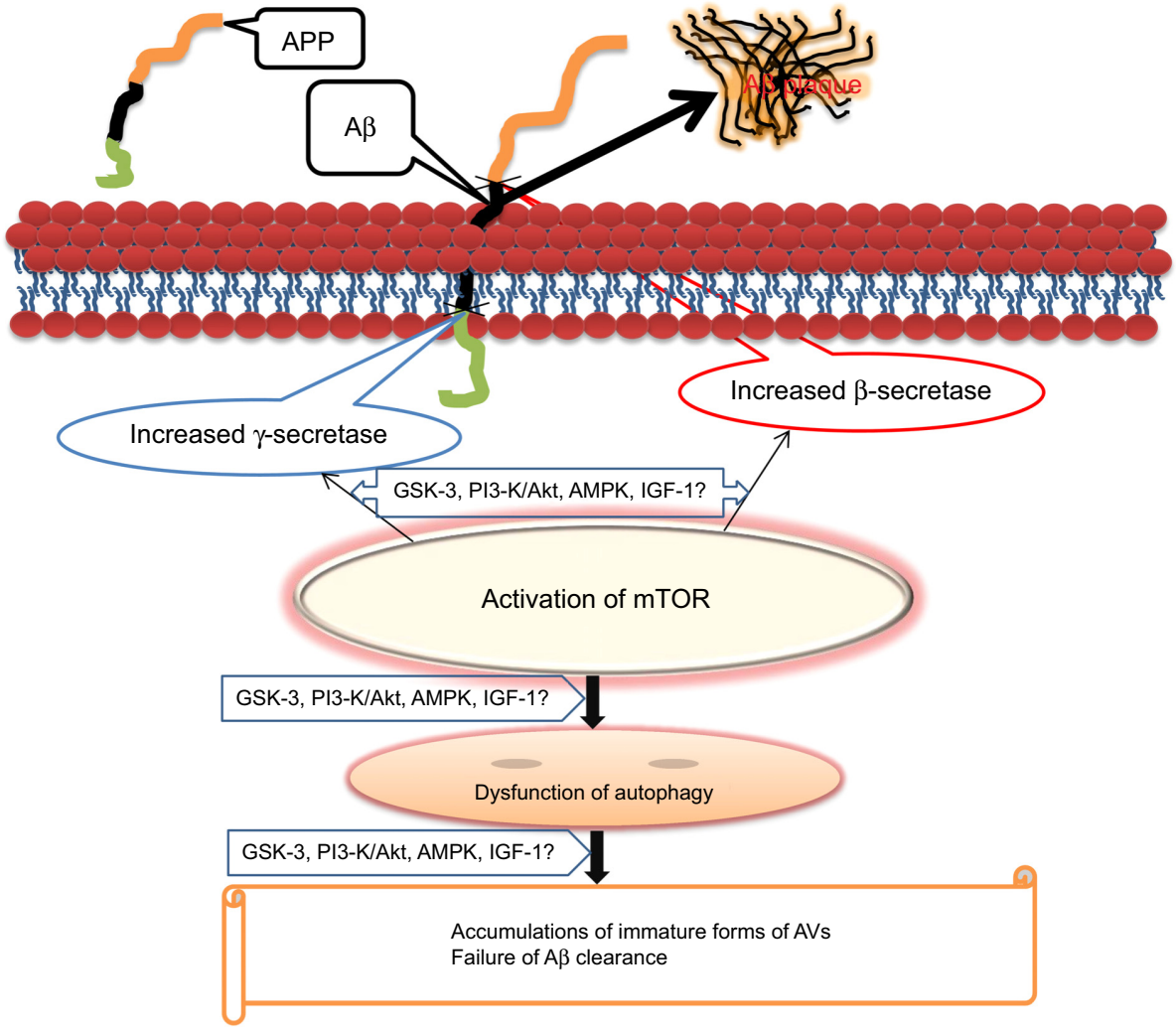


**Figure 1** Schematic diagram of the potential mechanism by which the activation of mTOR regulates Aβ.
**Notes:** Aβ is generated from APP by the sequential cleavage of β-secretase and γ-secretase. The activation of mTOR could upregulate β- and γ-secretases in the process of Aβ generation. Additionally, the activation of mTOR contributes to the dysfunction of autophagy, which leads to accumulations of immature forms of AVs, enhancing the failure of Aβ clearance and the Aβ deposition and formation of Aβ plaques.
**Abbreviations:** Akt, protein kinase B; AMPK, AMP-activated protein kinase; APP, amyloid precursor protein; AVs, autophagic vacuoles; GSK-3, glycogen synthase kinase 3; IGF-1, insulin-like growth factor 1; mTOR, mammalian target of rapamycin; PI3-K, phosphoinositide 3-kinase.

pathological processes, such as cancer,[54,55] liver and kidney diseases,[54,56,57] immune diseases,[58,59] pathogen infection,[60] aging and neurodegeneration,[61–63] including Huntington's, Alzheimer's, and Parkinson's diseases.

