

REVIEW ARTICLE OPEN

The mammalian target of rapamycin at the crossroad between cognitive aging and Alzheimer's disease

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Age-dependent cognitive decline is a major debilitating event affecting even individuals who are otherwise healthy. Understanding the molecular basis underlying these changes may increase the healthspan of the elderly population. It may also reveal insights into the pathogenesis of numerous neurodegenerative disorders characterized by cognitive deficits, as aging is the major risk factor for most of these disorders. Alzheimer's disease (AD), the most common neurodegenerative disorder, first manifests itself as deficits in encoding new memories. As AD progresses, these deficits spread to other cognitive domains that further debilitate the person before contributing to their demise. Suppression of the mammalian target of rapamycin (mTOR) increases healthspan and lifespan in several organisms. Numerous reports have linked alterations in mTOR signaling to age-dependent cognitive decline and the pathogenesis of AD. This review will discuss recent work highlighting the complex role of mTOR in cognitive aging and in the pathogenesis of AD.

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INTRODUCTION

People over the age of 65 years represent the fastest growing segment of the population. There will be an estimated two billion people in the world and 88.5 million people in the United States alone, over the age of 60 by the year 2050.^{1,2} These estimates suggest that aging and age-related diseases should be a top public health concern. Thus, discovering novel treatments that promote healthy aging and decrease the incidence of age-related diseases would have a major and long-lasting beneficial impact on the society.

Overwhelming data suggest that decreasing the activity of the mammalian target of rapamycin (mTOR) increases lifespan and healthspan. This effect has been found in several species, including *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster* and rodents.³ There is no direct evidence that inhibiting mTOR activity promotes healthy aging and increases longevity in primates. However, caloric restriction-mediated protection against some age-related changes in primates, including humans, appears to be mediated by reductions in mTOR activity.^{4,5} These findings suggest that mTOR is a valid molecular target at which to develop new approaches that promote healthy aging.

In addition, mTOR has a role in several neurodegenerative diseases including Alzheimer's disease (AD), Down syndrome, Huntington's disease and Parkinson's disease.^{6–8} Several laboratories have reported that mTOR is hyperactive in the brains of AD patients, and that this dysregulation may contribute to disease pathogenesis.^{9–11} However, not all studies agree with this notion.¹² This review takes a balanced approach and discusses seminal and current research findings regarding mTOR's role in brain aging and AD.

BRIEF OVERVIEW OF mTOR FUNCTIONS

mTOR is a serine/threonine protein kinase, which is involved in the regulation of both protein synthesis and degradation, longevity

and cytoskeletal formation.^{13,14} mTOR is the key catalytic unit of two separate large multimeric protein complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2; Figure 1). mTORC1 consist of mTOR, raptor, the mammalian lethal with sec-18 protein 8 (mLSTR8), the DEP domain-containing mTOR-interacting protein (Deptor), the Tti1/Tel2 complex and the proline-rich Akt substrate 40 kDa (PRAS40).¹³ mTORC2 consist of mTOR, rictor, mLSTR8, deptor, Tti1/Tel2 and mammalian stress-activated MAP kinase-interacting protein 1.¹⁵ mTORC1 is regulated by signaling from insulin, growth factors, amino acids and oxidative stress.¹⁶ It promotes cell growth and proliferation (by facilitating mRNA translation and protein synthesis), lipid biogenesis, regulates mitochondrial metabolism and modulates autophagy.^{17–19} In contrast, mTORC2 appears to be strictly under the control of growth factors and it is thought to function primarily in cytoskeleton assembly and cell size.^{20,21} Both mTORC1 and mTORC2 are involved in the regulation of longevity.^{14,16}

mTORC1 regulates protein translation mainly by controlling the activity of ribosomal protein S6 kinase-1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1), which directly control the activity of several initiation factors.^{15,16,22,23} Malnutrition, stress, insulin, growth factors and various other signaling pathways that converge on mTOR may differentially activate/inhibit protein synthesis.^{15,16}

