Molecular Neurodegeneration

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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 (ptau) 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 rapalogs 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 mGlu-R-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

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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, 4E-BP1 (eIF-4E binding protein) and ribosome biogenesis, p70S6K1 (p70 ribosomal protein S6 kinase 1) [17]. As synaptic plasticity and dendritic spine maintenance require *de novo* protein synthesis, mTORC1 supports the biological processes that underlie learning and long-term memory [17–19]. Accordingly, neuronal growth factors known to support learning and memory, such as BDNF and EGF, do so through mTOR activation [20, 21]. By contrast, the pharmacologic mTORC1 inhibitor, rapamycin, or genetic reductions in mTORC1, block several types of memory consolidation such as fear conditioning and late phase-LTP (long-term potentiation) [6, 7, 22]. Analogous to brain, knockout of either Raptor or mTOR or application of specific inhibitors in skeletal muscle results in a muscular dystrophy [23, 24]. Inhibition of autophagy (see below) and stimulation of mitochondrial respiration are other key mTOR roles [25, 26] affecting cell growth, division, proliferation, survival and aging.

The Tuberous Sclerosis protein complex, TSC1/2, proximally inhibits mTORC1 by preventing the conversion of the mTORC1 activator, Rheb (Ras homolog enriched in brain protein), into its active GTP-bound form (Fig. 1). Insulin/Akt signaling leads to the inactivating phosphorylation of TSC1/2, thus, activated Akt can release mTOR from TSC1/2-mediated inhibition [27, 28]. Neurotrophin-induced activation of mTOR takes place at lysosomal and plasma membranes [29, 30].

AMP-activated protein kinase (AMPK), another important nutrient sensor and cell energy broker that is activated by low substrate (glucose) levels and low ATP conditions (high ADP-AMP/ATP ratio), i.e. energy stress, is an important negative regulator of mTOR [31, 32]. Whereas insulin/Akt signaling leads to the inhibitory phosphorylation of TSC2 (on Ser-939, Ser-1088, and Thr-1422), AMPK phosphorylates TSC2 on a stimulatory residue (Ser-1387) [33–35]. AMPK itself is also negatively regulated by Akt [36]. By inhibiting mTORC1 via TSC2, one consequence of activated AMPK is to facilitate autophagy [37, 38]. Another is to inhibit protein translation [31]. A second mechanism by which AMPK inhibits protein synthesis is by phosphoactivating the elongation factor kinase, eEF2K (pS398). The target of eEF2K action is eEF2, which becomes inhibited (pT56). The consequence is to turn off the elongation step in mRNA translation [39, 40]. This action of AMPK therefore opposes the effect of mTORC1/p70S6K, which is to inhibit eEF2K (pS366). On the other hand when AMPK is inhibited, for instance in the palmitate model of insulin resistance, mTOR is stimulated [41]. Under the latter condition, as well under others such as endoplasmic reticulum stress and apoptosis, mTOR induction becomes detrimental to cell health. Rapamycin reverses this process by binding to FK506-binding protein- 12 (FKBP12) in a complex that allosterically blocks the catalytic activity of the mTOR subunit [41–46]. Akt and AMPK can also bypass TSC, to oppositely influence mTOR directly, via PRAS40 and Raptor phosphorylations, respectively.

One target of mTORC1, p70S6K, has an additional negative feedback role to down-regulate insulin/Akt signaling through an inactivating phosphorylation of the insulin receptor substrate 1 (IRS-1) [47] (Fig. 1). This function of stimulated mTORC1 to negatively regulate sustained Akt activation by insulin [48, 49] has central importance to the widely held notion that the AD brain is an insulin resistant organ [50, 51].

In synergy with insulin, the branched chain amino acids (BCAAs), especially leucine, potently stimulate mTOR to induce protein synthesis (reviewed in [52, 53]). It has long been known that mTOR is a nutrient sensor for amino

