Mammalian/mechanistic target of rapamycin (mTOR) complexes in neurodegeneration

Henry Querfurth* and Han-Kyu Lee

Abstract

Novel targets to arrest neurodegeneration in several dementing conditions involving misfolded protein accumulations may be found in the diverse signaling pathways of the Mammalian/mechanistic target of rapamycin (mTOR). As a nutrient sensor, mTOR has important homeostatic functions to regulate energy metabolism and support neuronal growth and plasticity. However, in Alzheimer’s disease (AD), mTOR alternately plays important pathogenic roles by inhibiting both insulin signaling and autophagic removal of β-amyloid (Aβ) and phospho-tau (p-tau) aggregates. It also plays a role in the cerebrovascular dysfunction of AD. mTOR is a serine/threonine kinase residing at the core in either of two multiprotein complexes termed mTORC1 and mTORC2. Recent data suggest that their balanced actions also have implications for Parkinson’s disease (PD) and Huntington’s disease (HD), Frontotemporal dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). Beyond rapamycin; an mTOR inhibitor, there are rapalog having greater tolerability and micro delivery modes, that hold promise in arresting these age dependent conditions.

Keywords: Alzheimer’s, mTOR, Rapamycin, Insulin signaling, Akt, Parkinson’s

Introduction

Aging represents the major biologic process common to most all neurodegenerations, driving the accumulation of damaging changes to organ systems and their cells over time. The core metabolic pathologies involved in chronic disease states of the central nervous system (CNS) are oxidative stress, inflammation, mitochondrial/energy failure and insulin resistance [1–3]. Neurodegenerative disorders are further distinguished from other chronic disease conditions such as cancer and cardiovascular disease by the deposition of characteristic misfolded proteins. Nevertheless, certain essential, universally shared cell signaling pathways become deranged in all of them. Mechanistic target of rapamycin (mTOR) refers to two protein complexes, mTORC1 and mTORC2, that function as master switches in the cell’s nutrient sensing pathways. The mTOR signaling pathway integrates extracellular growth factors and cellular nutrient status to regulate growth and metabolism during aging [4, 5]. It is of major relevance to neurodegeneration that intact mTOR signaling is critical to long lasting forms of synaptic plasticity (NMDA-R-dependent late phase LTP and mGluR-dependent LTD) [6, 7], as well as to spatial learning [8]. The evidence points in support of de novo synaptic protein synthesis by mTOR [9, 10]. Further, mTOR is necessary for dendritic spine morphological changes in association with LTP induction [11].

On the other hand, there is overwhelming evidence that decreasing mTORC1 activity, for instance via caloric restriction [12] or through dietary administration of rapamycin, increases lifespan in model organisms, including yeast, C. elegans, D. melanogaster, and mice [13, 14]. Even mice fed rapamycin beginning in later life lived longer [13–15]. It is noteworthy that primates also had extended lifespans with fewer age-related pathologies when calorically
restricted beginning in adulthood. This includes preservation of brain grey matter volume [16]. In addition to the above physiologic roles, the central role of mTORC1 signaling in the development of neurodegenerative diseases is a topic of great research and therapeutic interest. This is, in part, because mTORC1 not only supports protein synthesis via translation regulation, but controls both protein and organelle degradation through autophagy. The autophagy / lysosomal system is a cellular recycling process required to prevent the buildup of misfolded protein aggregates that contribute to the development of neurodegenerative diseases. These include β-amyloid (Aβ) and phospho-tau (p-tau) oligomers in Alzheimer’s disease (AD) and α-synuclein in Parkinson’s disease (PD), discussed below.

Herein, we first review the mTOR pathways and their regulation, prior to discussing complex changes in mTOR activity as are reported in various AD models. This is followed by summarizing its contribution to the pathogenesis of lesser studied neurodegenerative diseases including Parkinson’s disease (PD), Huntington’s disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal dementia (FTD). Throughout we emphasize alterations in autophagy and insulin signaling. The rationale and prospects for the treatment of neurodegeneration across disease contexts is laid out, based on both beneficial and deleterious effects of mTORC1 inhibition. We conclude with an argument favoring a balance involving mTORC2 stimulation.

Mechanistic Target of Rapamycin: Pathways and Regulation

mTORC1

The mTOR complex 1 (mTORC1) is comprised of the 289 kDa mTOR serine-threonine kinase, its rapamycin-sensitive regulatory protein Raptor, as well as three other proteins: GβL/mLST8, a 40 kDa proline-rich Akt substrate (PRAS40) and Deptor. It acts as a crucial cellular energy and nutrient sensor as well as growth factor (Insulin, IGF-1, BDNF) transducer. mTORC1 controls protein synthesis by phosphorylating downstream targets essential to mRNA translation [39, 40]. This action of AMPK there-
acids in an Akt-independent manner [54, 55]. Insight in this field came from studies on rodent and human skeletal muscle where infusion or ingestion of leucine (often in combination with resistance exercise) was tested to combat age-related muscle mass (sarcopenia) [56–58]. Mechanistically, leucine administration causes the mTORC1-mediated phosphorylation of both 4E-BP1 and p70S6K1, two proteins that each play critical roles in mRNA translation (4E-BP1 facilitates the interaction between the 5’-cap and the 40S ribosome, whereas p70S6K enables translation of poly-pyrimidine mRNAs) [59, 60]. As a result, BCAAs in normal concentrations induce protein synthesis in an mTORC1-dependent manner.

More recently, the mechanism of BCAA-induced mTOR stimulation has been expanded to involve a multiprotein complex on the lysosomal surface composed of: Rags (Ras-related GTPases), Regulator (an anchoring protein) and the vacuolar (H+)-ATPase (responsible for endosomal and lysosomal acidification) [61–63]. Another complex with similar function consists of Hvps34 (human vacuolar sorting protein 34) and phospholipase D1. These complexes recruit mTOR to the lysosomal surface, where it is activated by Rheb. Since mTOR is activated at the lysosome membrane and amino acids enable its translocation to the lysosome, normal mTOR activity is dependent on these anabolic amino acids [64].

The contribution of amino acid availability to mTORC1 activity in neurodegenerative disease is unknown. However, it’s worth noting that BCAA levels are positively associated with obesity and the development of type II diabetes mellitus (T2DM) [65, 66]. Further evidence suggests that excess BCAAs may be a marker of insulin resistance or even be causative [67, 68]. Considering that insulin resistance is an underlying pathology of several neurodegenerative diseases, it is plausible that excess BCAAs persistently overstimulate mTORC1, resulting in the p70S6K1-mediated negative feedback on IRS-1. The consequential uncoupling of insulin action, in turn, could promote protein catabolism and an increase in harmful aminoacidemia. Furthermore, the metabolites of BCAAs are mitochondrial toxins, thus inducing oxidative stress and further exacerbating the CNS insulin resistant phenotype. On the one hand, amino acid depletion is catabolic and stimulates autophagy. Also, as noted, supplemental BCAA might be beneficial in some instances. The negative role of excess BCAAs in neurodegenerative disease is speculative, but deserves further exploration.
Lastly, SIRT1, an NAD+-dependent and resveratrol-responsive deacetylase that enables caloric restriction-mediated longevity, negatively regulates mTORC1 [69] by interacting with TSC1/2 [70].

**mTORC2**

mTORC2 is a relatively (though not completely) rapamycin-resistant complex comprising mTOR and Rictor (rapamycin-insensitive companion of mTOR; thereby contrasting Raptor in mTORC1), in addition to GβL/mLST8, mSin1, PRR5/Protor and Deptor proteins. Therefore, both mTOR complexes share mTOR, mLST8 and Deptor, and are distinguished by Raptor and PRAS40 (mTORC1) and Rictor, mSin1, and Protor (mTORC2).

mTORC2 also differs from mTORC1 in terms of its regulation. mTORC1 and 2 are inhibited and activated, respectively, by TSC1/2 [34, 71]. Moreover, while not directly regulated by nutrients, mTORC2 is activated by trophic factors insulin/IGF-1 in a yet to be defined manner that requires PI3K and involves ribosome binding [72] (Fig. 2).

In terms of downstream targets, mTORC2 amplifies the activation of Akt by acting as an Akt-kinase (PDK2) (see excellent reviews: [73, 74]). mTORC2 phosphorylates Akt on Ser-473, secondarily to the phosphorylation of Thr-308 by PDK1 [75–81]. Ser-473 phosphorylation is required for full Akt activation. When mTORC2 function is impaired in skeletal muscle for instance, Akt function is diminished and glucose intolerance ensues [82]. Thus, mTORC2 opposes the indirect negative regulation of Akt by the mTORC1/IRS-1 pathway. Other targets of mTORC2 include the actin cytoskeleton and serum/glucocorticoid-regulated kinase 1 (SGK-1), which activates certain ion channels and regulates cell volume and growth [83, 84]. Thus, mTORC2 is important in cytoskeleton remodeling and electrolyte homeostasis. In the mouse CNS, conditional ablation adversely affects neuron morphology and post-synaptic excitatory currents [85], attesting to its functional importance in the brain.

Consistent with both mTOR complexes as having opposing effects on Akt, it makes sense that mTORC1 can also inhibit mTORC2 via Rictor (Thr-1135) and mSin1 phosphorylations through p70S6k1 action, in order to further dampen insulin/Akt signaling as part of a negative feedback system [86, 87]. Consequently, selective inhibition of mTORC1 with short-term rapamycin treatment (or with mTORC1-specific compounds [88]) may activate Akt by both relieving p70S6K-mediated IRS-1/Akt suppression [47] and permitting mTORC2-mediated activation. Long-term rapamycin on the other hand disassembles mTORC2, ultimately leading to insulin resistance [78, 89–91]. It is interesting that mTORC2 can mediate the degradation of IRS-1 that has been inactivated (pS307) by persistent mTORC1 [92].

**mTOR control of protein synthesis and autophagy**

mTOR’s control of protein synthesis and autophagy are thought to account for its contribution to neurodegenerative diseases. In general, mTOR supports protein synthesis by regulating cap-dependent translation through the phosphorylations of p70S6K and 4E-BP1 [72]. Rapamycin and related mTOR antagonists inhibit protein manufacturing in response to the cell’s energy needs and dietary state [93]. By supporting protein synthesis in dendrites and their synapses [17], mTOR promotes synaptic plasticity [7, 94] and hippocampal memory consolidation and maintenance [95, 96].

Parkinson’s disease protein 7 (PARK7, a.k.a. DJ1) is an example of a protein relevant to neurodegeneration, whose translation depends on mTORC1. PARK7/DJ1 has beneficial chaperone and anti-oxidant properties. Loss of function mutations in PARK7 cause early onset, recessive PD. Inhibition of mTORC1 with rapamycin reduced neuroprotective PARK7/DJ1 levels in rodent cortical synapses. Conversely, genetic over-activation of mTOR (using a TSC1 knock-out Tuberous Sclerosis disease model) doubles normal PARK7 levels. This observation highlights the nuance of therapeutically targeting mTOR, suggesting that blindly inhibiting...
mTORC1 could have negative consequences in certain conditions.

Autophagy (here referring to macroautophagy, as opposed to the lesser-studied microautophagy and chaperone-mediated autophagy), is a conserved cellular pathway for removing unnecessary or toxic protein aggregates and recycling damaged organelles (particularly mitochondria). Autophagy involves the formation of a double-membrane autophagosome around the protein or organelle targets, that later fuse with lysosomes, resulting in their degradation. It is activated by low nutrient availability, as well as by protein aggregation and organelle damage [97]. mTORC1 is a master negative regulator of autophagy, as mTORC1-mediated phosphorylations block complex formation between Atg13 (autophagy-related gene product) and the autophagy initiation protein, ULK1/2 (Unc-51 like kinase), thereby preventing autophagosome formation [98, 99]. mTORC1 further suppresses the induction of autophagy by interfering with AMPK’s direct phosphorylation of ULK1/2 [100]. Other mechanisms include negatively regulating TFEB, the transcription factor responsible for lysosomal biogenesis and inhibiting the activation of LC3BII/III [101] (Fig. 1). It should be mentioned that autophagy begins to fail in neurodegenerative disorders because itself becomes the target of toxic protein oligomers [97, 102].