An analysis of the molecular mechanisms has shown that the induction of autophagy is a neuroprotective response and that defective autophagy is a favorable factor for neurological damage in most neurological disorders.[32,64,65] Autophagy is the main mechanism in neurodegeneration, and autophagy deficiency is a major contributor to abnormal protein aggregation such as the aggregates of Aβ and tau in AD, the aggregates of α-synuclein in Parkinson's disease, and the Huntingtin aggregates in Huntington's disease.[66,67] Distinctively, inhibition of mTOR activity and induction of autophagy ameliorate the pathogenic aggregates of misfolded proteins and delay the process of neurodegeneration in Huntington's, Alzheimer's, Parkinson's disease, and Lewy body diseases.[68,69]

Several research findings point to the notion that a chronic deterioration of the autophagy/lysosome pathway is an important factor in the failure of Aβ clearance from the AD brain, while the autophagy/lysosome system determines the outcome of Aβ in the AD brain.[23,46,48,70] Additionally, mTOR, inhibitor of autophagy, is closely associated with the levels of Aβ. Accordingly, inhibition of mTOR activity induces autophagy, lessens the aggregates of Aβ, and enhances the process of Aβ clearance.[23]

Normally, Aβ is most degraded by the autophagy/lysosome pathway that can participate in protein quality control and

in the removal of aberrant forms of protein. The immaturity of autophagolysosomes plays a significant role in a massive accumulation of autophagic vacuoles (AVs) that may be sites of Aβ generation.[71,72] Failure of Aβ clearance, generating from the accumulation of AVs that were colocalized within Aβ deposits, subsequently leads to the occurrence of Aβ accumulation and the formation of amyloid plaque in AD, which deteriorates from impaired clearance of AVs.[72] It is recognized that inducing or inhibiting autophagy by regulating mTOR signaling induces corresponding changes in AVs proliferation and Aβ generation.[65,73] In 3xTg-AD mice without the formation of amyloid plaques and tangles, autophagy induction via rapamycin ameliorates cognitive deficits, implying that rapamycin will be beneficial for the early treatment of AD.[74] Recent research has demonstrated that chronic rapamycin intervention retards the progression of Alzheimer's-like deficits and decreases Aβ levels through autophagy enhancement in the human amyloid precursor protein (PDAPP) mouse model, while rapamycin maintains proteostasis by the upregulation of classical chaperones/heat shock proteins (HSPs) in the brains of rapamycin-fed PDAPP mice.[70]

## mTOR modulates APP process

The metabolic process of APP determines the onset of the amyloid pathogenic formation in AD as a result of sequential APP proteolysis.[75] APP is a single-chain transmembrane protein and is metabolized by a series of sequential proteases under extensive posttranslational modification such as phosphorylation, glycosylation, and tyrosine sulfation.[76,77] The metabolic process of APP occurs mainly by two pathways: 1) nonamyloidogenic process involving sequential cleavage by α-secretase and γ-secretase,[78] 2) amyloidogenic process sequentially cleaved by β-secretase and γ-secretase.[79] γ-secretase is a large multisubunit complex whose components include presenilin that has been identified as a major genetic risk factor for AD.

The involvement of mTOR signaling in the pathogenesis of AD is the regulation of autophagy, while the autophagy/lysosome pathway is an important regulator of the processing of APP.[44,80] In vitro study notes that it is a vital Aβ-generating pathway via increasing mature APLP1 (amyloid precursor-like protein 1) APP that is degraded through the autophagy/lysosome pathway.[81] Recent findings suggest that inhibition of mTOR signaling alters APP processing by autophagosome accumulation in insulin-resistant conditions.[44] Thus, mTOR modulates the APP process via autophagy intermediary. β- and γ-secretases are two essential enzymes for Aβ generation. mTOR may regulate postsecretase APP-CTF catabolism via autophagy/lysosomal proteolysis to influence the Aβ generation.[82]