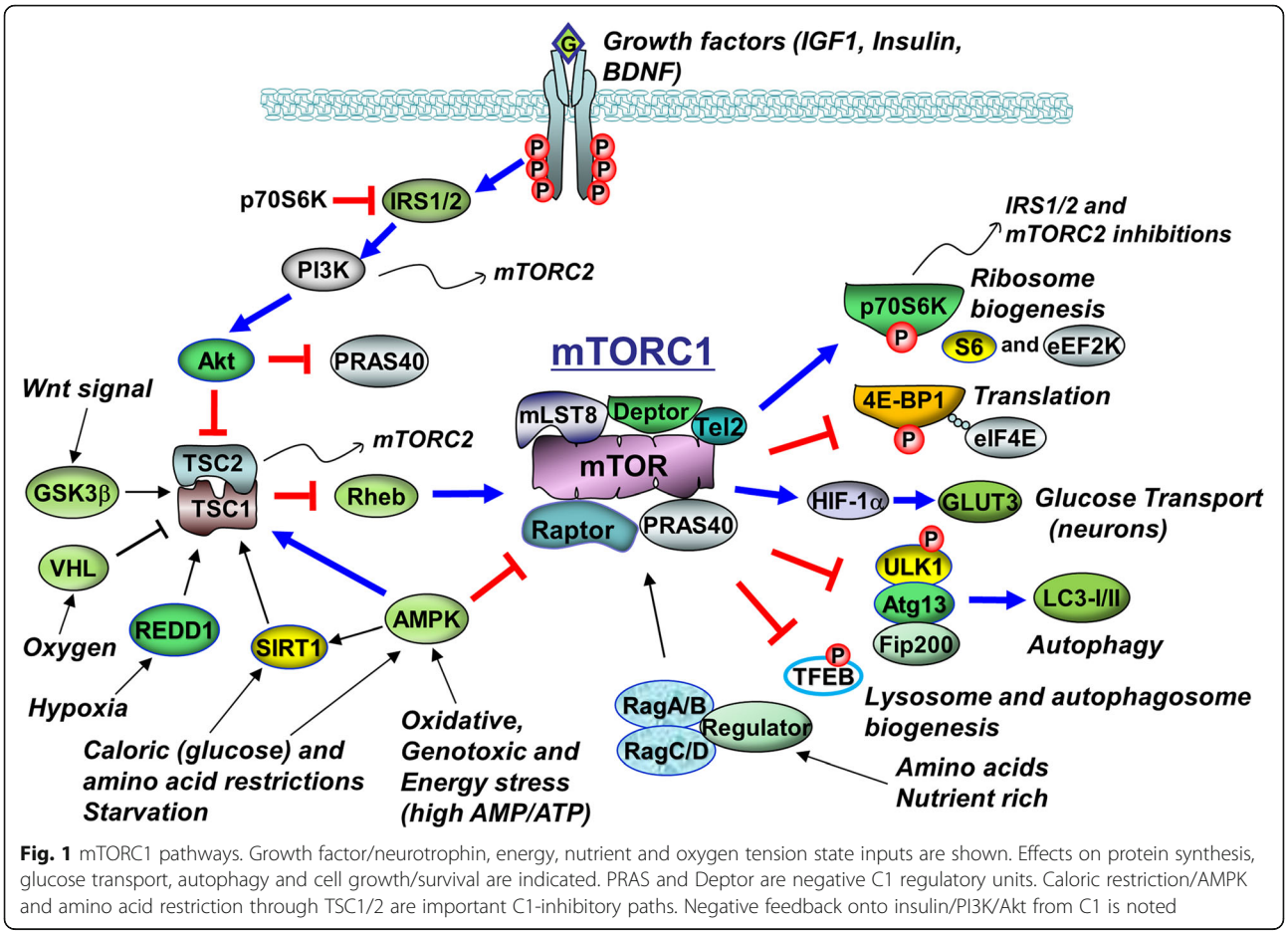


Fig. 1 mTORC1 pathways. Growth factor/neurotrophin, energy, nutrient and oxygen tension state inputs are shown. Effects on protein synthesis, glucose transport, autophagy and cell growth/survival are indicated. PRAS and Deptor are negative C1 regulatory units. Caloric restriction/AMPK and amino acid restriction through TSC1/2 are important C1-inhibitory paths. Negative feedback onto insulin/PI3K/Akt from C1 is noted

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 polypyrimidine 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), Ragulator (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 to the development of type II diabetes mellitus (T2DM) [65, 66]. Further evidence suggests that excess BCAA 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 have 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