The essential role of autophagy in neurodegeneration is demonstrated by the deletion of autophagy genes (Atgs), which results in age-dependent neurodegeneration and proteostasis in model systems [103, 104]. Pharmacological downregulation of mTORC1 enhances autophagy and is generally neuroprotective [105]. Lifestyle interventions that inhibit mTORC1 are also being investigated to arrest neurodegeneration [106]. As mentioned, amino acid deprivation inhibits mTORC1, reducing protein synthesis and stimulates autophagy. Nutrient rich conditions or basal neurotrophin availability reverse starvation-induced catabolic states, normalize homeostatic autophagy and promote neuronal survival [107]. Under neurodegenerative conditions however, inhibition of mTORC1 (e.g. by rapalogs or activation of AMPK), will stimulate autophagy and the removal of misfolded proteins [108, 109], including Aβ [110]. Mechanistically, these measures promote Atg transcription and recruitment to the phagophore by disinhibiting ULK-1/2 complex formation [111, 112].

Alzheimer’s disease
AD is the most common form of neurodegeneration (60%), impacting 10% of the world’s population over 65. The AD brain often features cerebrovascular pathology and is clinically overlapping or co-morbid with vascular cognitive impairment and dementia (VCID) in another 20% of cases [113]. AD is characterized by the accumulation of protein aggregates, namely amyloid β-peptide (Aβ) in the form of extracellular plaques and intracellular phospho-tau (p-tau) in the form of neurofibrillary tangles. The plaques become foci of an inflammatory reaction and neuritic dystrophy. These are associated with synaptic damage and neuronal loss, particularly in the hippocampal and the medial temporal/inferior parietal lobules regions of the brain, resulting in early memory dysfunction [114, 115]. Age is by far the greatest risk factor for sporadic Alzheimer’s disease such that prevalence of AD per age group is 3% in 65-74; 17% in 75-84; and 32% in ≥ 85 age range (www.Alz.org Facts and Figures 2020).

Lifespan Extension
As AD and PD are age-related diseases, the relationship between mTOR inhibition and the extension of lifespan is relevant to discuss. Increased longevity, often associated with an increase in cognitive health span, has been achieved in several in vitro and in vivo, transgenic and wild type rodent, model systems via means that inhibit mTOR, including: 1) down regulation of insulin/IGF-1 signaling pathway [116, 117], 2) caloric restriction/SIRT1 stimulation [70, 118] and 3) mTOR inhibition with rapamycin treatment [119]. A particularly impressive study demonstrated that, in mice, carbohydrate restriction decreased mTORC1 activity, increased the resilience of memory function to ageing, and increased median lifespan by 13% [120].

The evidence for lifespan extension in mice fed rapamycin or primates placed on caloric restriction, even when implemented in adulthood was raised earlier. This sits favorably with the neuroprotective role of rapamycin in AD models, as will be discussed below. In contradistinction to the longevity research, there is a large body of evidence favoring the upregulation, or at least restoration, of insulin/IGF1 signaling for neuroprotection in symptomatic AD [121, 122]. Since insulin also activates mTOR, this may seem counterintuitive. However, as we consider AD and insulin resistance, as well as disease stage, inhibiting just mTORC1 may sufficiently reset insulin sensitivity.

Insulin Resistance
After ageing, systemic insulin resistance and diabetes also present as risk factors for AD [123], resulting in an odds ratio (~2.0), almost on par with inheriting a single APOE4 gene allele [124–126]. In support of a causal relation, experimental diabetes is shown to drive AD pathology [127, 128]. It is also well accepted that the AD brain is itself characterized by a unique form of diabetes mellitus, so called ‘type III DM’. The evidence points to a combination of insulin deficiency [129], attenuated insulin receptor expression [130] and insulin resistance [131, 132]. The mechanisms behind the insensitivity of the PI3K/Akt/mTOR pathway to the anabolic and neuroprotective action of insulin/IGF-1, are also multiple and include reduced ligand binding to cognate receptor (e.g. IR), IRS-1 deactivation or
desensitization, as well as other more downstream signal transduction impairments [133–136]. Exposure to synthetic or expressed Aβ peptide is experimentally shown to result in each of these, for example demonstrating that Aβ can compete with insulin for insulin receptor binding [137, 138]. Disruption of insulin/Akt signaling may also be induced in the live brain by exposure to neurotoxic Aβ oligomers, as shown in monkeys [139]. This cerebral insulin resistance can result in decreased synaptic activity and density [1, 140]. Correspondingly, stimulation of the insulin/mTOR pathway downstream of insulin, using Akt or PI3K activators, has been shown to rescue synaptic density and plasticity in rodent models of AD [141, 142].

mTORC1 in Alzheimer’s Disease and Down Syndrome: Hyperactivation
Numerous reports have linked altered actions in mTOR signaling to age-dependent cognitive decline and to the pathogenesis of AD [143]. However, there are differing accounts of mTOR status in AD brain, transgenic mice and cell models. Several groups report dramatic up-regulation of basal (unstimulated) mTOR signaling markers in AD, mild cognitive impairment (MCI) and preclinical AD patients. These include increased p-Akt (Ser473), p-PI3K (Tyr508), p-mTOR (Ser2448), p-p70S6K (Thr389) and p-4E-BP1 (Thr37/46) over their respective total protein levels. One group took these as evidence for the general overactivation of the PI3K/Akt/mTOR signaling axis and made further correlations with decreased autophagy marker expression and increased inhibitory phosphorylation of IRS-1 [50, 51]. Similar abnormal activation markers have been found by several other groups [137, 144–151] (see Table 1). It is likely that these changes in mTOR activity are disease stage dependent. To illustrate, hyperactivation of mTOR is found in early to mid-stage AD brain by some [145, 178], but only in severely affected AD cases by others [152].

The same hyperactivation of mTOR and Akt, as well as changes in autophagy markers and substrate p-p70S6K, are found in the Down Syndrome (DS) brain. These correlate with tau hyperphosphorylation [153]. The neuropathology of AD and DS similarly involves impaired mitochondrial function, increased oxidative stress, and proteostasis from derangements in the pathways that maintain the structural, quantitative, and functional stability of intracellular proteins [179]. The interconnected systems that govern protein homeostasis include the ubiquitin-proteasome system, autophagy network, endoplasmic reticulum, and mTOR pathway [180].

The molecular causes behind the autonomous basal activation of PI3K/Akt (and mTOR downstream) have not been completely worked out. PTEN is a protein tyrosine and lipid phosphatase that negatively regulates PI3K/Akt/mTOR by removing a phosphate from the essential lipid signaling molecule, PI3P (phosphoinositol 3,4,5 triphosphate) to generate PI2P. First, it is suggested that Aβ directly inactivates PTEN (phosphatase and tensin homolog) and thereby disinhibits PI3K [51, 154]. mTOR was found overactivated in PTEN knockout mice and levels of neurodegeneration protein markers accumulate in hippocampal synaptosomes [181]. Paradoxically, PTEN was also found to positively regulate neuronal insulin signaling in N2a cells. This was ascribed to its protein phosphatase action in preventing detrimental ERK activation. PTEN suppression increased hyperphosphorylation of Tau [182]. These reports contrast with data collected on both transgenic (PS1/APP 2X) and in vitro viral-mediated AD models, where PTEN inhibition actually rescued synaptic and cognitive (object location and fear conditioning) impairments [183]. The beneficial effect of the PTEN inhibitor was mediated by the stimulation of PI3K/Akt. Conversely, PTEN overexpression led to synaptic depression (decreased LTP, augmented LTD). Aβ peptides applied to primary hippocampal neurons induced the same synaptic defects and dephosphorylations of Akt and GSK3 by recruiting PTEN to dendritic spines where it becomes overactivated [183]. A similar contrast in PTEN involvement is reported in AD post mortem brain, finding decreased inactivated (phospho) PTEN in one report [184] and PTEN downregulation (and Akt hyperactivation) in another [145]. Interestingly, mutations in the PTEN-induced kinase-1 (PINK-1), a ubiquitin kinase participating in mitochondrial quality control, cause recessive early onset Parkinson’s disease [185].

In addition to PTEN, the other major negative regulator of mTOR activation is AMPK (AMP-activated protein kinase), a master cell energy sensor that is stimulated (phospho-Thr 172) during low substrate stress. Activators of AMPK affect Aβ metabolism: resveratrol increases Aβ clearance by stimulating mTOR-sensitive autophagy [186] and quercetin reduces Aβ generation by AMPK-mediated downregulation of BACE-1 expression [187]. Aβ oligomers reciprocate by inhibiting AMPK activity and causing insulin resistance [188].

Next, the resistance to insulin/IGF action that characterizes AD brain has been mechanistically linked to the inhibitory feedback phosphorylations of IRS-1 (S616 and S636) by pS6K [136, 178]. Aβ has also been implicated in this phenomenon too by directly activating mTOR (and indirectly, mTOR target p70S6K) in studies using transgenic models [155, 156, 189]. Aβ enables the phosphorylation of PRAS40, an inhibitory subunit of the mTOR complex, thereby releasing mTOR activity [156]. The consequence is a decrease in IRS-1 levels [178, 190]. Here too there are conflicting reports, for instance a study in transgenic 2576 mice where Aβ is also co-localized to mTOR, but instead having an inhibitory role [157].
Actual insulin resistance was convincingly first demonstrated in post-mortem AD brain by Talbot et al [136]. Interestingly, it was the inhibited PI3K/Akt signaling response to insulin stimulation that was most impressively reduced (90%) in these viable human samples, even overshadowing the basal hyperactivated status of Akt and mTOR under unstimulated \textit{ex vivo} conditions. As pointed out, the targeting of IRS-1 for phosphorylation may actually involve kinases other than mTOR/p70S6K [136]. Additional mechanisms of proximal insulin resistance include reduced numbers and activity of Insulin and IGF-1 receptors [178, 191].

\textbf{β-Amyloid}

In cell models, using either transgenic primary cortical neurons (PCNs) or control PCNs exposed to Aβ oligomers, the abnormal hyperactivations of Akt (p-S473) and mTOR (p-4EBP1) were associated with aberrant cell cycle reentry [154]. In addition to the cell culture studies, \textit{mTOR} signaling was found to be abnormally upregulated after direct injection of Aβ oligomers into mouse hippocampus [156]. Basal (unstimulated) \textit{mTOR} signaling increases are also described in triple (3x) AD and PDAPP transgenic mice. In these models, inhibition of \textit{mTOR} with rapamycin rescued early learning and memory deficits and activated autophagy [156, 192]. In further experiments by the same group, intra hippocampal anti-Aβ antibody injections normalized the abnormal activation of \textit{mTOR}. In their model, Akt hyperactivation was deduced to drive PRAS40 phosphorylation, thereby de-repressing \textit{mTORC1} [156]. Recently, either genetic suppression or anti-Aβ immunization corrected abnormally hyperactivated \textit{mTOR} and Akt in transgenic APP mice [162]. Consistent with these findings, Metformin was reported to attenuate spatial

| Model system | mTOR signaling | Akt signaling | Reference |
|--------------|----------------|--------------|-----------|
| AD or DS Brain | Transgenic cell culture | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
memory deficits in double (2x)APP/PS1 mice by enhancing AMPK activation, leading to the reversal of abnormal hyperactivated mTOR [163].

Abnormal mTOR activation enhances both Aβ deposition (by inhibiting clearance) and possibly generation (indirectly, via insulin resistance, insulinemia and hyperglycemia) [137, 173, 192, 193]. Accordingly, either rapamycin treatment or AMPK-activation, by inhibiting mTORC1 and stimulating the autophagy machinery (Atg-1/ULK), are shown to enhance Aβ clearance, reduce deposition, and abate pathology in transgenic AD mice [110, 192, 194–196]. Direct effects of mTOR pathway components on the α-secretase processing of APP (preventing Aβ generation) or β- and γ-secretase amyloidogenic activities have not been extensively investigated. The anti-diabetic drug metformin activates AMPK, a negative mTOR regulator and stimulator of autophagy, promoted beta and gamma secretase cleavage activities and resulted in Aβ generation in SH-SY5Y cells and in an AD mouse model [197]. To the same end result, rapamycin treatment of APP-transfected N2a cells or transgenic AD mice resulted in enhanced Aβ production, but by inhibiting ADAM-10, an important α-secretase candidate [198]. Nevertheless, this area also requires more clarification as there is data pointing to an under-regulation of Rheb GTPase, a strong mTOR activator, that is correlated to elevated levels of BACE-1 in AD brain and where over-expression of Rheb reduced Aβ generation [199].