Autophagy refers to the process in which old, damaged or misfolded aberrant proteins and/or organelles are degraded and their constituents recycled in lysosomes.^{17,24,25} Autophagy is important for maintaining proper function of cells within various organs including the brain.^{22,24,26–28} There are three major subtypes of autophagy: microautophagy, chaperone-mediated autophagy and macroautophagy. While macro- and microautophagy involve the "in bulk" degradation of regions of the cytosol, chaperone-mediated autophagy is a more selective pathway and only proteins with a lysosomal targeting sequence are degraded.^{25,29,30} In this review, we will focus on macroautophagy

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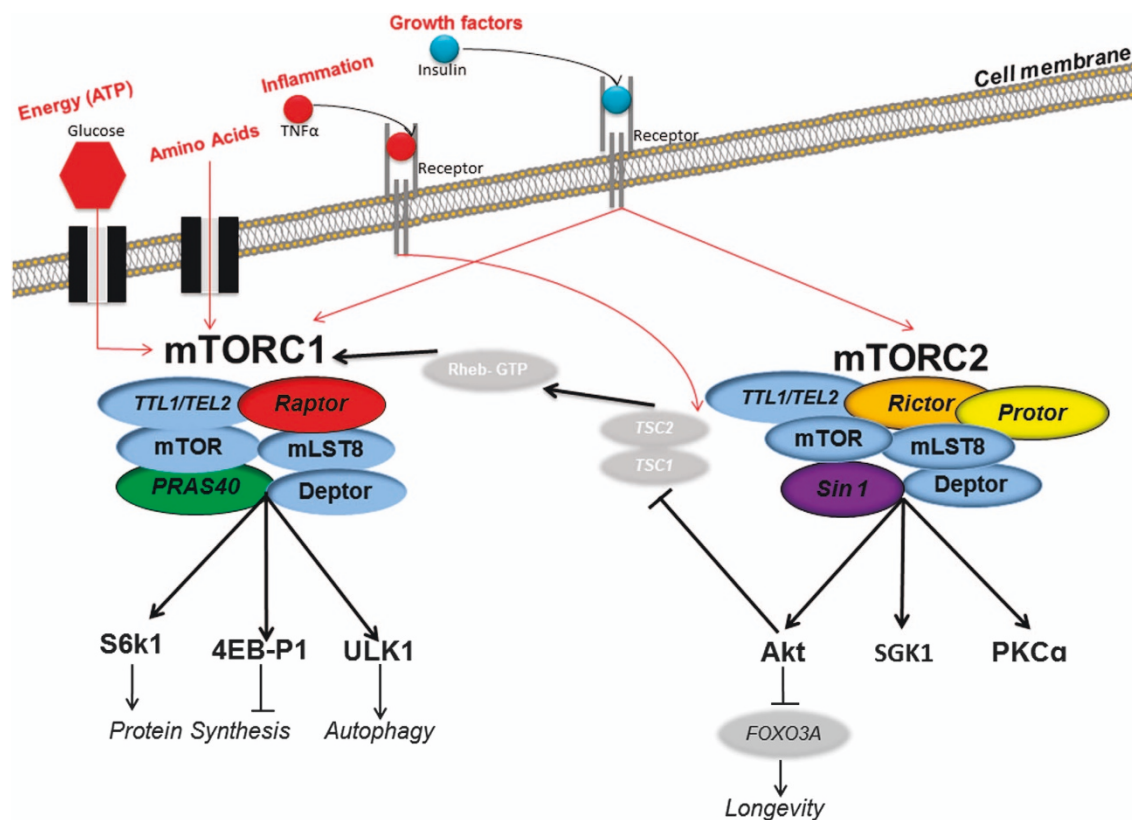