## mTOR regulates Aβ generation via some signaling pathways

Biomolecular evidence highlights the notion that the importance of both traditional and newly recognized interaction between mTOR and several signaling pathways has regulated Aβ generation to date, such as PI3-K/Akt, GSK-3, insulin/IGF-1, AMPK, and p70S6K.[32,83]

### PI3-K/Akt/mTOR

The PI3-K/Akt/mTOR signaling pathway has a central function in the regulation of crucial metabolism,[84,85] cell growth and proliferation,[86,87] apoptosis,[88] and secretion.[89] Protein kinase B (PKB, also known as Akt) acts as a central intersection between phosphoinositide 3-kinase (PI3-K) and mTOR by phosphorylating a variety of substrates.[90,91] Based on its crucial role in regulating critical cellular functions, it is highly plausible that the deregulation of PI3-K/Akt/mTOR participates in numerous disease disorders.[92–96] Recent research demonstrates that the abnormal PI3-K/Akt/mTOR signaling pathway has been shown to contribute to the occurrence and development of AD.[5] Aberrant activation of neuronal PI3-K/Akt/mTOR signaling is an early pathogenesis in the brains of AD individuals and a major candidate for pathophysiological change of Aβ product.[5] Insulin and IGF-1 may rescue and normalize aberrant PI3-K/Akt/mTOR signaling against the development of amyloid pathology and cognitive impairment.[5,97]

### GSK-3/mTOR

GSK-3, a multifunctional serine/threonine protein kinase, regulates numerous signaling pathways involved in a series of cellular processes, from glycogen metabolism to cell cycle regulation and proliferation. Excessive GSK-3 activation has recently been identified as an important factor in the onset of numerous diseases, including diabetes,[98] bipolar disorder,[99,100] cancer,[98,101] and neurodegeneration diseases.[102,103] The roles of GSK-3 in AD have been supported by the accumulating pathologic evidence, indicated in the generation of multiple pathological lesions,[104,105] including Aβ production, the formation of neurofibrillary tangles, and neuron loss.[106,107] An increasing amount of literature points out that GSK-3 is involved in the PI3K/Akt/mTOR signaling pathway.[108–111] GSK-3/mTOR signaling pathway not only modulates neuronal cell proliferation, migration,

and plasticity,[32,112,113] but also regulates glucose uptake and glucose transporter.[114,115] Both PI3-K/Akt and GSK-3 signaling pathways are important signaling machinery regulating the coming and leaving of Aβ in the pathogenesis of AD.[96,116] Recent in vivo and in vitro studies show that an inhibitor of GSK-3, L803-mts, reduces Aβ deposits, delays cognitive impairment, and restores lysosomal acidification and the activity of mTOR, which is an effective target activated by GSK-3 but inhibited by impaired lysosomal acidification,[117] implying that inhibition of GSK-3 rehabilitates lysosomal acidification that successively improves Aβ clearance via restoration of aberrant mTOR signaling and activation of autophagy.

## AMPK/mTOR

AMP-activated protein kinase (AMPK), a key energy enzyme, regulates cellular metabolism to maintain energy homeostasis in response to a fall in intracellular ATP levels. The structure and function of AMPK has been regulated by ADP levels.[118,119] AMPK is activated when cellular ADP levels increase coping with changes in cellular energy status.[119] Numerous research results related to AMPK have been implicated in many kinds of pathological processes such as diabetes,[120,121] obesity,[122,123] cancer,[124,125] aging,[126] and neurodegenerative diseases.[127,128] AMPK and mTOR act as a common regulator of autophagy through direct phosphorylation of Ulk since the Atg1/Ulk complex plays an essential role in the initiation of autophagy.[129,130] Specifically, AMPK directly modulates Ulk1 through phosphorylation of Ser317 and Ser777, which results in autophagy enhancement. The activation of mTOR inhibits phosphorylation of Ulk1 Ser757 and cuts off the interaction between Ulk1 and AMPK, weakening autophagy.[129] Moreover, molecular biological investigations into the role of AD have shown that both AMPK and mTOR participate in the regulation of the Aβ level.[20,47,131] Through autophagy enhancement, the activation of AMPK limits the generation of Aβ.[47,132] Conversely, the activation of mTOR is likely to promote Aβ production.[20,23] Based on the data that the Aβ level in the AD brain is determined by the overall functional status of autophagy and that AMPK activation inhibits mTOR signaling activity to facilitate autophagy and promotes lysosomal degradation of Aβ,[42,43,72] it is mainly through autophagy that the AMPK/mTOR signaling may regulate the Aβ level.