Finally, insulin impairments in transgenic AD mice were also found to be mTOR dependent. For instance, an improvement in central insulin dysregulation and reversal of impaired cognition was demonstrated when brain mTOR activity was genetically lowered by one copy in Tg2576 mice [161]. In another amyloid-based model with AD-like brain pathology, rats with T2DM and injected in the hippocampus with Aβ, revealed over-activation of the mTOR signaling pathway and suppression of activated AMPK. Rapamycin treatment produced a reduction of p-mTOR and partially restored p-AMPK levels, causing a reversal Aβ and tau deposition in the hippocampus and improvement in learning and memory [200].

**Tau**

Regarding the tau pathology in AD, mTOR hyperactivation may also be responsible for hyperphosphorylation and cytoplasmic vacuolar collections of tau [201]. By acting on multiple Tau kinases (e.g. p70S6K) [158], as well as by inhibiting PP2A (the major Tau phosphatase), an overstimulated Akt/mTOR axis can drive tau hyperphosphorylation [144, 146, 158, 201–204]. The role of GSK3β (Tau kinase-1) in this context is however uncertain, since Akt, if stimulated by Aβ as hypothesized, would be expected to and does drive GSK inhibition (phospho-S9) [51]. In any case, activated mTOR marker levels positively correlate with neurofibrillar tangle (NFT) load and total- and paired helical filament (PHF)-Tau burden [144, 146, 205, 206]. Abnormal mTOR activity can also drive excessive Tau mRNA translation, via p70S6K [144]. Consistent with this, rapamycin (by inducing autophagy) retards cognitive decline and clears tau pathology [155, 207].

Notably, AMPK is also a tau kinase (Thr231 and Ser 396/404). Activated phospho-AMPK (p-Thr172) accumulates in tau tangle-bearing AD neurons and in other tauopathies [208]. Increased p-AMPK, as well as the indirect mTOR target, p-eEF2K (via p70S6K), were also demonstrated by Western technique in postmortem AD and 2x APP/PS1 transgenic mice brain extracts. This pathological hyperactivation of AMPK correlated with impaired LTP and was rescued by an AMPK inhibitor, but mTOR status itself was not tested [172]. The concurrent activations of mTOR and AMPK were both found in post mortem AD brain and co-localized with Tau pathology [147]. This is an interesting pairing given the likelihood of overactive AMPK to both inhibit mTOR and to directly phosphorylate eEF2K, a repressor of protein elongation by phospho-inactivating eEF2. These two actions would reduce de novo synaptic mRNA translation and inhibit LTP neural plasticity [209]. AMPK activation may also reflect a compensatory response. Recently it was discovered that expression of the AMPKα1 isoform is increased in post mortem AD hippocampus and in AD mice models. Brain specific repression of this isoform in model mice alleviated: cognitive deficits (novel object recognition and spatial learning and memory in the MWM), restored hippocampal LTP, improved spine morphology and blunted the abnormal inhibitory hyperphosphorylation of eEF2 due to overactive AMPK, thereby increasing de novo synaptic protein synthesis [210]. These studies may paint a consistent picture of abnormal AMPK activation in AD, but it remains unproven if either AMPK or PTEN activation attenuate or aggravate AD pathology [211].

In a Drosophila Tauopathy model, mTOR activation was found to mediate cell cycle reentry and neurodegeneration [212] and blocking mTOR signaling rescued Tau-mediated toxicity in such flies [213]. The same neuroprotection was afforded by rapamycin in tau transgenic mice [202, 214] and in mice stereotactically injected with AAV-hTauP301L into the hippocampus [176]. Suppression of mTOR with rapamycin thus mitigates both Aβ and tau pathologies.

**Autophagy**

In addition to the insulin signaling derangement, the autophagy system of protein disposal and recycling is altered in AD [51, 215]. Autophagy is a major clearance mechanism for Aβ in neurons, working alongside
microglia, the Ubiquitin Proteasome System (UPS) and amyloid degrading enzymes [216–218]. In the early stages of AD or in animal model brains, autophagic vacuoles accumulate in dystrophic neurites. However, rather than primarily caused by changes in mTOR, it appears to come about primarily because lysosomal acidification, autophagosome fusion and/or clearance are reduced, resulting in net impairment of autophagic flux [194, 215, 219]. Nonetheless, inductions of autophagy-related protein Atg5, Beclin-1 and ULK-1 probably play a role in Aβ degradation, as demonstrated using a small molecule rapamycin enhancer or starvation in APP expressing N2a cells [108]. Autophagy marker levels (Beclin-1, LC3) were found decreased in mild cognitive impairment (MCI) and AD brain. This loss of autophagy correlated negatively with amyloid load and was associated with a hyperactivated PI3K/Akt/mTOR axis [51]. Consistent with these observations, the suppression of mTORC1 by rapamycin, induces autophagy flux and ameliorates cognitive deficits in transgenic mice [220]. Genetic reduction of mTORC1 in Tg2576 AD mice also reduced Aβ pathology, stimulated autophagy and rescued memory deficits [160]. Abnormal p-tau levels and pathology can also be cleared by mTOR-dependent autophagy [112, 221], an outcome similarly observed in 3x transgenic AD mice treated with rapamycin [155, 192]. Not surprising, p-Tau in turn may also impair autophagy [222].

**Synaptic Protein Synthesis**

Complementing mTOR’s role in suppressing protein removal, is its positive regulation of mRNA translation and protein synthesis at synapses. Ribosomes and mRNA are transported from soma to dendritic spines where mTORC1/2 are active [7, 10] and have an important role in plasticity and learning [9, 223]. One example of a TOP (5’ terminal oligopyrimidine)-mRNA that is translated in dendrites following LTP induction and mTOR activation is the elongation factor protein eEF1A [224]. Other mTOR-dependent, rapamycin-sensitive, specific synaptic target proteins driven by activity or BDNF/Insulin stimulation include NMDA-R, CamKII, PSD-95 and Arc [96, 225, 226]. How then is protein synthesis affected in the various neurodegenerative syndromes? The purported hyperactivity of mTOR in AD would be expected to result in excessive and detrimental synaptic protein synthesis. Genetic examples of this phenomenon include tumor growth in Neurofibromatosis 1 and Tubercous Sclerosis, wherein PI3K/Akt and mTOR are upregulated, respectively. Moreover, cognitive deficits and autism define both illnesses [227, 228]. The identity of the excessively translated mRNAs is however not yet clarified. Another example of mTOR-dependent synaptic protein synthesis and phosphorylation is the loss of function of the translational repressor, FMR protein, in the Fragile X syndrome - also defined by mental retardation and autism [229, 230]. The depressed translation of mRNA results in excessive proteins synthesis [231]. Returning to AD, despite reports citing overstimulation of mTOR, activity-dependent synaptic translation was impaired, not increased, in both an AD mouse model and in post-mortem AD brain. ROS-mediated damage to Akt and mTOR in the signaling pathway was the cited reason [168]. It remains for future research to determine if the mTOR-dependent production of other plasticity relevant proteins in dendritic spines such as NMDA-R1, αCaMKII, CPEB, and Arc [232] are affected in any of the neurodegenerative conditions.

**Vasculopathy**

Briefly, vascular dysfunction in AD is characterized by chronic hypoperfusion, blood brain barrier disruption, reduced vascular density and reactivity and impaired neurovascular coupling. Here too, unchecked mTOR activity has a deleterious role, in part by inhibition of NOS and decrease in NO (nitric oxide) bioavailability [233]. Transvascular Aβ clearance is also reduced. mTOR attenuation by rapamycin in hAPPJ20 AD mice can accordingly lessen these changes [234].

**mTORC1 in Alzheimer’s Disease and Down Syndrome: Hypoactivation**

In contrast to the aforementioned reports concluding hyperactivation of mTOR in various AD models, a substantial number of groups point to no change or even down-regulation of mTOR signaling, as well as neuroprotection from actually stimulating mTOR. These also deserve mention for balance (Table 1). For instance, in a recent study of autopsy brain, levels of p-mTORC1 (S2448 or S2481) and of total mTOR, revealed no statistical differences across the clinical groups (AD vs. control) [235]. In PDAPP mice, there is no reported difference in mTOR target p-p70S6K levels between untreated transgenic and wildtype mice [192]. On the other hand, p-mTOR (pS2448) and p-p70S6K were reduced in N2A cells affected by aggregated Aβ42 treatment, in 2x transgenic APP (sl)/PS1(M146L) mouse cortex and in AD lymphocytes, compared to controls [166, 236]. Moreover, APP (swe)/PS1(deltaE9) 2x transgenic mice display increased autophagic activity accompanied by decreased mTOR activity [237]. In yet another 2x model, APP (sl)/PS1(KI), mTOR itself was unchanged but downstream activation of p70S6K (pT389) was reduced rather than stimulated [171]. Consistent with these studies, but using a growth factor stimulation paradigm in rat PCNs, Aβ treatment inhibited BDNF-induced Akt/mTOR signal activation [173]. Similar inhibition of neurotrophin-stimulated Akt/GSK3-β-9 phosphorylations were found in N2a cells exposed to oligomeric Aβ-
containing fractions obtained from 2x AD transgenic mouse brain [238]. In the presymptomatic Tg2576 model, an early impairment of long-term potentiation (LTP) was correlated with inhibited mTOR signaling (lowered p-p70S6K and p-4E-BP1), similar to results in wild type brain slices exposed to either Aβ peptide or rapamycin [157, 239]. In the same model, up-regulation of mTOR rescued LTP [170]. The role of systemic insulin resistance in modifying mTOR signaling in AD was recently probed using two rat models; (‘T2DM’: intraperitoneal streptozotocin (STZ) on high fat diet and ‘AD’: hippocampal Aβ injection). In comparing the Control, T2DM, AD and T2DM+AD animal groups, total mTOR protein and mRNA levels in the hippocampus as well as the phosphorylation of tau protein were significantly increased only in the combined T2DM+AD group, not in the AD alone group compared to control [240]. How the sustained mTOR hyperactivation phenotype required concurrent Aβ toxicity and systemic insulin resistance is not clear. An intracerebral STZ-induced AD rat model evidenced reductions in all of Akt, IRS, p70S6K and mTOR, but p-mTOR was not tested [241]. Inhibited mTOR activity (p-p70S6K1), reduced fear conditioning memory and plaque pathology each characterize the 5X-transgenic AD mouse model. These defects were all rescued with an inhibitor of GSK3β, providing a novel mechanism to restore mTOR activity, reduce autophagy and improve lysosomal acidification. Tau pathology was not reported [177]. Finally, the reduction in mTOR signaling and basal phospho-Akt marker levels, as well as enzymatic activities, in synaptosomes from 2xAPP/PS1 mice and post-mortem AD brain, was correlated with inhibited BDNF-stimulated protein translation. Oxidatively damaged synaptic Akt was held responsible and Akt enhancement rescued protein translation [168]. The role of oxidative stress in AD-associated insulin resistance is elsewhere reviewed [242]. The observation that Aβ may stimulate AMPK, perhaps a compensatory effect, may partially explain the reduction in mTOR activity observed in some of these studies [135, 195, 243].

mTORC2 in Alzheimer’s Disease

Some studies have started to look separately at mTORC1 (Raptor) and mTORC2 (Rictor). One group found neither total- nor phospho-mTOR levels (nor specific total and p-Raptor of mTORC1) were significantly changed in early to moderate AD hippocampus compared to control. p-mTORC1 and p-Raptor was however significantly increased in severe AD. The same work reported that Rictor (of mTORC2) levels were unaltered in AD [152]. In our work, both total mTORC1 and 2 (rictor) levels and respective enzymatic activities were reduced in advanced AD brain and transgenic models. Autophagy markers were increased and protein synthesis was inhibited [135]. Nevertheless, phospho-mTOR / total-mTOR was increased and we also found that application of rapamycin, by further reducing mTORC1, was cytoprotective. Interestingly, overexpression of Rictor was similarly beneficial. A proteomics study of neural cells expressing wild type mTOR also concluded up-regulation of C2, but not C1, increased cell viability by facilitating pro-survival and suppressing caspase-mediated apoptotic genes and by stimulating p-Akt (Ser473/Thr308) [244]. These results in AD models are consistent with mTORC2 survival promoting functions [245, 246].