Figure 1. The mTORC1 and mTORC2 have distinct constituent proteins and regulate different downstream targets. Both mTORC1 and mTORC2 share the catalytic mTOR subunit, the mammalian lethal with sec-13 protein 8 (mLST8), the Tti1 and Tel2 complex and the DEP domain-containing mTOR-interacting protein (deptor), all depicted in blue. The mTORC1 contains the rapamycin sensitive raptor subunit (depicted in red) and the proline-rich Akt substrate 40 kDa (PRAS40; depicted in green). Downstream effectors ribosomal protein S6 kinase beta-1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) have a critical role in protein translation by regulating the activation of initiation factors. Inhibition of mTORC1 decreases the phosphorylation of ULK1, which initiates the sequential activation of several autophagy-related proteins, culminating in the formation of AVs. In contrast, the mTORC2 contains the rictor subunit (depicted in orange), the protor component (depicted in yellow) and the mammalian stress-activated MAP kinase-interacting protein 1 (sin1; depicted in purple). Downstream effectors of mTORC2 are involved in regulating longevity, cellular stress response and cytoskeletal dynamics. The mTORC1 receives signals from growth factors, glucose, inflammatory cell signaling proteins and extracellular amino acids. The mTORC2 receives signals primarily from growth factors. AV, autophagosome; mTORC, mammalian target of rapamycin complex.

as most of the work connecting autophagy to aging and AD is linked to macroautophagy.

Macroautophagy (herein referred to as autophagy) is a multi-step process by which proteins and cytosolic organelles are targeted for degradation and sequestered by a double or multi-membrane spherical structure known as an autophagosome (AV). After it is formed, the AV is delivered to the lysosome for degradation.³¹ mTORC1 is a negative regulator of autophagy.^{31,32} Indeed, inhibition of mTORC1 decreases the phosphorylation of ULK1, which initiates the sequential activation of several autophagy-related proteins, culminating in the formation of AVs.^{31–34}

mTOR IN AGING: AN OVERVIEW

The first evidence of TOR's involvement in aging came from work conducted in *S. cerevisiae*. Deletion of the gene encoding the yeast orthologue of S6K1 resulted in a doubling of the chronological lifespan.³⁵ Shortly after, inhibition of raptor or S6K1 was shown to extend lifespan in *C. elegans*.^{36,37} These initial studies have been confirmed and expanded to other species.^{14,38} To this end, a landmark report showed that rapamycin, an mTOR inhibitor, fed to genetically heterogeneous mice, increased their lifespan.³⁹ The involvement of mTOR in regulating lifespan in mammals has also been shown using two independent genetic approaches. The first

one highlighted that the deletion of S6K1, a downstream target of mTOR, extends lifespan and healthspan in both male and female mice by ~9%.⁴⁰ The second report found that mice with two hypomorphic alleles that reduce mTOR expression by 25% compared with wild-type levels showed an ~20% increase in the median lifespan.⁴¹ Notably, complete inhibition of TOR signaling during development leads to premature lethality,^{42–44} indicating that TOR signaling is an important and evolutionarily conserved regulator of longevity, which operates within a narrow range in order to maintain homeostasis and health. The role of mTOR in aging has been extensively discussed elsewhere.^{14,45}

mTOR, COGNITION AND BRAIN AGING

mTOR is highly expressed throughout the brain, primarily in neurons, but it is also found in astrocytes.^{46,47} In addition to regulating brain energy levels, mTOR is linked to synaptic plasticity and cognition.^{18,21,48} For example, mTOR activity is necessary for the expression of the late phase of long-term potentiation in the hippocampus, by modulating *de novo* protein synthesis after long-term potentiation induction.^{48,49} In addition, mTOR coordinates the timing and location for the synthesis of new proteins.^{48,49} A critical role for mTOR in cognition has also been shown by conditionally removing rictor, and therefore mTORC2 activity, from excitatory neurons in limbic and cortical

regions after development.⁵⁰ These conditional rictor knockout mice, which still have a fully functional mTORC1, are incapable of establishing long-term potentiation and consequently show cognitive deficits.⁵⁰ These deficits appear mediated by alterations in actin-dynamics, which are known to regulate the growth of dendritic spines necessary for memory formation.⁵⁰