### Insulin/IGF-1/mTOR

Insulin/insulin-like growth factor 1 (IGF-1) signaling is an important biochemical pathway that regulates glucose storage and uptake, cell growth and mitosis, protein synthesis, lipid synthesis, and the activity of numerous enzymes.[133] Numerous studies have revealed that conduction disturbance of insulin/IGF-1 signaling has an intimate connection with the pathological process of many diseases related to metabolic disorders, such as aging,[134–135] cancer,[136,137] diabetes,[138,139] and neurodegenerative disorders.[140,141] Many data have suggested that conduction disturbance of insulin/IGF-1 signaling is an important mechanism of Aβ generation and deposition, including the increased Aβ level induced by hyperglycemia,[142–144] the Aβ generation elicited by hyperinsulinemia,[145,146] the APP modulation by hyperinsulinemia or hyperglycemia,[143,147–149] and the failure of Aβ clearance triggered by the receptor for advanced glycation end products (RAGE) that is thought to be a primary transporter of Aβ across the blood–brain barrier (BBB) into the brain from the systemic circulation.[150–153]

Insulin/IGF-1 signaling regulates mTOR signaling by controlling the TSC GTPase activator function toward the Rheb GTPase.[154] The insulin/IGF (IR, IGF-1R, IRS-1, PTEN, Akt, GSK3α, and GSK3β) to mTOR (TSC2, mTOR, p70S6K, and RPS6) signaling pathway is essential for the growth, proliferation, and survival of cells.[155,156] More studies are in favor of the negative intermodulation between mTOR and the insulin/IGF-1 signaling pathway.[157,158] It is clarified that the mTOR signaling pathway is activated by inhibiting the activity of insulin/IGF-1 signaling key components, including insulin receptor, insulin receptor substrate 1 (IRS-1), and IGF-1R.[156,159–161] Furthermore, mTOR can induce insulin resistance by phosphorylation of IRS-1 on serine307 residues.[162] Clearly, the insulin/IGF-1/mTOR signaling pathway is a negative cycle loop that regulates a variety of pathophysiological features.

It is well recognized that insulin and rapamycin (the inhibitor of mTOR) play a neuroprotective role in many neurological disorders,[163,164] especially in neurodegeneration including AD.[6,165] The striking similarity is the results from the insulin intervention and the inhibition of mTOR by rapamycin that rescue cognitive impairment and retard Aβ pathology in AD animal models.[22,23,166,167] Hence, delaying the process of AD via regulation of the insulin/IGF-1/mTOR signaling pathway may be a promising intervention.[140,168]

Nevertheless, considerable evidence exists to show that insulin can enhance the activation of mTOR via stimulation of 4EBP1 binding to dimeric mTOR complex 1,[169] and mediated by the Akt/PKB substrate PRAS40 (proline-rich Akt/PKB substrate 40 kDa).[170] From in vivo and in vitro studies, it seems that mTOR activation has a neuroprotective property

in the pathogenesis of AD, ameliorating Aβ pathology.[117] Thus, the roles of insulin/IGF-1/mTOR signaling in AD remain elusive under these contradictory findings. Maybe, different results will emerge under different species, different diseases, and different experimental conditions.

## The activation of mTOR: an enhancer of the hyperphosphorylation of tau?

Tau protein is a highly soluble microtubule-associated protein (MAP) that stimulates tubulin assembly into microtubules and stabilizes microtubules in the brain.[171] It is well established that abnormal hyperphosphorylation of tau has been linked to the pathogenesis of AD (major components of paired helical filaments and neurofibrillary tangles), although the mechanism of the hyperphosphorylation is still not fully understood.[172,173] The abnormal hyperphosphorylation of tau leads to massive detachment, which consequently weakens the stability of microtubules in nerve cells. This microtubule instability is one of the main causes of the symptoms of AD. Numerous scientific data have proved that abnormal tau hyperphosphorylation plays a central role in the formation of neurofibrillary tangles, which is a leading cause of neuronal death in AD.[171,174] Tau phosphorylation is dynamically regulated by tau kinases and tau phosphatases, including GSK-3β,[175,176] cyclin-dependent protein kinase 5 (cdk5), cAMP-dependent protein kinase,[177,178] stress-activated protein kinases (SAPK1c/JNK1, SAPK2a/p38α, SAPK2b/p38β, SAPK3/p38γ, and SAPK4/p38δ),[179,180] and mTOR.[164,181]