In conclusion, we noted AD models in which baseline mTORC1 is abnormally over-activated and other models in which markers of activation (e.g. p-p70S6K) are either unchanged or reduced. One obvious reason for contradictory findings reported by various laboratories in the activation state of mTOR and signal kinases in general is that the various disease models and/or assays may not comparable. The upstream factors that negatively control mTORC1 activation such as PTEN, AMPK and TSC1/2 (also a positive regulator of mTORC2 [71]) are not always assessed but may themselves be the proximate cause of variation between cell lines and models [87]. Another is that attention to both basal conditions and activation testing under neurotrophic stimulation is not always undertaken. A third is that phosphoprotein levels alone may not always be a proxy for actual enzyme activity in certain situations. An example of dissociation is that mTORC2 and PI3K can maintain Akt phosphorylation (perhaps compensatory) in the presence of a pharmacologic inhibitor of Akt activity (resulting in disruption of downstream GSK3β phosphorylation) [247]. There is also the disease stage and/or time course of experimental perturbation that needs to be controlled. For instance, the regulator of mTORC1 and target of C2, Akt (as well as its substrate GSK3β) undergo a biphasic, age dependent change in phosphorylation in PS1xAPP transgenic mice hippocampus (6 mo.-Akt activation vs. 18 mo.-Akt inhibition). This depends on the ratio of soluble APPα and oligomeric Aβ along the disease time line [238]. Duration of Aβ exposure showed similar biphasic results in primary neurons. With aging, changes in NMDA- and α-nicotinic ACh-receptors were implicated in biphasic opposing directions of Akt status [248]. Paradoxes such as rapamycin inhibiting mTOR-dependent synaptic plasticity-yet is neuroprotective in the various AD models (see below)- may find explanation in signal feedback and cross-talk complexity. For instance, rapamycin, while inhibiting mTORC1, can also induce Akt phosphorylation with overriding beneficial actions (in addition to the stimulation of autophagy). It does so by inhibiting p70S6K-T389 phosphorylation, thereby stabilizing IRS-1 [249, 250].

Regardless of the contradictory reports, most agree that the response of the Akt/mTOR axis to neurotrophin/insulin stimulation is suppressed in AD, consistent with a state of insulin resistance, and that mTORC1 inhibition with rapamycin is neuroprotective, reduces proteinopathy and...
actually restores memory formation and maintenance [155, 192]. Conversely, stimulation of mTORC2 might be beneficial. This underscores the duality of mTOR roles in health and disease with respect to synaptic plasticity [251].

Parkinson’s Disease

Sporadic PD is the second commonest neurodegeneration after AD. Aging is again the primary risk factor, as it affects 1-2% over age 65. Here mTOR also emerges as a novel therapeutic target [81, 252]. There is a large body of evidence that mTOR is perturbed in PD models [253, 254]. Perhaps more so than AD, oxidative stress (ROS) is a major contributor to the selective degeneration of dopaminergic neurons in PD [255]. A major source of ROS are the mitochondria in PD that are deficient in electron transport Complex 1 activity. In the MPTP-treated mouse model of PD for instance, mitochondrial ROS are shown to stimulate apoptosis [256]. Various other neurotoxins (e.g. ceramide, rotenone, H2O2, 6OH-DA, paraquat) are also used to model PD pathophysiology. In general, these manipulations suppress mTOR/Akt activity and restoring mTOR functions by overexpressions of either the wild type form or p70S6K rescues neuronal death in these models [254, 257]. In alignment with this view, rapamycin predictably potentiates the oxidative stress [258, 259]. One mechanism of ROS-mediated inhibition, at least as uncovered from using AD-affected synaptosomes, is oxidative damage to Akt/mTOR signaling enzymes, resulting in the functional loss of activity-dependent protein translation [168].

A significant body of data implicates pathologic induction of the gene for REDD1/RTP801 protein in Parkinson’s disease, the only function of which as a regulator is to suppress mTOR [253]. Up-regulation of RTP801 is shown in various PD neurotoxin cell models (6OHDA, rotenone and MPP+), as well as in post mortem PD substantia nigra neurons. RTP801 experimentally promotes cell death (protected by knock-out) via an interaction with TSC (relieved by TSC shRNA) to inhibit mTOR function (reducing p-mTOR and p-p70S6K levels). The TSC-2 requirement was confirmed [260]. Although mTOR activation status in PD brain was not reported on, it is clear that activation of the cell survival kinase Akt (phosphory T308 and S473) was inhibited in PD brain and experimentally reproduced in cells. Constitutive Akt expression also protected PC12 cells from either RTP801 or 6OHDA) [261]. The additional mechanism advanced to explain this phenomenon is that REDD1 also blocks mTOR-dependent phosphorylation of Akt. Accordingly, mTOR overexpression protected cells from 60HDA toxicity. Other examples of mTOR overexpression as beneficial to correct the deficiency were in an AD model cited earlier [157] and in a HD model discussed below.

On the flip side, there is a PD mouse model, where mTOR/Akt is upregulated 1 week out from a single injection of MPTP and autophagy markers proportionately reduced [262]. The nuanced role of mTOR was further elaborated using this model and confirmed in vitro by showing that the mTOR pathologically upregulated protein translation to toxic levels. Correspondingly, rapamycin proved neuroprotective by correcting this and restoration of Akt signaling [263]. Apparently, rapamycin also specifically blocks REDD1 protein synthesis, and so maintains Akt phosphorylation [263]. Interestingly, REDD1 is reported to be the target of metformin to inhibit mTOR, rather than AMPK [264]. Treatment with temsirolimus in vivo induced autophagy and maintained high Beclin-1, p62, and MAP (microtubule-associated protein) 1A/1B-light chain 3 (LC3) expressions, while inhibiting p70S6K expression in another MPTP model of PD [265]. Still others have found that inhibition of mTORC1 signaling also revert cognitive and affective deficits in a 6OHD A mouse model of PD [266].

Recently, the complex regulation of mTORC1/raptor and C2/rictor activations were examined in neuroblastoma cells and wild type mice either exposed to or injected with the mitochondrial toxin rotenone, respectively [267]. Under full serum and dietary nutrient conditions, rotenone activated mTORC1 and inhibited mTORC2/rictor, compared to baseline. These results indicate these two complexes, preferentially controlling cell growth and survival, respectively, are reciprocally regulated, both in the neurodegenerative context and depending on nutrient levels.

It is important to note that accumulation of α-Synuclein and Lewy body-like formations, the proteinopathy hallmark of PD, is generally lacking in 6OHDA- and MPTP-, but present in rotenone -ROS-generating models of PD such as the one just cited above. Genetic models of PD also generally do not form Lewy bodies, but the clear exception is transgene wild type or mutant α-Synuclein. α-Synuclein modulates synaptic activity and point mutations in the SNCA gene cause rare, early onset autosomal dominant PD [268]. Deficient autophagy may contribute to α-Synuclein accumulation in PD or Lewy Body Dementia and stimulation of autophagy by the mTOR inhibitors rapamycin or everolimus may promote its clearance [269–271].

In PD brain, as in AD, mTOR also appears upregulated and autophagosomes accumulate [272, 273] (Fig. 3). In neuronal cultures and mice expressing mutant A53T α-Synuclein, mTORC1 signaling is overactivated, also resulting in insulin resistance (via IRS-1, S636 phosphorylation). The changes were reversed by rapamycin [274, 275]. Metformin was also found to clear cytoplasmic α-Synuclein in hippocampal neurons, as did rapamycin, by inhibiting mTOR, but interestingly not via AMPK or autophagy induction [276]. The ubiquitin hydrolase UCHL1 and
PINK-1 proteins both activate mTORC2, predicting improved cell survival [277, 278]. The role of mTORC2 in PD clearly bears further investigation.

Figure 3 Legend of refs. [50, 51, 130, 135-137, 144-147, 150–153, 157–159, 164, 166, 168, 172, 175, 184, 205, 208, 210, 236, 244, 253, 261, 269, 273, 279-287]. Interestingly, several familial PD-linked proteins, affected by disease-causing recessive mutations in PINK-1/PRKN (Parkin) and DJ-1 (PARK7) genes and in the dominantly inherited LRRK2 gene, influence the autophagy-lysosomal pathway in response to mitochondrial damage in an mTOR-independent manner [288, 289]. Adding to the complicated story of mTOR in PD noted above, these studies have generated interest in stimulating autophagy by means other than rapamycin and analogs in order to improve α-synuclein removal, i.e. targeting mTOR-independent autophagy. These strategies employ agents such as curcumin and Trehalose [290–292]. Whereas mTOR negatively regulates TFE2 (transcription factor EB) to suppress autophagy, Trehalose acts on the Foxo-1 transcription factor to enhance autophagy protein expressions [293]. In light of this, the in vivo activation of autophagy through a combination of rapamycin and Trehalose treatment was shown to reverse both neuronal dopaminergic damage and behavioral deficits. Therefore, a dual therapy approach aimed at autophagy seems to hold promise for PD-like pathology [294].
Huntington’s Disease
Huntington’s disease is another dominantly inherited proteinopathy, resulting in a degenerative movement, psychiatric and cognitive disorder. Several reports clearly implicate abnormal synaptic plasticity, spatial memory cognition and dentritic spine loss early on in experimental mutant Huntington (mHtt) bearing mice [295–297]. In transfected cells bearing aggregating proteins with polyglutamine (polyQ) expansions, such as caused by the Huntington’s disease mutation in which the CAG tract in the Htt gene is expanded or by mutant Ataxin 1 in the case of spinocerebellar ataxia 1, blockade of mTORC1 with rapamycin or pan-mTOR catalytic inhibitors results in stimulated autophagy followed by removal of mutant protein aggregates and cytoprotection [298, 299]. Drosophila and mouse HD models also benefited from mTOR inhibition [300]. In a polyQ htt mouse model, deletion of TSC1 led to activation of mTORC1, accelerated motor incoordination and premature death. In striatal cells overexpressing the same mutation, mTORC1 activation was induced which then could be abrogated by knocking down Rheb [301]. The authors conclude that enhanced mTOR is pathogenic in HD. In neuroblastoma cells induced to express mutant Htt polyQ72 fragments, catalytic inhibitors of total mTOR or mTOR specific siRNA, induced autophagy and reduced protein aggregates [298, 299]. Each of p70S6K, p4E-BP and p-Akt, downstream substrates of mTOR, REDD1 (RTP801) is also upregulated and mediates cell death, as the case in PD [285]. Accordingly, downregulation of RPT801 prevented motor learning deficits in the mouse. However, contrary to PD, Akt was hyperactivated, from increased Rictor activity, invoking a compensatory effect. The activated Akt pattern was also confirmed by others in genetic mouse models of HD [305, 306]. One study points to a scenario where further increasing Rictor in striatal cells actually prevented neurodegeneration from mHtt expression [286]. In this mouse model and in HD putamen, rictor, Akt and mTOR activations were already increased, again pointing to a partially effective compensatory reaction. The same authors found evidence for excessive de novo protein translation in genetic HD mice, attributed to an increase in phosho-inactivation of 4EBP1. This hypofunction of 4EBP1 was confirmed in human HD putamen specimens, however it was left unclear if excessive mTOR was culprit [287]. In a forementioned study, RPT801 silencing proved to normalize the Akt hyperphosphorylation by reducing Rictor and enhancing autophagy regulator, perhaps in synergy with the binding of mTOR at the lysosome membrane [307, 308].

In a model incorporating another ALS-causing gene mutation (G93A in SOD-1), autophagy markers were also increased in spinal motor neurons [309]. Using this model, a small molecule that enhanced mTOR and suppressed autophagy suppression was found to be neuroprotective [310]. Moreover, Rapamycin actually accelerated disease progression [311, 312]. Interestingly, when mTOR-independent autophagy was activated with Trehalose, motor neuron lifespan was prolonged and protein aggregations were reduced. Therefore, in the context of these models, as contrasted with AD, motor neuron viability appears dependent on mTOR activity [311].