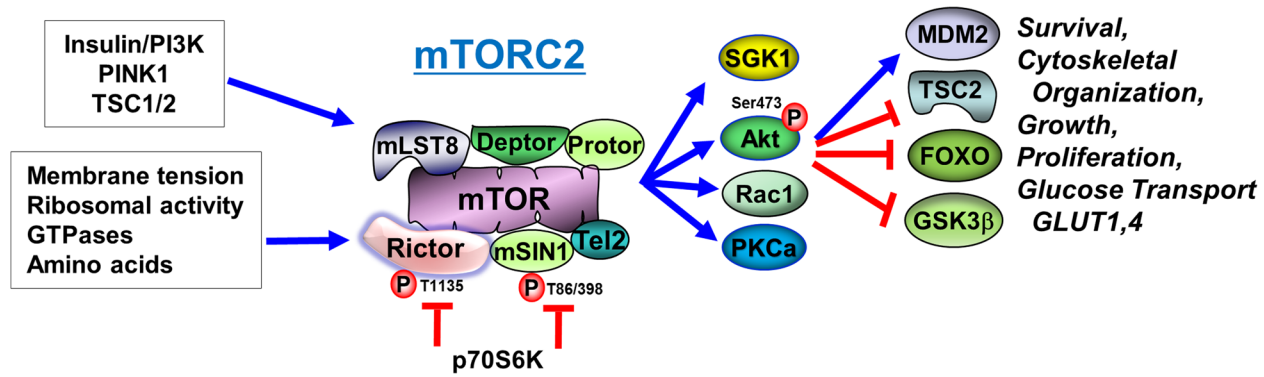


Fig. 2 mTORC2 pathways. The regulation of C2 is less clear, but is also responsive to the neurotrophins. Positive feedback onto Akt from C2 is noted. See abbreviations

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 LC3BI/II [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 $\geq$ 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 lll 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 alterations 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].

Table 1 mTOR dysregulation in Alzheimer's Disease

Model system			mTOR signaling						Akt signaling				Reference
AD or DS Brain	Trangenic mice	cell cultur or *in vitro*	phospho-mTORC1 S2448,S2481	phospho-p70S6K T389,T421,S424 /4EBP1	Autophagy markers Beclin,LC3-II	mTORC1 activity	protein translation	phospho-mTORC2	phospho-Akt, basal S473,T308	phospho-Akt,stim	Akt activity	phospho-GSK3B-S9	
•			↑						↑			↑	Griffin J Neurochem 2005; O'Neill Exp Gerontol 2013 145, 137
•				↑/									An Am J Pathol 2003; Pei FEBS lett 2006; Pei J Alz Dis 2008 144, 148, 158
	•	•	NC or ↑	/↑					↑				Bhaskar Mol Neurodegen 2009 154
	•	•	NC	↑/↑		↑							Caccamo JBC 2011,2010 155, 156
•	•			↑/↑	NC								Caccamo J Neurosci 2014,2015 159, 160
	•			↑/					↑			↓	Caccamo Neurobiol Dis 2018 202
•			↑	↑/	↓				↑				Perluigi BBA 2014; NBD 2015 50, 164
•			↑	↑/↑									Iyer J Neuro Exp Neurol 2014 153
•			↑	/↑	↓								Li FEBS J.2005 146
•			↑(adv.AD)	↑/				NC					Sun J Alz Dis 2014 152
•			↑	↑/↑	↓				↑				Tramutola J Neurochem 2015 51
		•		↑/↑									Norambuena Alz and Dem 2017 165
•			↑(↓to Ins)						↑	↓		NC or ↑	Talbot J Clin Invest 2012 136
•			↑										Majd Curr Alz Res 2018 147
		•		↑									Chiang J. Exp Med 2018 162
		•	↑	↑									Ou Brn Behav Immun 2017 163
•WBC	•	•	↓	↓(biphasic)					NC				Lafay-Chebassier J Neurochem 2005; J Neurosci Res 2006 166, 167
•	•		↓	↓/↓			↓		↓		↓		Ahmad Antiox Redox Sig 2017 168
•	•	•	↑(adv.AD)	NC or ↑	NC or ↑	↓(↓/2)	↓	NC	↓	↓	↓		Lee HK. J Alz Dis 2017; Mol Biol Cell 2009 135, 169
	•		↓	↓/↓	↓/NC								Francois J Neuroinflam 2014 170
	•		NC	↓/NC					↑				Damjanac Neurobiol Dis 2008 171
•	•	•		↓/↓					↓				Ma PLoS-1 2010; J Neurosci 2014 157,172
		•	↓							↓			Chen J Neurosci Res 2009 173
		•	↓		↑				↓				Xue Eur J Pharm 2014 174
•				↓/									Chano Brain Res 2007 175
	•			↓/	↑								Siman PLoS-1 2015 176
	•			↓	NC				NC			↓	Avrahami J Biol Chem 2013 177