Compelling scientific results support the critical role of mTOR in the tau-related pathological progress, implying that the activity status of mTOR determines the abnormal hyperphosphorylation of tau, the onset of paired helical filaments, and the formation of NFTs.[164,181–183] The activation of mTOR signaling promotes tau pathology, while inhibiting mTOR signaling slows down the progress of tau pathology.[181]

A recent study has shown that mTOR activated in diabetic condition accelerates the extent of tau hyperphosphorylation and promotes the occurrence of AD by impairing insulin signaling.[164] Consistent with the discovery of the above, rapamycin (an inhibitor of mTOR, by inhibiting mTOR activity) reduces tau phosphorylation at Ser214 through the regulation of cAMP-dependent kinase, while tau phosphorylation at Ser214 may prepare tau for further phosphorylation by other kinases.[184]

It has been evidenced that mTOR signaling pathway has a close link to tau phosphorylation and the formation of PHFs and NFTs through autophagy function. Rapamycin-induced autophagy may enhance the clearance of the hyperphosphorylated tau.[184] Inhibition of mTOR by rapamycin retards cognitive deficits and reduces the abnormal hyperphosphorylation of tau by autophagy enhancement in AD models.[23,183] mTOR, coupled with PI3-K signaling, regulates protein phosphatase 2A and GSK-3-dependent phosphorylation of tau, while GSK-3β, antagonized by protein phosphatase 2A, regulates tau phosphorylation at many sites.[111] It may be an effective therapeutic target for AD that mTOR regulates tau phosphorylation by controlling autophagy pathway.

## The upstream and downstream components of mTOR signaling in AD

As shown in Table 1, the upstream and downstream components of the mTOR signaling pathway are involved in the pathogenesis and progression of AD.[6,32,164] Considerable work has been dedicated to elucidating that mTOR-related signaling components have been identified as potential biomarkers of cognitive impairments in the clinical diagnosis of AD and as a critical target for a therapeutic program in AD.[185,186]

### The upstream components of mTOR signaling associated with AD

mTORC is regulated by numerous signaling components, including PI3K/Akt, AMPK, MAPK, p53, GTPase, LKB1, ERBB2, IRS-1, PTEN, GSK-3, insulin/IGF-1, and AMPK.[32,83,187,188] It has been found that several upstream components of mTOR signaling (PI3K/Akt, AMPK, GSK-3, insulin/IGF-1, and AMPK) play a critical role in the regulation of Aβ generation and the aberrant phosphorylation of tau.[5,32,47,187] In fact, there are many specific mechanisms that are also well addressed about the status of the mTOR upstream components in AD.

### PI3-K/Akt

mTOR is a member of the PIKK (PI3-K-related Kinase) family, present in two distinct multiprotein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Activation of the PI3-K/Akt regulates mTORC1 by phosphorylating the tuberous sclerosis complex 2 (TSC2), blocking TSC2 from forming a heterodimer with tuberous sclerosis complex 1 (TSC1), and phosphorylating PRAS40, separating PRAS40 from mTOR. Preclinical research evidence also supports that coupling of mTOR with the PI3-K/Akt pathway regulates protein phosphatase 2A- and GSK-3-dependent phosphorylation of tau.[111] The most striking is that the activation of PI3-K/Akt acts on mTOR to enhance autophagy