ALS and FTD
In another expansion mutation, a hexanucleotide repeat in the C9ORF72 gene causes the most common form of inherited ALS and FTD. The loss of protein function encoded by this gene promotes TDP43 accumulation in ubiquitin-containing inclusions. In a C9ORF72 knockout model, autophagic flux is increased and correlated with reduced mTOR activity (less p-p70S6K1). Hence, C9ORF72 protein is postulated to act as a negative autophagy regulator, perhaps in synergy with the binding of mTOR at the lysosome membrane [307, 308].

Another FTD transgenic mouse in which TARDP43 overexpression yields TDP43/ubiquitin containing inclusions, produced a different result. In this case, rapamycin treatment and mTOR inhibition-autophagy activation (LC3-1/LC3-II) proved neuroprotective against memory loss and inclusion formation [314]. Finally, in a mouse FTD model bearing a tau mutation in which the observed mTOR overactivation is associated with Tau accumulation and hyperphosphorylation, rapamycin also corrected behavioral deficits and afforded neuroprotection [202]. Based...
on these latter reports, a phase 2 clinical trial of rapamycin in ALS is ongoing [315].

**mTOR-based treatment**

Rapamycin (sirolimus), the prototypical mTORC1 inhibitor, is an immunosuppressant and anti-proliferative FDA-approved agent for kidney transplantation, coronary stents, cardiac hypertrophy and renal cell carcinoma [316]. It binds FK506 and allosterically stabilizes raptor-mTOR in a kinase-inactive complex. The discovery of the apparently paradoxical protective action of rapamycin in many models of neurodegeneration (see below and Fig. 4) arose from the early recognition that mTOR transduces the action of insulin and IGF-1 via Akt in both the periphery and brain. Other trophic factors (EGF, BDNF) also require some mTOR activity to promote enable their neuroprotective and cell survival functions [20, 317]. Moreover, the AD brain is intrinsically insulin resistant and does not metabolize glucose properly where needed. There is also a complex relationship to insulin resistance in the periphery since systemic T2DM doubles the risk for AD [126]. Therefore, much effort is devoted toward the development of anti-diabetic drugs to treat AD that include metformin, glimepiride (a sulfonylurea), GLP-1 and Liraglutide (a glucagon-like peptide analog) and intranasal insulin [318, 319]. These strategies appear to enhance the Akt/mTOR signaling axis. The resistance to insulin signaling that characterizes AD brain would further predict that restorative mTOR activation would be neuroprotective. Therefore, a balanced treatment of the matter relating to the pros of rapamycin therapy should include the other instances where mTOR activation is favored.

Indeed, there are disease states, AD aside, where direct mTOR activation is neuroprotective. These involve CNS models of ischemia, trauma and oxidative stress and is attributed to the inhibition of apoptosis or repression of autophagy [259, 320, 321]. In one example, the cytokine and hormone erythropoietin that signals through mTOR activation, is regarded to prevent neuronal apoptosis during oxidative stress or hypoxia [322] and Aβ exposure [323]. Relating to Parkinson’s disease, an mTOR-activating protein protected dopaminergic cells from H2O2 mediated oxidative stress [259]. REDD1 (RTP8011) is an endogenous mTOR inhibitor that is increased in dopaminergic neurons and contributes to neuronal death, mTOR activation is protective in this model too [253]. A number of physiological studies also support the notion that mTOR activation may counter neurodegeneration. mTORC1 control over activity-related 5’ TOP mRNA translation initiation (via 4EBP1 and p70S6K phosphorylations) and dendritic protein synthesis is critical to synaptic plasticity (LTP and LTD) and memory formation [324, 325]. Rapamycin is accordingly found detrimental to normal synaptic plasticity by many laboratories [6, 7, 10, 95, 96, 326]. In agreement with this, is the loss of mTORC1 signaling found in two AD animal models (transgenic and wild type exposed to exogenous Aβ42) or in wild-type mice treated with rapamycin, causing impairment of late phase hippocampal LTP (and LTD) [157]. In behavioral correlates of activity-dependent synaptic strengthening, early studies show activations of mTORC1 and p70S6K during the consolidation phases of both spatial (Morris water maze) and fear conditioning paradigms. These long-term memory processes were understandably inhibited by either rapamycin or AMPK stimulation [8, 20, 95]. mTORC2 is also necessary for synaptic plasticity, perhaps via association with polysomes or cytoskeletal protein polymerization [223, 327]. These considerations auger for mTOR stimulation and by the same logic, against rapamycin treatment for AD.

However, it is the inhibition of mTORC1, downstream in the insulin pathway, with Rapamycin that consistently increases lifespan in mammals [13], rescues several forms of neurodegeneration [328], mitigates synaptic/neuronal losses and restores synaptic plasticity and/or cognition in several animal and cell disease models (summarized in Fig. 4). As we have seen for instance, rapamycin prevents loss of learning and memory in the Morris Water Maze in several AD mice models when given at young (2 mos.) or mid ages (4-7 mos.) [155, 192, 234, 329]. Perhaps surprisingly given its aforementioned negative effects on long term synaptic plasticity and memory, lifelong treatment with rapamycin even improved spatial memory in 2-4 mo. control and wild type mice [5, 189, 192]. However, neither LTP or spine morphological changes were assessed. A clear example of this principle is the TSC2 haplodeficient mouse, in which cognitive deficits are directly linked to hyperactivation of mTOR; rapamycin restores synaptic plasticity and cognitive function [330]. The excessive activation of mTOR associated with AD progression, as found in many studies and human brain samples (but by no means all, see Table 1, Fig. 3), also favors rapamycin-based therapy for the disease context [331]. In this regard, a major effect of rapamycin is to decrease proteotoxic aggregates, such as Aβ42 [332] via autophagy/lysosome induction [119]. Rapamycin/Temsirolimus appear beneficial in alleviating proteotoxicity in several transgenic AD [155, 192, 234, 329] and tauopathy mice strains [176, 202]. Cellular models under toxic stress from β-amyloid [333] and other aggregate-prone proteins are also alleviated by rapamycin [298]. In Parkinson disease cell-based and transgenic models where α-synuclein accumulation is proteotoxic, mTOR inhibition with rapamycin and/or autophagy induction with Beclin or Atg7 were cytoprotective [269, 334]. In the latter reference, total and phospho-mTOR levels were increased in DLB and α-synuclein
transgenic brains. However, the concept of rapamycin rescue may hold regardless of the basal activation status of mTORC1. In certain HD drosophila and mice models for instance, although basal mTOR activity is already down-regulated, further inhibition with rapamycin stimulated autophagy, cleared polyQ Htt protein fragments and was cytoprotective [300]. This scenario applied to some AD models as well [135]. Mixed pathologies are also amenable to therapy. Examples include rats with experimental hippocampal AD pathology on a T2DM background [200] and vasculopathy with blood-brain barrier breakdown in transgenic hAPP/20 mice [335]. In one instance, rapamycin was even found helpful in protecting hypoxic primary cortical neurons from apoptosis by stimulating autophagy [336]. Another caveat is that once the neurodegeneration is too advanced, rapamycin may become ineffective [220].

One conclusion is that where toxic proteins accumulate in neurodegenerative disorders, the advantage of autophagy induction by inhibiting mTOR may outweigh the antiapoptotic and pro-synaptic effects of its activation. As well, the effects of mTOR inhibition in normal tissue studies doesn’t have to coincide with its effects in the various disease states. This situation could possibly arise from crosstalk between C1 and C2 circuitry [87]. It seems likely therefore that these two mTOR activities are differentially altered in neurodegenerative conditions, arising from changes to the gain of their positive regulators and negative feedback loops (e.g TSC1/2, PI3K, p70S6K). Underscoring the fine balance in their circuitry, both chronic activation of mTORC1/p70S6K [71, 337] and conversely, prolonged rapamycin treatment [90], can each result in mTORC2 inhibition and lead to insulin resistance.

Other mTOR strategies

Unfortunately, rapamycin has a systemic toxic profile that includes pneumonitis, stomatitis, poor wound healing, nephrotoxicity and immunosuppression [338, 339]. These limit its application to abate neurodegeneration. Moreover, rapamycin can be toxic to mitochondrial respiration and biogenesis via the disruption of peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) [25, 26, 91]. Finally, long-term use can produce insulin resistance, including inhibition of mTORC2 function and Akt phosphorylation as well as reductions in IRS-2 levels and glucose uptake [340]. These predict an exacerbation of T2DM [78, 341].

Formulating rapamycin or rapalogs for preferential brain delivery may overcome these systemic objections, as exampled by experimental intracerebral infusions [269, 342]. More practical strategies are being developed. So far, systemically administered nanoparticles, micelle, exosome and nanoemulsion-based rapamycin delivery systems, seeking to advantage the increased BBB permeability in AD and other neurodegenerations, is proving a challenge [343, 344]. Trials of intranasal (IN) delivery of insulin for AD has inspired a study on IN rapamycin in a mouse model of Down syndrome, finding that radial arm maze and object recognition cognitive dysfunctions are rescued along with positive effects on measures of autophagy and tau phosphorylation [345]. Small molecule catalytic mTOR inhibitors that compete with ATP have also been successfully used in Huntington models as an alternative to the allosteric rapalogs [299, 346]. Selective mTORC1 catalytic inhibitors, sparing C2, might be favored in neurodegeneration and some have been identified [347]. Alternatively, if the goal is to abate the concurrent overactivation of both Akt and mTORC1/2, dual PI3K/mTOR ATP analogues (as are in current cancer trials) could be tested. Additional approaches to selective C1 inhibition include a small molecule inhibitor of Rheb, NR1 [280].

Rapalogs such as temsirolimus and everolimus and second generation mTOR inhibitors represent major improvements in tolerance [347, 348] and hold promise as therapies against aging and AD [5]. Temsirolimus restores spatial learning and memory in 5-month-old double mutant AD transgenic mice, associated with autophagic clearance of Aβ and anti-apoptosis [349, 350]. Similar results in p-tau clearance and memory are reported in a mutant tauP301S model [214]. Intrathecal everolimus inhibited central mTOR and restored cognitive function in 3X AD mice [351].

Other drugs, affecting mTOR, are being investigated for therapy in AD. For instance, metformin, which activates AMPK (indirectly suppressing mTOR) and may also directly suppress Raptor/mTOR, can stimulate autophagy like rapamycin. Although there is some concerning epidemiological evidence pointing to an increase in AD risk in those treated with metformin [352], one clinical trial concluded that it mitigated cognitive dysfunction in MCI/AD [353]. Several in vitro and in vivo AD models also report conflicting results with metformin, either promoting amyloid aggregation and memory dysfunction or rescuing synaptic plasticity and preventing neuropathological changes. The agent cilostazol increases AMPK expression (in a Sirt-1-dependent manner), suppresses mTOR activation, increases autophagy markers beclin-1, Atg and LC3-II and promotes autophagic clearance of Aβ in N2A neurons [354]. Direct Sirt-1 overexpression, by inhibiting mTOR, promotes neurite outgrowth and cell survival during Aβ exposure [118]. Caloric restriction also stimulates AMPK, activating autophagy and preventing AD pathology in triples transgenic mice [355]. Dietary curcumin and resveratrol either reduce mTOR levels to disrupt the C1 complex or inhibit mTORC1 by activating AMPK, thereby inducing autophagy and rescuing cognitive impairment in 2X AD...
transgenic mice [356]. mTOR independent stimulation of autophagy, with Trehalose, is another alternative to the above approaches [357]. Several additional novel compounds that modulate mTOR and autophagy for treatment of neurodegeneration are presented in a recent review [88].