Summary of the literature directly reporting on mTOR. The model systems employed by the various authors/laboratories referenced on the far right, are noted in the far left. 'Alzheimer or Down syndrome brain' may include other human cell types and either be post-mortem fixed, frozen or *ex vivo*. 'Transgenic mice' are rodent models that harbor human disease-causing mutations but include β-amyloid- or viral transgene-injections into wild type animals. 'Cell culture' refers to the use of primary neurons, immortalized lines, or mouse brain tissue slices that are transfected or exposed to β-amyloid, APP, tau or Presenilin as models of AD injury. Also included therein are other *in vitro* assays. mTOR signaling changes include phospho-mTOR, downstream targets phospho-p70S6K or p-4EBP-1, and enzymatic activity measurements as evidence for activation. The direction of change is noted, e.g. (↑) indicates hyperstimulation. Whether macroautophagy is initiated is also indicated. If data on Akt activation (p-Akt, insulin-stimulated p-Akt, downstream target phospho-GSK3β, or enzymatic activity is provided, a hyperactivation (↑) or inhibition (↓) is noted. A change qualified by context is noted by an 'or'. NC= no change. Most, but by no means all, studies favor hyperactivation of Akt and mTOR in various amyloid injury models, (top half of table) vs. inhibition (bottom half). Significant differences in model employed, stage of disease severity, time course, and other technical issues, account for the dichotomous findings (see text). Note that very few report on actual enzymatic activity assay. mTORC2 is relatively understudied in AD. See abbreviations. The compilation is illustrative only and not meant to be exhaustive. The authors apologize for any inaccuracies and unintended omissions

Table references are cited as : First Author, Journal, Year and reference number

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 *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].

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-S2448)/4E-BP1(p-S65) were associated with aberrant cell cycle reentry [154]. In addition to the cell culture studies, mTOR signaling was found to be abnormally upregulated after direct injection of Aβ oligomers into mouse hippocampus [156]. Basal (unstimulated) mTOR signaling increases are also described in triple (3x) AD and PDAPP transgenic mice. In these models, inhibition of 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 mTOR. In their model, Akt hyperactivation was deduced to drive PRAS40 phosphorylation, thereby de-repressing mTORC1 [156]. Recently, either genetic suppression or anti-Aβ immunization corrected abnormally hyperactivated mTOR and Akt in transgenic APP mice [162]. Consistent with these findings, Metformin was reported to attenuate spatial

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 has not been extensively investigated. The antidiabetic 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 overexpression 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 neurofibrillary 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, CamKIIα, PSD-95 and Arc [96, 225, 226]. How then is protein synthesis affected in the various neurodegeneration 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 Tuberous 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 derepressed 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/GSK3β-S9 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 postmortem 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 neurotrophin 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].

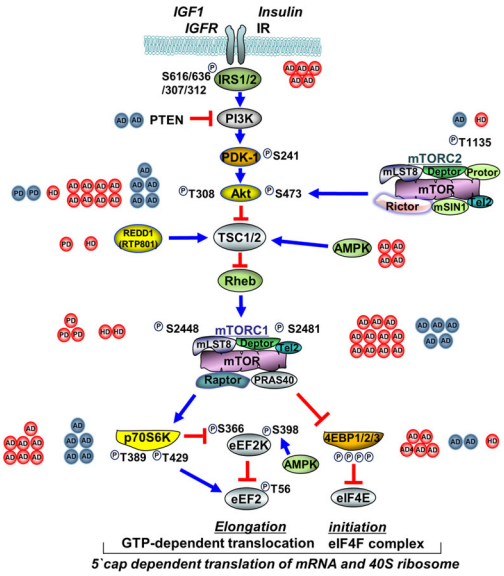
A significant body of data implicates pathologic induction of the gene for REDD1/RTP801 protein in Parkinson's disease, the only function of which as a regulator is to suppress mTOR [253]. Up-regulation of RTP801 is shown in various PD neurotoxin cell models (6OHDA, rotenone and MPP+) as well as in post 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 (phospho 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 6OHDA 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 6OHDA 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



Legend of refs.