**Table 1** The upstream and downstream components of mTOR signaling network associated with AD

| Molecule involved | mTOR activity | Position in mTOR signaling | Proposed mechanism in AD | References |
|---|---|---|---|---|
| PI3-K/Akt | ↓ | Upstream of mTORC1 and downstream of mTORC2 | The activation of PI3-K/Akt inhibits mTOR from enhancing autophagy and lysosomal degradation of Aβ, and limits the level of hyperphosphorylation of tau. Coupling of mTOR with PI3-K pathway by activated Akt regulates protein phosphatase 2A- and GSK-3-dependent phosphorylation of tau. | 47,192,193 |
| AMPK | ↓ | Upstream of mTORC1 | AMPK targets mTOR to trigger autophagy and lysosomal degradation of Aβ. AMPK/mTOR signaling may improve insufficient energy metabolism and effect on amyloid plaque and neurofibrillary tangles via autophagy pathway. | 47,132,198,199 |
| MAPK | ↑ | Upstream of mTORC1 | The interaction between mTOR and p38MAPK is a potent mediator in the pathogenesis of AD as a link between neuroinflammation, the formation of amyloid plaque, and the hyperphosphorylation of tau protein. | 202,203 |
| p53 | ↓ | Upstream of mTORC1 | p53, regulated by TSC2, is a molecular link between mTOR signaling pathways and RNA-activated protein kinase (PKR) as a center of cellular response to different stress signals and a critical target in AD. | 185,186 |
| GSK-3 | ↑ | Upstream of mTORC1 | GSK-3/mTOR signaling may be an effective actor in regulating the production of Aβ and hyperphosphorylation of tau. | 32,83,114 |
| LKB1 | ↓ | Upstream of mTORC1 | The LKB1/AMPK signaling negatively regulates mTOR signaling. LKB1/AMPK signaling pathway is associated with the pathogenesis of AD. The LKB1 complex in response to increase in the AMP/ATP ratio regulates Aβ generation and the aberrant phosphorylation of tau. | 47,210,211 |
| HER2 | ↑ | Upstream of mTORC1 | The activation of HER2 leads to Aβ production and the aberrant phosphorylation of tau by regulating MAPK, PI3K/Akt, PKC, and STAT signaling while these signaling pathways are all related to mTOR signaling. | 216–219 |
| IRS-1 | ↓ | Upstream of mTORC1 | IRS-1 has been implicated in Aβ generation and the aberrant phosphorylation of tau. The interaction between insulin/IRS-1 and mTOR is a critical regulator of Aβ generation and the aberrant phosphorylation of tau. | 164,187,193,225 |
| S6K/S6, p70S6K | ↓ | Downstream of mTORC1 | The levels of total p70S6 kinase and p70S6 kinase phosphorylated at Thr421/Ser424 are correlated with the levels of tau. The level of ribosomal protein S6 is significantly increased in AD, while phosphorylated forms of mTOR and p70S6k are decreased in the cortex. p70S6K and S6 phosphorylate tau protein. The p70S6K can phosphorylate tau at S262, S214, and T212 sites, releasing tau from microtubules and resulting in microtubule disruption. | 22,226,229,230,233 |
| eIF2, eIF4E, 4EBP | ↓ | Downstream of mTORC1 | mTOR activation stimulates translation initiation processes involving both 4EBP and p70S6 kinase/ribosomal S6 protein. The eIF2α levels were significantly increased in lymphocytes of AD patients and correlated with cognitive function. Phosphorylated 4EBP enhances total tau protein synthesis in the hippocampus. eIF4E phosphorylation is correlated with total- and hyperphosphorylated taus. The PKR/eIF2α pathway is responsible for the posttranscriptional increase in BACE1, which determines the Aβ pathogenesis. | 19,185,235,237,240,241 |

**Notes:** ↓ means decreasing or decreased; ↑ means increasing or increased.

**Abbreviations:** AD, Alzheimer's disease; Akt, protein kinase B; AMPK, AMP-activated protein kinase; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; 4EBP, eIF4E/4E-binding protein; eIF2, eukaryotic Initiation Factor 2; eIF4E, eukaryotic translation initiation factor 4E; GSK-3, glycogen synthase kinase 3; HER2, human epidermal growth factor receptor-2; IRS-1, insulin receptor substrate-1; LKB1, liver kinase B 1; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3-K, phosphoinositide 3-kinase; PKC, protein kinase C; STAT, signal transducer and activator of transcription; TSC2, Tuberous Sclerosis Complex 2.

and lysosomal degradation of Aβ, and limits the level of the hyperphosphorylation of tau.[47,131,189] According to the previous findings that both PI3-K/Akt and mTOR signaling are effective regulators in the pathogenesis of AD,[46,190,191] it is obvious that the PI3-K/Akt/mTOR signaling or the interaction between PI3-K/Akt and mTOR has a critical effect on the development and progression of AD pathology.[47,192,193]

## AMPK

AMP-activated protein kinase (AMPK) maintains cellular energy homeostasis and acts as a metabolic master switch regulating many intracellular systems. Emerging studies have demonstrated that the AMPK signaling is closely associated with the major hallmarks of AD (insufficient energy metabolism, amyloid plaque, and NFTs).[194–197] As an activator of autophagy function, AMPK activation retards the progress of AD pathology in respect to mTOR that plays a fundamental role in regulating autophagy state.[47,132,198,199] AMPK targets mTOR to trigger autophagy and lysosomal degradation of Aβ.[47] It is likely that the AMPK/mTOR signaling may improve insufficient energy metabolism and effect on amyloid plaque and NFTs via the autophagy pathway.