**Conclusion**

Autonomous overactivation of the Akt/mTOR axis and upregulation of mTOR activity targets has been noted in several transgenic models and in AD brain (Table 1 and Fig. 3). β-amyloid is partially responsible through mechanisms including inactivation of PTEN (disinhibiting PI3K), degrading functional IRS-1 levels, and activation of mTOR. These amyloid-driven mechanisms result in a state of relative insulin/IGF resistance (inhibited homeostatic Akt activation) [358] and oxidative stress [359]. Tau phosphorylation is also driven by Akt/mTOR hyperactivation. Several interventions may break this chain of pathogenesis. For example, either genetic suppression of Aβ production or passive anti-Aβ immunization in an AD mouse model will reverse the hyperactivation of mTOR and improve cognition [162]. Similarly, genetic reduction of mTOR by one copy in transgenic 2576 AD mice is sufficient to improve central insulin signaling and cognition [160, 161].

Although some manifestation of mTOR dysregulation is unquestionably present in AD brain, and for that matter in numerous tissues of individuals with T2DM [360, 361], a definitive accounting of the exact nature and sequence of mTOR axis dysregulation is elusive. Part of this uncertainty comes from studies that have found no change or even reduced mTOR activation and/or activity parameters in AD brain and various transgenic models. Aside from the use of widely differing models, contradictions can arise from variances in disease duration and severity as well as confounding changes to mTOR-regulating and signal crosstalk proteins. Nevertheless, most all *in vivo* and *in vitro* models of AD recommend a rapamycin-like strategy. Furthermore, manipulation of mTOR is a strong treatment strategy to pursue in PD/HD and ALS.

The overall goal of mTOR-based treatment then is to either restore activity where deficient or inhibit it when excessive, in order to re-establish basal levels, reactivity to neurotrophin stimulation and nutrient status and downstream effector homeostasis. This will probably depend on the particular neurodegenerative process and type of protein aggregation, as well as disease stage. Attempts to block mTOR activity must be kept partial, in consideration of important roles in facilitating memory formation [21, 362, 363] and tissue repair involving progenitor cells [364]. The latter relates particularly to neurodegeneration and ischemic injury [365]. The balancing act includes maintenance of insulin/Akt axis homeostasis and mTORC1-dependent protein translation. Thus, over-inhibition of mTORC1 could lead to feedback hyperactivation of Akt and unchecked tumor proliferation. The inadvertent over-activation of mTOR also has the potential of tumorigenesis (for example resulting from the loss of tumor suppressor TSC1/2 function, as in Tuberous Sclerosis), but also loss of autophagy function.
Use of rapamycin or analogs to treat AD holds promise due to its many actions to increase longevity and remove toxic proteins, but toxicity concerns persist. This leaves open the possibility to target other mTOR-dependent effectors such as p70S6K1/2[159, 371] as well as direct therapy to more selective brain regions[5]. The balance between IRS-1 inhibition (mTORC1-directed negative feedback) and Akt responsiveness to insulin (mTORC2/Rictor directed positive feedback) should be swung to favor homeostatic insulin signaling. The compelling preclinical record reviewed above calls for clinical trials to test rapamycin or other mTOR inhibitors and/or possibly mTORC2 agonists, beginning in patients with Alzheimer’s disease[372].

Funding
This study was funded by NIA NIH AG044871-01 to HWQ, institutional funds and through an award from the Bennett Foundation. We thank Nicholas Norwitz for contributing edits and references.

Competing interests
Authors declare that there is no conflict of interest.

Received: 29 May 2020 Accepted: 1 February 2021

Published online: 02 July 2021

References
1. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014;63:2262–72.
2. Moreira PI, Santos MS, Seia R, Oliveira CR. Brain mitochondrial dysfunction as a link between Alzheimer’s disease and diabetes. J Neurol Sci. 2007;257:206–14.
3. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. Biochim Biophys Acta. 2014;1842:1693–706.
4. Saxton RA, Sabatinis DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017;169:361–71.
5. Richardson A, Galvan V, Lin AL, Oddo S. How longevity research can lead to therapies for Alzheimer’s disease: The rapamycin story. Exp Gerontol. 2015;68:1–8.
6. Hoeffer CA, Klann E. mTOR signaling: at the crossroads of plasticity, memory and disease. Trends Neurosci. 2010;33:67–75.
7. Tang SJ, Reis G, Kang H, Gingeras AC, Sonenberg N, Schuman EM. A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. Proc Natl Acad Sci U S A. 2002;99:467–72.
8. Dash PK, Ori SI, Moore AN. Spatial memory formation and memory-enhancing effect of glucose involves activation of the tuberous sclerosis complex-Mammalian target of rapamycin pathway. J Neurosci. 2006;26:8946–56.
9. Costa-Mattioli M, Sossin WS, Klann E, Sonenberg N. Translational control of long-lasting synaptic plasticity and memory. Neuron. 2009;61:479–89.
10. Sutton MA, Schuman EM. Dendritic protein synthesis, synaptic plasticity, and memory. Cell. 2006;127:49–58.
11. Henry FE, Hockeimer W, Chen A, Mysore SP, Sutton MA. Mechanistic target of rapamycin is necessary for changes in dendritic spine morphology associated with long-term potentiation. Mol Brain. 2017;10:50.
12. Blagosklonny MV. Calorie restriction: decelerating mTOR-driven aging from cells to organisms (including humans). Cell Cycle. 2010;9:6838–8.
13. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009;460:312–5.
14. Lamming DW, Ye L, Sabatini DM, Baur JA. Rapalogs and mTOR inhibitors as anti-aging therapeutics. J Clin Invest. 2013;123:980–9.
15. Kim S, McDonald BC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009;325:201–4.
16. Swiecichowski M, Malik A, Jaworski J. Role of mTOR in physiology and pathology of the nervous system. Biochim Biophys Acta. 2008;1784:116–32.
17. Ebert DH, Greenberg ME. Activity-dependent neuronal signalling and autism spectrum disorder. Nature. 2013;493:327–37.
18. Santini E, Huynh TN, Klann E. Mechanisms of translation control underlying long-lasting synaptic plasticity and the consolidation of long-term memory. Prog Mol Biol Transl Sci. 2014;122:131–67.
19. Silpzcuk L, Bekinschtein P, Katche C, Cammarota M, Izquierdo I, Medina JH. BDNF activates mTOR to regulate GluR1 expression required for memory formation. PLoS One. 2009;4:e6007.
20. Ramanan VK, Nho K, Shen L, Roacher SL, Kim S, McDonald RC, et al. FSTL1 is associated with memory and hippocampal structure in older mice. Mol Psychiatry. 2015;20:1197–204.
21. Stoica L, Zhu PJ, Huang W, Zhou H, Kozma SC, Costa-Mattioli M. Selective pharmacogenetic inhibition of mammalian target of Rapamycin complex I (mTORC1) blocks long-term synaptic plasticity and memory storage. Proc Natl Acad Sci U S A. 2011;108:3791–6.
96. Gong R, Park CS, Abbassi NR, Tang SJ. Roles of glutamate receptors and the
95. Parsons RG, Gafford GM, Helmstetter FJ. Translational control via the
94. Hou L, Klann E. Activation of the phosphoinositide 3-kinase-Akt-mammalian
90. Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al.
86. Julien LA, Carriere A, Moreau J, Roux PP. mTORC1-activated S6K1
75. Hresko RC, Mueckler M. mTOR.RICTOR is the Ser473 kinase for Akt/protein
74. Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, et al. Mammalian
63. Vingtdeux V, Chandakkar P, Zhao H, d’Abramo C, Davies P, Marambaud P.
61. Watson GS, Craft S. The role of insulin resistance in the pathogenesis
59. Goodwin CA, Mayhew DL, Hornberger TA. Recent progress toward
57. Sarbassov DD, Ali SM, Kim DH, Guertin DA, Latek RR, Erdjument-Bromage H,
52. Kaushik S, Cuervo AM. The coming of age of chaperone-mediated
47. Zhu Z, Yang C, Iyaswamy A, Krishnamoorthi S, Sreenivasmurthy SG, Liu J, et al.
44. Chan TO, Tsichlis PN. PDK2: a complex tail in one Akt. Sci STKE. 2001;2001:
31. Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307:1098–
30. Sparks CA, Guertin DA. Targeting mTOR: prospects for mTOR complex 2 inhibitors in cancer therapy. Oncogene. 2010;29:3733–44.
29. Thomanetz V, Angliker N, Cluett L, Luster M, Klose C, Schwaegether M, Olver F, et al. Ablation of the mTORC2 component rictor in brain or
28. Kumar A, Harris TE, Keller SR, Choi KM, Magnuson MA, Lawrence JC Jr. Muscle-specific deletion of rictor impairs insulin-stimulated glucose transport and enhances basal glycogen synthase activity. Mol Cell Biol. 2008; 2861–70.
27. Cybulski N, Hall MN. TOR complex 2: a signaling pathway of its own. Trends Biochem Sci. 2009;34:560–7.
26. Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, et al. Mammalian
25. Hou L, Klann E. Activation of the phosphoinositide 3-kinase-Akt-mammalian
24. Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al. Autophagy and Neurodegeneration: Pathogenic Mechanisms and
23. Sarbassov DD, Ali SM, Kim DH, Guertin DA, Latek RR, Erdjument-Bromage H, et al. Rictor, a novel binding partner of mTOR, defines a rictor- and raptor-independent pathway that regulates the cytokinase. Curr Biol. 2004;14:1296–302.
22. Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell. 2006;22:159–68.
21. Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005;307:1098–
20. Chan TO, Tischkis PN. PDK2: a complex tail in one Akt. Sci STKE. 2001;2001: 
19. Zhu Z, Yang C, Iyaswamy A, Krishnamoorthi S, Sreenivasmurthy SG, Liu J, et al. Balancing mTOR Signaling and Autophagy in the Treatment of Parkinson’s Disease. Int J Mol Sci. 2015;20:2726.
18. Kumar A, Harris TE, Keller SR, Choi KM, Magnuson MA, Lawrence JC Jr. Muscle-specific deletion of rictor impairs insulin-stimulated glucose transport and enhances basal glycogen synthase activity. Mol Cell Biol. 2008; 2861–70.
17. Cybulski N, Hall MN. TOR complex 2: a signaling pathway of its own. Trends Biochem Sci. 2009;34:560–7.
16. Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, et al. Mammalian
15. Hou L, Klann E. Activation of the phosphoinositide 3-kinase-Akt-mammalian
14. Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science. 2012;335:1638–43.
13. Ye L, Varamini B, Lamming DW, Sabatini DM, Baur JA. Rapamycin has a biphasic effect on insulin sensitivity in C2C12 myotubes due to sequential disruption of mTORC1 and mTORC2. Front Genet. 2012;3:177.
12. Kim SJ, DeStefano MA, Oh WJ, Wu CC, Vega-Cotto NM, Finlan M, et al. mTOR complex 2 regulates proper turnover of insulin receptor substrate-1 via the ubiquitin ligase subunit Fbw8. Mol Cell. 2012;48:785–87.
11. Janfuleta JM, Jordan AE, Lenz K, Sorger PK. Autophagy is required for mTOR signaling in 3T3-L1 adipocytes. J Biol Chem. 2005;280:40406–
10. Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science. 2012;335:1638–43.
9. Ye L, Varamini B, Lamming DW, Sabatini DM, Baur JA. Rapamycin has a biphasic effect on insulin sensitivity in C2C12 myotubes due to sequential disruption of mTORC1 and mTORC2. Front Genet. 2012;3:177.
8. Kim SJ, DeStefano MA, Oh WJ, Wu CC, Vega-Cotto NM, Finlan M, et al. mTOR complex 2 regulates proper turnover of insulin receptor substrate-1 via the ubiquitin ligase subunit Fbw8. Mol Cell. 2012;48:785–87.
7. Starfel MN, Shamieh LS, Kaeberlein M, Kennedy BK. The TOR pathway comes of age. Biochim Biophys Acta. 2009;1790:1067–74.
6. Hou L, Klann E. Activation of the phosphoinositide 3-kinase-Akt-mammalian
5. Parsons RG, Gafford GM, Helmstetter FJ. Translational control via the mTORC1 mammalian target of rapamycin signaling pathway is required for metabolic glutamate receptor-dependent long-term depression. J Neurosci. 2004;24: 6352–61.
4. Parsons RG, Gafford GM, Helmstetter FJ. Translational control via the mammalian target of rapamycin pathway is critical for the formation and stability of long-term fear memory in amygdala neurons. J Neurosci. 2006; 26:12977–83.
3. Gorg R, Park CS, Abbas NR, Tang SJ. Roles of glutamate receptors and the mammalian target of rapamycin (mTOR) signaling pathway in activity-dependent dendritic protein synthesis in hippocampal neurons. J Biol Chem. 2006;281:18802–15.
2. Menezes FM, Fleming A, Caricasole A, Bento CF, Andrews SP, Ashkenazi A, et al. Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities. Neuron. 2017;93:1015–34.
1. Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, et al. ULK1-Atdg13-FIP200 complexes mediate mTORC1 signaling to the autophagy machinery. Mol Biol Cell. 2009;20:1992–2003.
125. Luchinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007;64:392–8.