Although mTOR activity is necessary for normal cognition, mTOR hyperactivity is also detrimental to brain function. The primary evidence comes from clinical cases of tuberous sclerosis, in which mTOR hyperactivity leads to cognitive deficits.⁵¹ Consistent with these observations, mTOR hyperactivity in mouse models of tuberous sclerosis is linked to synaptic and cognitive deficits.⁵² Mechanistically, the cognitive deficits in these mice are mediated by an inability to maintain late-phase long-term potentiation, which is regulated by mTOR activity.^{48,49} Interestingly, reducing mTOR activity via a 2-week administration of rapamycin ameliorates synaptic and cognitive deficits in tuberous sclerosis mice.⁵² The link between hyperactive mTOR signaling and cognitive dysfunction has been widely confirmed by others.^{53,54} Currently, there are ongoing clinical trials aimed at determining whether reducing mTOR activity with everolimus and sirolimus (two rapamycin analogs) ameliorates different aspects of tuberous sclerosis symptoms, including brain mTOR hyperactivity and cortical hyperexcitability (ClinicalTrials.gov Identifiers: NCT02451696 and NCT00490789). mTOR is also hyperactive in developmental disorders, such as Down syndrome, Rett syndrome and fragile X syndrome.⁵⁵

mTOR also has a role in cognitive decline associated with aging. To this end, life-long rapamycin administration ameliorates age-dependent spatial memory deficits in C57Bl/6 mice.⁵⁶ These rapamycin-mediated improvements were associated with decreased mTOR signaling and brain inflammation, as well as increased hippocampal NMDA signaling.⁵⁶ Notably, in the same study, mice that were given rapamycin at 15 months of age for 3 months show no detectable changes in cognitive functions.⁵⁶ These findings have been confirmed by independent studies, which suggest that in addition to cognition, rapamycin also improves anxiety-related behaviors.^{57,58} Further, the age-dependent decrease in autophagy function may lead to increased protein accumulation, which may interfere with normal brain function.^{22,26,32,34} Inhibition of mTOR increases autophagy induction, which presumably maintains cellular function during aging by counteracting the age-dependent protein accumulation. Given the role of mTOR in several signaling pathways, it is plausible that multiple molecular mechanisms might link the reduction of mTOR signaling to improvements in age-dependent cognitive function. Future studies are necessary to establish why reducing mTOR signaling in older mice has no effects on cognition. It is tempting to speculate that there is a critical period of time before, but not after which, changes in brain function that occur during aging can be mitigated by reducing mTOR. Identifying why some age-dependent changes in brain function are reversible and others are not may have long-lasting effects on the field's understanding of age-dependent cognitive deficits.

In summary, a large body of work spanning decades has revealed that mTOR signaling is an important regulator of protein homeostasis, by simultaneously controlling protein synthesis and protein degradation. Alterations in this delicate balance could disrupt the production of key proteins involved in synaptic plasticity leading to deficits in cognition. In other words, there is clear evidence that either excessive or insufficient mTOR signaling has detrimental effects on cognitive function.

mTOR AND AD

Amyloid plaques and neurofibrillary tangles, comprised primarily of amyloid- β (A β) and tau, respectively, are the histopathological hallmarks of AD.⁵⁹ A β is generated from the amyloid precursor

protein (APP), a soluble transmembrane glycoprotein.⁵⁹ The β -site APP cleaving enzyme 1 (BACE-1) cleaves APP to generate a C-terminal fragment of 99 amino acids (C99), which is then cleaved by the γ -secretase complex to produce A β .⁵⁹ Presenilin 1 (PS1) or PS2 are the major catalytic unit of the γ -secretase complex.

Tau, in its normal state is a soluble protein, which promotes microtubule assembly and stabilization.⁶⁰ In addition, tau regulates postsynaptic glutamate receptors, directly interfaces with synaptic signaling proteins and influences the function of synaptic mitochondria.⁶⁰ Pathological tau, by contrast, exhibits altered solubility properties, is abnormally phosphorylated and forms intracellular inclusions.^{61–64} Tau accumulation is not unique to AD and is found in other neurodegenerative diseases such as frontotemporal dementia with Parkinsonism, Pick's disease, progressive supranuclear palsy and corticobasal degeneration.^{60,65,66} The signaling pathways involved in AD pathogenesis have been reviewed elsewhere.⁶⁷ In the following sections, we will focus on the interaction between mTOR and the two hallmark lesions of AD, namely A β and tau.