## MAPK

Accumulating evaluation of p38MAPK significance involved in the pathophysiology and pathogenesis of AD has evidenced that the MAPK signaling may be a great contributor to the development of AD.[200] The activation of p38MAPK brings about mTOR inactivation and leads to the induction of autophagy.[201] The activation of mTOR decreases the activity of p38MAPK and reduces autophagy.[202] It seems that the interaction between mTOR and p38MAPK is a potent mediator in the pathogenesis of AD as a link between neuroinflammation, the formation of amyloid plaque, and the hyperphosphorylation of tau proteins.[203] Accordingly, inhibition of mTOR via MAPK may potentially prevent neurodegeneration from occurring in AD.

## p53

p53 (protein 53 or tumor protein 53) is a tumor suppressor protein that plays a major role in preventing tumor development. It responds to a range of potentially oncogenic stresses by activating protective mechanisms, most notably cell cycle arrest and apoptosis. It has been noted that the level of p53 increases in AD and that p53 induces phosphorylation of human $_2N_4R$ tau at the tau-1/AT8 epitope in $HEK_{293a}$ cells.[204] Thus p53 and mTOR are both associated with the progress of neurodegenerative disorders in AD. It has been evidenced that p53, regulated by TSC2, is a molecular link between the mTOR signaling pathways and RNA-activated protein kinase (PKR) as a center of cellular response to different stress signals and a critical target in AD.[185,186]

## GSK-3

GSK-3 participates in a wide range of signal transduction cascades involving cellular processes, ranging from glycogen metabolism, gene transcription, protein translation to cytoskeletal organization, cell cycle regulation, and proliferation. GSK-3 plays a crucial role in the hyperphosphorylation of tau and neurofibrillary lesions since GSK-3 phosphorylates tau in most serine and threonine residues.[111] The production and aggregation of Aβ is promoted by GSK-3 but reduced by pharmacological inhibition.[117] It may be an integrating link between amyloid pathology and tauopathies via the activation of GSK-3.[205,206] Identified as an upper regulator of mTOR,[32,83,114] GSK-3/mTOR signaling may be an effective actor to regulate the production of Aβ and the hyperphosphorylation of tau.

## LKB1

LKB1, a primary upstream kinase of AMPK, is a necessary element in cell metabolism that is required for maintaining energy homeostasis. The LKB1/AMPK signaling negatively regulates mTOR signaling.[207–209] The LKB1 complex, in response to an increase in the AMP/ATP ratio, regulates Aβ generation and the aberrant phosphorylation of tau.[47,210,211] Accordingly, it is possible that the LKB1/AMPK/mTOR signaling acts as a controller of Aβ generation and the aberrant phosphorylation of tau.

## HER2

HER2 (Human Epidermal Growth Factor Receptor 2), a member of the epidermal growth factor receptor (EGFR/ErbB) family, has been shown to play an important role in the pathogenesis and progression of AD, and it has evolved to become an important biomarker and target of therapy for AD.[212–215] Comprehensive research literature suggests that the activation of HER2 leads to Aβ production and the aberrant phosphorylation of tau through the regulation of MAPK, PI3K/Akt, protein kinase C (PKC), and signal transducer and activator of transcription (STAT) signaling, while these signaling pathways have all related to mTOR signaling.[216–219]

## IRS-1

Insulin receptor substrate 1 (IRS-1) serves an important biological function for both metabolic and mitogenic pathways

from the insulin and insulin-like growth factor-1 (IGF-1) receptors to downstream signaling pathways, including PI3K/Akt,[220] mTOR, the stress kinase c-jun N-terminal kinase (JNK), and MAPK/ERK.[221,222] Both IRS-1 and its downstream signaling pathways have been implicated in the pathogenesis and progression of Aβ generation and the aberrant phosphorylation of tau.[187,223,224] Many studies have also suggested that the interaction between insulin/IRS-1 and mTOR is a critical regulator of Aβ generation and the aberrant phosphorylation of tau.[164,187,193,225]

## The downstream components of mTOR signaling associated with AD

The eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and ribosomal protein S6 kinase 1 (S6K1) are well-known downstream targets of mTORC1 via an interaction between raptor and a TOR signaling (TOS) motif in S6K and 4EBP. Numerous findings have evidenced that downstream mTOR signaling might be causally linked to AD and deregulation of downstream mTOR signaling could be a novel mechanism for AD.[226,227]