126. Schrijvers EM, Witterman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010;75:1982–7.

127. Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer’s disease. FASEB J. 2004;18:902–4.

128. Zhao L, Teter B, Mohrara T, Lim GP, Ambegaokar SS, Ubeda OJ, et al. Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer’s disease intervention. J Neurosci. 2004;24:11120–6.

129. Rivera EJ, Goldin A, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer’s disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 2005;8:247–68.

130. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer’s disease—is this type 3 diabetes? J Alzheimers Dis. 2005;7:63–80.

131. de la Monte SM, Wands JR. Alzheimer’s disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol. 2008;2:1101–13.

132. Correia SC, Santos RX, Perry G, Zhu X, Moreira PI, Smith MA. Insulin-resistant brain state: the culprit in sporadic Alzheimer’s disease? Ageing Res Rev. 2011;10:264–73.

133. de la Monte SM. Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer’s Disease. Drugs. 2017;77:47–65.

134. Diedi T, Mullins R, Kapogiannis D. Insulin resistance in Alzheimer’s disease. Transl Res. 2017;183:26–40.

135. Lee HK, Kwon B, Lemere CA, de la Monte S, Itamura K, Ha AY, et al. Expression-Induced Insulin Resistance and Toxicity in Rat Primary Cortical Neurons. J Alzheimers Dis. 2017;56:1015–36.

136. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, et al. Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest. 2012;122:1316–38.

137. O’Neill C, PI3-kinase/Akt/mTOR signaling: impaired on/off switches in aging, cognitive decline and Alzheimer’s disease. Exp Gerontol. 2013;48:467–537.

138. Zhao WQ, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, et al. Amyloid beta oligomers induce impairment of neuronal insulin receptors. FASEB J. 2008;22:246–60.

139. Loureiro MV, Clarke JR, Frozza RL, Bomfim TR, Hofman A, Daut AF, et al. TNF-alpha mediates PI3K-dependent memory impairment and brain IGF-1 resistance induced by Alzheimer’s disease beta-amyloid oligomers in mice and monkeys. Cell Metab. 2013;18:831–43.

140. Norwitz NG, Mota AS, Norwitz SG, Clarke K. Multi-Loop Model of Alzheimer’s Disease. Antioxid Redox Signal. 2017;27:1269–94.

141. Griffin RJ, Moloney A, Kelliher M, Johnston JA, Ravid R, Dockery P, et al. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PKB are features of Alzheimer’s disease pathology. J Neurochem. 2005;93:105–17.

142. Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ. Levels of mTOR and its downstream targets 4E-BP1, eEF2, and eEF2 kinase in relationships with tau in Alzheimer’s disease brain. FEBS J. 2005;272:421–10.

143. Majd S, Power JHT. Oxidative Stress and Decreased Mitochondrial Superoxide Dismutase 2 and Peroxiredoxins 1 and 4 Based Mechanism of Concurrent Activation of AMPK and mTOR in Alzheimer’s Disease. Curr Alzheimer Res. 2018;15:764–76.

144. Pei JJ, Bjorkdahl C, Zhang H, Zhou X, Winblad B. p70 S6 kinase and tau in Alzheimer’s disease. J Alzheimers Dis. 2008;14:385–92.

145. Pei JJ, Hugon J. mTOR-dependent signalling in Alzheimer’s disease. J Cell Mol Med. 2008;12:2525–32.

146. Pei JJ, Khatoon S, An WL, Nordlinder M, Tanaka T, Braak H, et al. Role of protein kinase B in Alzheimer’s neurofibrillary pathology. Acta Neuropathol (Berl). 2003;105:381–92.

147. Sonoda Y, Toyoyama L, Maeda K, Akiyama H, Kawamura T. S6 kinase phosphorylated at T229 is involved in tau and actin pathologies in Alzheimer’s disease. Neuropharmacology. 2016;36:325–32.

148. Sun YX, Ji X, Mao X, Xie L, Jia J, Galvan V, et al. Differential activation of mTOR complex 1 signaling in human brain with mild to severe Alzheimer’s disease. J Alzheimers Dis. 2014;38:437–44.

149. Iyer AM, van Schepingen J, Milenkovic I, Anink JJ, Adle-Biassette H, Kovacs GG, et al. mTOR Hyperactivation in down syndrome hippocampus appears early during development. J Neuropathol Exp Neurol. 2014;73:671–83.

150. Bhaskar K, Miller M, Chudzinski A, Herrup K, Zagorski M, Lamb BT. The PI3K-Akt-mTOR pathway regulates Abeta oligomer induced neuronal cell cycle events. Mol Neurodegener. 2009;14.

151. Caccamo A, Majumder S, Richardson A, Strong R, Oddy S. Molecular Interplay between mammalian target of rapamycin (mTOR), amyloid-beta, and Tau effects on cognitive impairments. J Biol Chem. 2010;285:13107–20.

152. Caccamo A, Maldonado MA, Majumder S, Medina DX, Holwein B, Magri A, et al. Naturally secreted amyloid-beta increases mammalian target of rapamycin (mTOR) activity via a PI3K/Akt-mediated mechanism. J Biol Chem. 2011;286:8924–32.

153. Ma T, Hoeffe CA, Capetillo-Zarate E, Yu F, Wong H, Lin MT, et al. Dysregulation of the mTOR pathway mediates impairment of synaptic plasticity in a mouse model of Alzheimer’s disease. PLoS One. 2010;5:12845.

154. Pei JJ, An WL, Zhou YW, Nishimura T, Nishi Y, Benedix E, et al. P70 S6 kinase mediates tau phosphorylation and synthesis. FEBS Lett. 2006;580:107–14.

155. Caccamo A, Branca C, Talboom JS, Shaw DM, Turner D, Ma L, et al. Reducing Ribosomal Protein S6 Kinase 1 Expression Improves Spatial Memory and Synaptic Plasticity in a Mouse Model of Alzheimer’s Disease. J Neurosci. 2015;35:14042–56.

156. Caccamo A, De Pinto V, Messina A, Branca C, Oddy S. Genetic reduction of mammalian target of rapamycin ameliorates Alzheimer’s disease-like cognitive and pathological deficits by restoring hippocampal gene expression signature. J Neurosci. 2014;34:7988–98.

157. Caccamo A, Belfiore R, Oddy S. Genetically reducing mTOR signaling rescues central insulin dysregulation in a mouse model of Alzheimer’s disease. Neurobiol Aging. 2014;35:659–62.

158. Zhang ACA, Fowler SW, Savagyi RR, Hilsenbeck SG, Wallace CE, Cirrito JR, et al. Combination anti-Abeta treatment maximizes cognitive recovery and rebalances mTOR signaling in APP mice. J Exp Med. 2018;215:1349–64.

159. Ou Z, Kong X, Sun X, He X, Zhang L, Gong Z, et al. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. Brain Behav Immun. 2018;69:331–63.

160. Perlugi M, Di Domenico F, Butterfield DA. mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy. Neurobiol Dis. 2015;84:39–49.

161. Norambuena A, Wallrabe H, McMahon L, Silva A, Swanson E, Khan SS, et al. mTOR and neuronal cell cycle reentry: How impaired brain insulin signaling promotes Alzheimer’s disease. Alzheimers Dement. 2017;13:152–67.

162. Lafay-Chebassier C, Perault-Pochat MC, Page G, Riffard MC, Duggan EC, Wallrabe H, et al. Concurrent Activation of AMPK and mTOR in Alzheimer’s Disease. Antioxid Redox Signal. 2021;16:44.
169. Lee HK, Kumar P, Fu Q, Rosen KM, Querfurth HW. The insulin/Akt signaling pathway is targeted by intracellular beta-amyloid. Mol Biol Cell. 2009;20:1533–44.

170. Francois A, Rioux Bilan A, Querfurth HW, Chen SS. AMP-activated protein kinase signaling alleviates impairments in hippocampal synaptic plasticity induced by amyloid beta. J Neurosci. 2014;34:12293–8.

171. Chano T, Okabe H, Hulette CM. RB1CC1 insufficiency causes neuronal deficits by reducing IL-1beta and enhancing NMDA signaling. Aging Cell. 2012;11:326–37.

172. Xue Z, Guo Y, Zhang S, Huang L, He Y, Fang R, et al. Beta-arsenate attenuates amyloid beta-induced apoptosis via Akt/mTOR pathway in PC12 cells. Eur J Pharmacol. 2014;71:195–204.

173. Snider DD, Wormhoudt A, Rhee GT, Wu Q, Simon JE, et al. AMP-activated protein kinase signaling alleviates impairments in hippocampal synaptic plasticity induced by amyloid beta. J Neurosci. 2014;34:12293–8.

174. Apostolou S, Caccamo A, Magri A, Medina DX, Wisely EV, Lopez-Aranda MF, et al. PTEN recruitment controls synaptic and cognitive function in Alzheimer’s disease. Neuron. 2013;80:229–41.

175. Cai Z, Yan Li, Li K, Quazi SH, Zhao B. Roles of AMP-activated protein kinase in Alzheimer’s disease. NeuroMolecular Med. 2012;14:1–14.

176. Jiang Y, Zhang Y, Wang Y, Wang D, Su Y, Yang W, et al. Rapamycin promotes beta-amyloid plaques by the modulation of ADAM-10. Biochim Biophys Acta. 2013;1838:137–41.

177. Shahani N, Piyro W, Swaminaray B, Khodobiv A, Chinnakara G, Burke RE, et al. RhoGTPase regulates beta-secretase levels and amyloid beta generation. J Biol Chem. 2014;289:799–808.

178. Liu Y, Li W, Wang X, Yang C, Deng SP, et al. Rapamycin inhibits activation of AMPK-mTOR signaling pathway in Alzheimer’s disease model. Neurochem Res. 2013;38:59–69.

179. Caccamo A, Magri A, Medina DX, Wisely EV, Lopez-Aranda MF, Silva AJ, et al. mTOR regulates tau phosphorylation and degradation: Implications for Alzheimer’s disease. Biochim Biophys Acta. 2013;1835:1646–57.

180. Rivetti A, Di Domenico F, Tramutola A, Foppoli C, Head E, Perluigi M, Butterfield DA. The mTOR Inhibitor Rapamycin Mitigates –to Alzheimer disease-like deficits in mice modeling the disease. J Neurochem. 2013;124:880–93.

181. Uyama T, Chiba T, Kojima T, Sato K, Hanada T, Ohkawa H, et al. mTOR regulates tau phosphorylation and degradation: Implications for Alzheimer’s disease and other tauopathies. Aging Cell. 2013;12:370–80.

182. Barzilai N, Grand RJ, Perlman E, Maraganore DM. Metformin reduces tau phosphorylation and degradation: Implications for Alzheimer’s disease and other tauopathies. Acta Neuropathol. 2011;121:137–49.

183. Lee MJ, Lee JH, Rubinsztein DC. Tau degradation: the ubiquitin-proteasome system versus the autophagy-lysosome system. Prog Neurobiol. 2013;105:49–59.