A β and mTOR

The relationship between A β and mTOR has been extensively studied and a complex picture has emerged. Early *in vitro* reports showed that exposure of mouse neuroblastoma cells to 20 μ mol/l A β_{42} for 24 h was sufficient to decrease mTOR signaling.¹² However, when applied at lower and more physiological concentrations, A β has the opposite effects on mTOR signaling. For example, mTOR is upregulated in chinese hamster ovary (CHO) cells and mouse neuroblastoma cells (N2A) stably transfected with mutant APP.^{68,69} mTOR hyperactivity was also induced in wild-type N2A cells by application of A $\beta_{25–35}$.⁶⁸ In mutant CHO cells, which are known to secrete low concentration of low molecular weight A β oligomers,⁷⁰ the effects on mTOR were prevented by blocking A β production.⁶⁹ Consistent with these findings, intrahippocampal injection of naturally secreted A β oligomers was sufficient to increase mTOR signaling in the brains of wild-type mice.⁷¹

Work in transgenic mice has also generated conflicting results. To this end, it has been reported that 12-month-old APP/PS1 mice have lower mTOR signaling than age-matched wild-type mice,¹² which directly contradicts an earlier report showing hyperactive mTOR signaling in 9-month-old APP/PS1 mice.⁶⁸ In Tg2576 mice, mTOR signaling is downregulated in young pre-pathological mice. In contrast, in aged Tg2575 mice with established A β pathology, mTOR activity is similar to age-matched wild-type mice.⁷² Other reports have shown an age- and regional-dependent increase in mTOR signaling in 3xTg-AD mice.^{69,71} Notably, genetically or immunologically preventing A β accumulation was sufficient to reduce mTOR signaling to wild-type levels, indicating that mTOR hyperactivity was due to A β accumulation.⁷¹ The results in the 3xTg-AD mice are in agreement with studies in postmortem human AD brains, which consistently show an upregulation of mTOR signaling.^{73–78}

Although the mechanisms by which A β alters mTOR activity remain elusive, confocal microscopy data showed a direct interaction between intraneuronal A β_{42} and mTOR.⁷² Furthermore, the A β -mediated increase in mTOR activity can be prevented by blocking the phosphorylation of PRAS40, suggesting that the build-up of A β may facilitate PRAS40 phosphorylation.⁷¹ Consistent with this observation, the steady-state levels of phosphorylated PRAS40 were significantly higher in the brains of 3xTg-AD mice.⁷¹ In summary, a large body of evidence suggests a direct or indirect interaction between A β and mTOR; however, this picture is complex as both *in vivo* and *in vitro* work have often revealed opposite effects. Although it is hard to dissect the causes explaining these divergent effects, strain and age of the mice, as

well as different levels of A β can have differential effects on mTOR. For example, mTOR hyperactivity in 3xTg-AD mice precedes the formation of A β plaques and it is most likely due to high soluble A β levels.⁶⁹ In contrast, in APP/PS1 mice mTOR hyperactivity has been reported when the mice have widespread A β plaque deposits throughout the brain.¹²