### S6/S6K/p70S6K1

The p70 ribosomal S6 kinase (p70S6K) and S6, the most well-known downstream components of mTORC1, can phosphorylate tau protein and regulate Aβ production.[227–229] The levels of total p70S6K and p70S6K phosphorylated at Thr421/Ser424 are significantly correlated with the levels of both total tau and PHF-tau rather than at Thr389,[230] whereas zinc induces rapamycin-dependent p70S6K phosphorylation at Thr421/Ser424 and Thr389.[231] The p70S6K can also phosphorylate tau at S262, S214, and T212 sites, releasing tau from microtubules and resulting in microtubule disruption.[226] The level of p-p70S6K was significantly correlated with p-tau at S262, S214, and T212. These suggested that p70S6K is closely related to tau pathology in AD.[232] In AD patients, the level of ribosomal protein S6 is significantly increased, and phosphorylated forms of mTOR and p70S6k decreased in the cortex.[22] Moreover, the level of phosphorylated p70S6k is significantly decreased in the lymphocytes of Alzheimer's patients, and correlated with Mini Mental Status Examination (MMSE) scores, while the decline of cognition in AD patients corresponds to the decrease in p70S6k levels.[22,233]

### 4EBP1

The activation of mTORC1 leads to the phosphorylation of two main downstream components, 4EBP1 and S6K1. 4EBP1 inhibits the initiation of protein translation by binding and inactivating eIF4E (eukaryotic translation initiation factor 4E). mTORC1 can phosphorylate 4EBP1 at multiple sites to dissociate eIF4E from 4EBP1, inhibiting 4EBP1 on eIF4E-dependent translation initiation. The eukaryotic initiation factor 2alpha (eIF2α) levels are significantly increased in the lymphocytes of AD patients and significantly correlated with cognitive and memory test scores.[19] Similarly, increased phosphorylated eIF2α exists in AD patients' brains and may account for cognitive impairment by decreasing synaptic plasticity.[234,235] Phosphorylation of eIF2α is associated with the degeneration of neurons in AD due to the involvement in the autophagy process.[236] The mTOR/eIF2α pathway is responsible for a posttranscriptional increase in BACE1, which determines the Aβ pathogenesis.[237–239] A dramatic increase in phosphorylated eIF4E has occurred in the late stages of neurofibrillary changes. The level of eIF4E phosphorylation is markedly consistent with total and hyperphosphorylated tau, implying that the increase in eIF4E phosphorylation contributes to the formation of neurofibrillary changes.[240] Phosphorylated 4EBP, the substrates of mTOR, enhances tau protein synthesis in the hippocampus. Taken together, levels of mTOR and its downstream targets 4EBP1, eIF2, and eIF4E have a close association with tau pathology.[241]

## Conclusion and perspective

This review summarizes the roles of mTOR in the pathogenesis of AD and the advancements that the upstream and downstream components of mTOR signaling are involved in a wide variety of AD pathogenesis. The activation of mTOR enhances Aβ generation and deposition since the activation inhibits the autophagy/lysosome system, accounting for the Aβ generation and clearance. The activation of mTOR also modulates APP turnover via increasing β- and γ-secretase. mTOR may regulate Aβ generation via interaction with several key signaling pathways such as PI3-K/Akt, GSK-3, AMPK, and insulin/IGF-1. The activation of mTOR promotes the occurrence of tau pathology, whereas the inhibition of mTOR signaling retards the progress of tau pathology. It has been evidenced that the components of mTOR signaling are associated with the pathogenesis and progression of AD. These findings have implicated a profound clinical application for further development of interventions by inhibiting mTOR activation for the treatment and prevention of AD.

mTOR signaling plays a central role in maintaining protein homeostasis, and negatively regulates the autophagy/lysosome system. The activation of mTOR is involved in

the pathogenesis of AD, and inhibiting mTOR activity by rapamycin will rescue cognitive impairments and retard the progression of AD pathology. However, several studies point out that the activation of mTOR may benefit the recovery of AD pathology. Inhibiting mTOR activity seems to be a nonneuroprotective property and induces detrimental outcomes. Rapamycin increases Aβ generation by reducing the activity of a disintegrin and metallopeptidase domain-10 (ADAM-10), an important α-secretase candidate that inhibits Aβ generation.[242] Herein, the activation of mTOR may undertake a dual function in different situations. In acute stress, the activation of mTOR may be neuroprotective, and in chronic conditions, the activation of mTOR will be harmful. The activation of mTOR will benefit AD by slowing its pathologies, but whether it is an enemy remains uncertain. Thus, basic and clinical research is necessary to further clarify the roles of the mTOR activation in AD pathogenesis.

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## Disclosure

The authors report no conflicts of interest in this work.

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