184. Liu X, An WL, Alafuzoff I, Scinini H, Winblad B, Peri JJ. Phosphorylated eukaryotic translation factor 4E is elevated in Alzheimer brain. Neuroreport. 2004;15:2237–40.
278. Murata H, Sakaguchi M, Jin Y, Sakaguchi Y, Futami J, Yamada H, et al. A new
279. Yarchoan M, Toledo JB, Lee EB, Arvanitakis Z, Kazi H, Han LY, et al. Abnormal
280. Mahoney SJ, Jackson-Lewis V, Przedborski S, Greene LA. Rapamycin prevents against neuron death in vitro and in vivo models of Parkinson's disease. J Neurosci. 2010;30:1166–75.
281. Liu Y, Liu F, Grunde-Iqbal I, Iqbal K, Gong CX. Deficient brain insulin signaling pathway in Alzheimer's disease and diabetes. J Pathol. 2011;225:54–62.
282. Ricker A, Bogdanovic N, Vollman I, Winblad B, Ravid R, Cowburn RF. Akt activity in Alzheimer's disease and other neurodegenerative disorders. Neuroreport. 2004;15:955–9.
283. Chang RC, Wong AK, Ng HK, Hugon J. Phosphorylation of eukaryotic initiation factor-2alpha (eIF2alpha) is associated with neuronal degeneration in Alzheimer's disease. Neuroreport. 2002;13:2429–32.
284. Wills J, Credle J, Oaks AW, Duka V, Lee JH, Jones J, et al. Parapat, but not maneb, induces synucleinopathy and tauopathy in striata of mice through inhibition of proteasomal and autophagic pathways. PLoS One. 2012;7:e92745.
285. Martin-Flores N, Perez-Sigues L, Creus-Muncunill J, Masana M, Gines S, Alberch J, et al. Synthetic RPT801 contributes to motor-learning dysfunction in Huntington's disease. Cell Death Dis. 2020;11:569.
286. Creus-Muncunill J, Wass M, Alcaida-Ri V, Barillas-Rodriguez R, Romani-Aumedes J, Marco S, et al. Increased Levels of Rictor Prevent Mutant Huntington-Induced Neuronal Degeneration. Mol Neurobiol. 2015;55:7728–42.
287. Creus-Muncunill J, Barillas-Rodriguez R, Garcia-Forn M, Masana M, Garcia-Daz Barriga G, Gualdino-Corral A, et al. Increased translation as a novel pathogenic mechanism in Huntington's disease. Brain. 2019;142:3158–75.
288. Manzoni C, Manasi A, Roosen DA, Dhanish C, Soutar MP, Plun-Favarella H, et al. mTOR independent regulation of macroautophagy by Leucine Rich Repeat Kinase 2 via Beclin-1. Sci Rep. 2016;6:35106.
289. Zhang Y, Nguyen DT, Ozbomer EM, Poon GP, Cole NJ, Puvanendran A, et al. Rescue of Ptk1 Deficiency by Stress-Dependent Activation of Autophagy. Cell Chem Biol. 2017;24:471–80 e474.
290. Jiang TF, Zhang YJ, Zhou HY, Wang HM, Tian LP, Liu J, et al. Curcumin ameliorates the neurodegenerative pathology in A53T alpha-synuclein cell model of Parkinson's disease through the downregulation of p70S6K signaling and the recovery of macroautophagy. J Neuroimmunol Pharmacol. 2013;8:356–69.
291. Redmann M, Wani WY, Volpicelli-Daley L, Darley-Usmar V, Zhang J. Trehalose does not improve neuronal survival on exposure to alpha-synuclein pre-formed fibrils. Redox Biol. 2017;11:429–37.
292. Sarker S, Davies JE, Huang Z, Tunnacliffe A, Rubinsztein DC. Trehalose, a non-reducing disaccharide, delays the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons. Autophagy. 2013;9:1308–20.
293. Pupyshev AB, Tikhonova MA, Akopyan AA, Tenditnik MV, Dubrovina NI, Korolenko TA. Therapeutic activation of autophagy by combined treatment with rapamycin and trehalose in a mouse MPTP-induced model of Parkinson's disease. Pharmacol Biochem Behav. 2019;177:1–11.
294. Richardson AJ, Cummins DM, Dailler GM, Brown JY, Vats avayai SC, Milnerwood AJ, Cummings DM, Dallerac GM, Brown JY, Vats avayai SC, et al. Rapamycin alleviates toxicity of different aggregate-prone proteins. Hum Mol Genet. 1999;8:839–48.
295. Jiang TF, Zhang YJ, Zhou HY, Wang HM, Tian LP, Liu J, et al. Curcumin ameliorates the neurodegenerative pathology in A53T alpha-synuclein cell model of Parkinson's disease through the downregulation of p70S6K signaling and the recovery of macroautophagy. J Neuroimmunol Pharmacol. 2013;8:356–69.
296. Pupyshev AB, Tikhonova MA, Akopyan AA, Tenditnik MV, Dubrovina NI, Korolenko TA. Therapeutic activation of autophagy by combined treatment with rapamycin and trehalose in a mouse MPTP-induced model of Parkinson's disease. Pharmacol Biochem Behav. 2019;177:1–11.
297. Redmann M, Wani WY, Volpicelli-Daley L, Darley-Usmar V, Zhang J. Trehalose does not improve neuronal survival on exposure to alpha-synuclein pre-formed fibrils. Redox Biol. 2017;11:429–37.
298. Sarker S, Davies JE, Huang Z, Tunnacliffe A, Rubinsztein DC. Trehalose, a novel mTOR-independent autophagy enhancer, accelerates the clearance of mutant huntingtin and alpha-synuclein. J Biol Chem. 2007;282:5461–52.
299. Castillo K, Nassif M, Valenzuela V, Rojas F, Matus S, Mercado G, et al. Trehalose delays the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons. Autophagy. 2013;9:1308–20.
300. Pupyshev AB, Tikhonova MA, Akopyan AA, Tenditnik MV, Dubrovina NI, Korolenko TA. Therapeutic activation of autophagy by combined treatment with rapamycin and trehalose in a mouse MPTP-induced model of Parkinson's disease. Pharmacol Biochem Behav. 2019;177:1–11.
301. Milnerwood AJ, Cummins DM, Dailler GM, Brown JY, Vats avayai SC, Milnerwood AJ, Cummings DM, Dallerac GM, Brown JY, Vats avayai SC, et al. Rapamycin alleviates toxicity of different aggregate-prone proteins. Hum Mol Genet. 1999;8:839–48.
302. Pupyshev AB, Tikhonova MA, Akopyan AA, Tenditnik MV, Dubrovina NI, Korolenko TA. Therapeutic activation of autophagy by combined treatment with rapamycin and trehalose in a mouse MPTP-induced model of Parkinson's disease. Pharmacol Biochem Behav. 2019;177:1–11.
303. Murphy KP, Carter RJ, Lisse LA, Mangiarini L, Mahal A, Bates GP, et al. Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. J Neurosci. 2000;20:5115–23.
304. Udsin MT, Shelbourne PF, Myers RM, Madison DV. Impaired synaptic plasticity in mice carrying the Huntington's disease mutation. Hum Mol Genet. 1999;8:839–46.
305. Berger Z, Ravi Kumar B, Menzies FM, Oroz LG, Undervood BR, Pangaloos MN, et al. Rapamycin alleviates toxicity of different aggregate-prone proteins. Hum Mol Genet. 2006;15:433–42.
306. Rosic A, Baldo B, Crochemore C, Marcellin D, Papagetti P. Induction of autophagy with catalytic mTOR inhibitors reduces huntingtin aggregates in a neuronal cell model. J Neurochem. 2011;119:398–407.
307. Ravi Kumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, et al. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet. 2004;36:585–95.
308. Pryor WM, Bagnoli M, Shahani N, Swamkr S, Huang WC, Page DT, et al. Huntington promotes mTORC1 signaling in the pathogenesis of Huntington's disease. Sci Signal. 2014;7:ra103.
347. Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. Nat Rev Drug Discov. 2011;10:868–80.

348. Chiarelli F, Evangelisti C, McCubrey JA, Martelli AM. Current treatment strategies for inhibiting mTOR in cancer. Trends Pharmacol Sci. 2015;36:124–35.

349. Jiang T, Yu JT, Zhu XC, Tan MS, Wang HF, Cao L, et al. Temsirolimus promotes autophagic clearance of amyloid-beta and provides protective effects in cellular and animal models of Alzheimer’s disease. Pharmacol Res. 2014;81:54–63.

350. Jiang T, Yu JT, Zhu XC, Zhang QQ, Cao L, Wang HF, et al. Temsirolimus attenuates tauopathy in vitro and in vivo by targeting tau hyperphosphorylation and autophagic clearance. Neuropharmacology. 2014;85:121–30.

351. Cassano T, Magino A, Giovagnoli S, Polchi A, Calcagnini S, Pace L, et al. Early intrathecal infusion of everolimus restores cognitive function and mood in a murine model of Alzheimer’s disease. Exp Neurol. 2019;311:88–105.

352. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer’s disease: a population-based case-control study. J Am Geriatr Soc. 2012;60:916–21.

353. Koenig AM, Mechanic-Hamilton D, Xie SX, Combs MF, Cappola AR, Xie L, et al. Effects of the Insulin Sensitizer Metformin in Alzheimer Disease: Pilot Data From a Randomized Placebo-controlled Crossover Study. Alzheimer Dis Assoc Disord. 2017;31:107–13.

354. Park SY, Lee HR, Lee WS, Shin HK, Kim HY, Hong KW, et al. Glosostanol Modulates Autophagic Degradation of beta-Amyloid Peptide via SIRT1-Coupled LKB1/AMPKalpha Signaling in Neuronal Cells. PLoS One. 2016;11:e0160620.

355. Salminen A, Kaarniranta K, Haapasalo A, Soininen H, Hiltnen M. AMP-activated protein kinase: a potential player in Alzheimer’s disease. J Neurochem. 2011;118:460–74.

356. Wang C, Zhang X, Teng Z, Zhang T, Li Y. Downregulation of PI3K/Akt/mTOR signaling pathway in curcumin-induced autophagy in APP/PS1 double transgenic mice. Eur J Pharmacol. 2014;740:312–20.

357. Sarkar S, Perlstein EQ, Imarios S, Pineau S, Cordenier A, Maglathlin RL, et al. Small molecules enhance autophagy and reduce toxicity in Huntington’s disease models. Nat Chem Biol. 2007;3:331–8.

358. Vieira MNN, Lima-Filho RAS, De Felice FG. Connecting Alzheimer’s disease to diabetes: Underlying mechanisms and potential therapeutic targets. Neuropharmacology. 2018;136:60–71.

359. Butterfield DA, Boyd-Kimball D. Oxidative Stress, Amyloid-beta Peptide, and Altered Key Molecular Pathways in the Pathogenesis and Progression of Alzheimer’s Disease. J Alzheimers Dis. 2018;62:1345–67.

360. Liang H, Nie J, Van Skike CE, Valentine JM, Orr ME. Mammalian Target of Rapamycin at the Crossroad Between Alzheimer’s Disease and Diabetes. J Alzheimers Dis. 2018;62:1345–67.

361. Mannaa M, Kramer S, Boschmann M, Gollasch M. mTOR and regulation of energy homeostasis in humans. J Mol Med (Berl). 2013;91:1167–75.

362. Tischmeyer W, Schicknick H, Kraus M, Seidenbecher CI, Staak S, Scheich H, et al. Rapamycin-sensitive signalling in long-term consolidation of auditory cortex-dependent memory. Eur J Neurosci. 2003;18:942–946.

363. Yang H, Shi O, Jin Y, Henri-Chaouch P, Qiao H, Cai C, et al. Functional protection of learning and memory abilities in rats with vascular dementia. Restor Neurol Neurosci. 2014;32:689–700.

364. Romine J, Gao X, Xu XM, So KF, Chen J. The proliferation of amplifying neural progenitor cells is impaired in the aging brain and restored by the mTOR pathway activation. Neurobiol Aging. 2015;36:1716–26.

365. Xie R, Wang P, Ji X, Zhao H. Ischemic post-conditioning facilitates brain recovery after stroke by promoting Akt/mTOR activity in nude rats. J Neurochem. 2013;127:723–32.

366. Maiese K. Neuronal Activity, Mitogens, and mTOR: Overcoming the Hurdles. Adv Exp Med Biol. 2019;1128:185–190.

367. Jahrling JB, Laberge RM. Age-Related Neurodegeneration Prevention Through mTOR Inhibition: Potential Mechanisms and Remaining Questions. Curr Top Med Chem. 2015;15:2139–51.

368. Kaeberlein M, Galvan V. Rapamycin and Alzheimer’s disease: Time for a clinical trial? Sci Transl Med. 2019;11:eaar4289.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.