Recent evidence suggests that, just as A β affects mTOR, mTOR also affects A β .¹⁰ This indicates that the two proteins interact closely with one another and elucidating the mechanism(s) of this interaction may reveal previously unknown aspects of AD pathogenesis. The first *in vivo* evidence indicating that modulation of mTOR signaling had a direct effect on A β pathology came from pharmacological studies using 3xTg-AD mice. Specifically, 3xTg-AD and wild-type mice were given rapamycin starting at the onset of cognitive deficits, for 10 weeks.⁶⁹ Rapamycin restored the hyperactive mTOR signaling in 3xTg-AD mice to control levels, rescued cognitive deficits and decreased A β and tau pathology.⁶⁹ This study highlighted a crosstalk between A β and mTOR as it demonstrated that reducing high levels of mTOR activity reduced A β deposition, just as the application of A β increased mTOR activity. Consistent with this finding, reducing mTOR signaling by rapamycin or temsirolimus, ameliorated AD-like pathology and cognitive deficits in hAPP(J20) mice or in APP/PS1 mice, respectively.^{79,80} Furthermore, rapamycin also reduced the formation of A β plaques and tangles when administered prior to their formation.⁸¹ Conversely, administration of rapamycin to 15-month-old 3xTg-AD mice, with established AD-like neuropathology, had no effect on cognitive deficits or plaque and tangle load.⁸¹ The rapamycin-mediated reduction in AD neuropathology was linked to an increase in autophagy induction,^{69,81} which may explain why rapamycin administration to mice with established pathology does not decrease A β or tau pathology. To this end, elegant work by the Nixon laboratory has shown that AVs accumulate in human AD brains as well as in a mouse model of

AD, suggesting a deficit in their clearance.^{82,83} Consistent with this theory, inducing autophagy after the deficit in autophagy flux occurs (most likely following AD-like neuropathology) would simply increase AV formation, which would fail to fuse to lysosomes for content degradation.^{10,25} Indeed, compelling evidence suggests that substrate-filled AVs drastically accumulate in AD and animal models.^{81–83} Thus, increasing autophagy induction (e.g., by rapamycin) may further lead to the accumulation of AVs, which may exacerbate AD pathogenesis as A β can be generated in and released from these vesicles.²⁵

Genetic studies strengthened the link between mTOR and AD pathogenesis. To this end, genetically and selectively reducing mTOR signaling in the brains of Tg2576 mice was sufficient to rescue memory deficits. This rescue of cognitive deficits was associated with reduced A β deposits and a change in the abnormal pattern of hippocampal gene expression of the Tg2576 mice to a more similar pattern found in wild-type control mice.⁸⁴ Collectively, these studies suggest that hyperactive mTOR in AD contributes to the accumulation of A β .

Tau and mTOR

The evidence linking mTOR to tau is less controversial and several laboratories have consistently shown that hyperactive mTOR contributes to tau pathology. In postmortem human AD brains, hyperactive mTOR signaling was found in neurons that were predicted to develop tau pathology.⁷³ Work in animal models has confirmed and expanded on this initial observation. Hyperactive TOR in *Drosophila* facilitates the development of tau pathology and the associated neurodegeneration.⁸⁵ Consistent with these observations, blocking TOR signaling rescued tau-induced toxicity, while genetically increasing TOR signaling enhanced tau-induced toxicity in *Drosophila*.⁸⁶ Mice with hyperactive mTOR also have increased brain levels of total and phosphorylated tau.⁸⁷

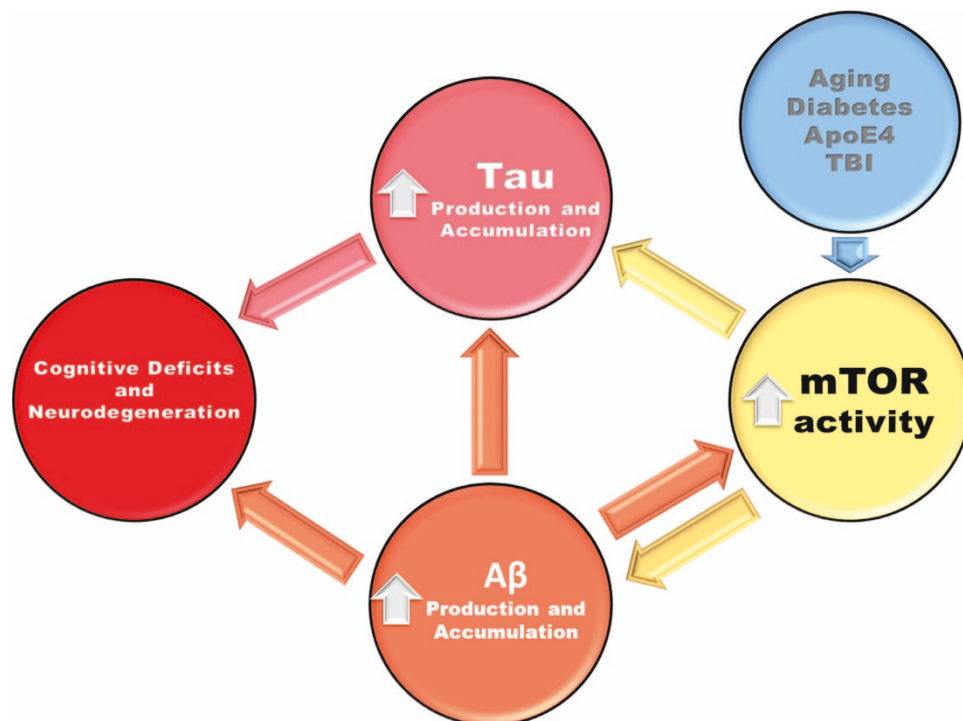


Figure 2. Diagram illustrating the proposed crosstalk among mTOR, A β and tau. In AD, hyperactive mTOR increases A β and tau production, A β positively feeds back on to mTOR further increasing mTOR activity. Many factors including diabetes, traumatic brain injury and ApoE4 may all influence the crosstalk of these proteins and the aberrant cycle they create leading to AD pathogenesis. AD, Alzheimer's disease; A β , amyloid- β ; ApoE4, apolipoprotein E4; mTOR, mammalian target of rapamycin.

Conversely, reducing mTOR has beneficial effects on tau pathology. To this end, reducing mTOR with rapamycin in a transgenic mouse expressing mutant human tau decreased tau pathology and improved the associated motor deficits.⁸⁷ Similar to these observations, chronic treatment with the rapamycin ester CCI-779/Temsirolimus in Tg30 mutant tau mice, decreased mTOR signaling, stimulated autophagy, reduced tau levels and neurofibrillary tangle density, which led to an attenuation of motor deficits.⁸⁸

The mechanism underlying these observations is likely multifactorial. For example, hyperactive mTOR signaling decreased autophagy turnover, which is a known degradation pathway for tau.^{89,90} mTOR can also regulate tau levels by increasing translation of its mRNA. Indeed, direct evidence from primary hippocampal neurons showed that inhibition of mTOR by rapamycin suppresses tau translation, while constitutively active mTOR signaling increased tau translation.⁹¹ In addition, mTOR can directly regulate tau phosphorylation. To this end, mTOR and S6K1 phosphorylate tau at multiple residues.^{92–94} mTOR also suppresses the activity of the protein phosphatase 2A, an enzyme known to remove phosphate groups from tau.^{13,95} One startling implication of these observations is that long-term exposure to hyperactive mTOR might increase tau translation and decrease its degradation/turnover, while concomitantly increasing tau phosphorylation. Collectively, these studies highlight multiple pathways by which mTOR signaling contributes to tau pathology.

CONCLUDING REMARKS

We propose a crosstalk between mTOR and the two neuropathological hallmarks of AD, A β and tau (Figure 2). Specifically, A β accumulation increases mTOR signaling, which in turn further increases A β accumulation by decreasing autophagy induction. mTOR regulates tau pathology by controlling its phosphorylation and degradation (via autophagy). Furthermore, mTOR directly increases overall tau levels by regulating translation of its mRNA. This model predicts that factors (e.g., environment, genetic) known to increase mTOR may contribute to the development of AD. Consistent with this prediction, several AD risk factors, such as high fat diet, diabetes, traumatic brain injury and the inheritance of the apolipoprotein E4 gene, also increase mTOR activity. In summary, mTOR plays a key role in aging and AD pathogenesis. Therefore, modulating mTOR activity is an attractive avenue to discover new therapies to enhance healthy brain and body aging, as well as attenuating age-related disease progression and treating age-related diseases, including AD.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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