AD/DS	p-mTORC1 (p-activated)	Talbot 2012 (basal) [136] Griffin 2005 [145] O'Neill 2013 [137] Perluigi 2014, 2015 [50, 164] Tramutola 2015 [51] Iyer 2014 [153] Sun 2014 [152] Tang 2014 [244] Li 2005 [146] Majd 2018 [147] Lee 2017 (basal) [135]	Talbot 2012 (activation) [136] Paccalin 2006 (WBCs) [236] Ahmad 2017 [168] Lee 2017 (activity) [135] Lafay-Chebassier 2005 (WBCs) [166]
	p-mTORC2 (p-activated)		Lee 2017 (basal and activity) [135]
	p-IRS-1 (p-inactivated)	Yarchoan 2014 [279] Talbot 2012 (basal) [136] Mahoney 2018 [280] Tramutola 2015 [51]	Talbot 2012 (activation) [136]
	p-Akt (p-activated)	Talbot 2012 (basal) [136] Griffin 2005 [145] O'Neill 2013 [137] Perluigi 2014 [50] Tramutola 2015 [51] Pei 2003 [150] Rickle 2004 (activity) [282] Yarchoan 2014 [279]	Talbot 2012 (activation) [136] Ahmad 2017 [168] Lee 2017 [135] Liu 2011 [281] Steen 2005 [130]
	p-p70S6K (p-activated)	An 2003, Pei 2006 [144, 158] Caccamo 2015 (activity) [159] Perluigi 2014, 2015 [50, 164] Tramutola 2015 [51] Iyer 2014 [153] Sonoda 2016 [151]	Ahmad 2017 [168] Ma 2010, 2014 [157, 172] Chano 2007 [175] Paccalin 2006 (WBCs) [236] Lafay-Chebassier 2005 (WBCs) [166]
	p-4EBP1 (p-inactivated)	Perluigi 2014, 2015 [50, 164] Tramutola 2015 [51] Iyer 2014 [153] Li 2005 [146]	Ahmad 2017 [168] Ma 2010, 2014 [157, 172]
	p-EIF4E, p-EIF2α	Iyer 2014 [153] Chang 2002 [283] Li 2004 [205] Paccalin 2006 (WBCs) [236]	
	p-eEF2K (p-inactivated)	Li 2005 [146]	
	p-AMPK (p-activated)	Majd 2018 [147] Zimmerman 2020 [210] Ma 2014 [172] Vingtdeux 2011 [208]	
	p-PTEN (p-activated)		Rickle 2006 [184] Tramutola 2015 [51] Griffin 2005 [145]
PD	mTOR (total)	Crews 2010 [269] Dijkstra 2015 [273] Wills 2012 [284]	
	p-Akt or total		Malagelada 2008 [261] Dijkstra 2015 [273]
	REDD1	Malagelada 2006 [253]	
HD	p-mTOR, p-Akt (p-activated)	Martin-Flores 2020 [285] Creus-Muncunill 2018 [286]	
	REDD1	Martin-Flores 2020 [285]	
	4EBP1 (total)		Creus-Muncunill 2019 [287]

Fig. 3 mTORC1 pathway and regulatory protein changes in human brain. Relative levels of phosphorylated forms and activity status of several major mTOR pathway components and regulators (PTEN, mTORC2, REDD1, AMPK) in neurodegenerative disorders. Only those studies that examined human AD/DS (Alzheimer's, Down's Syndrome), PD (Parkinson's), HD (Huntington's) or ALS (Amyotrophic Lateral Sclerosis) brain or peripheral cells (WBCs) are listed. In addition to those studies cited in Table 1, that examined mTOR pathway proper, we include those here that did not but still focus on one or more of the other components. In so far as the number of studies supporting a given direction of change (references reporting decreased levels in blue, increased in red, in affected vs. control brain) can be taken as some measure of consensus, each publication listed is represented visually by a single red (increased) or blue (decreased) dot next to the respective pathway protein. The dot also indicates the corresponding disease. Most studies only examined basal phospho-levels, whereas a few specified insulin-induced activations or assayed the enzymatic activity. For example, the majority of studies in AD brain favor *basal* mTORC1 over-activation (vs. inhibition; n=11 vs. 5); increased IRS-1 phospho-inhibition (5); AMPK over-activation (4) and increased 4EBP1 phospho-inhibition (5 vs. 2), whereas a more modest majority, favors Akt over-activation (8 vs. 5) and p-p70S6K hyperactivation (7 vs. 5). Nevertheless, the Akt and mTOR activation responses to insulin are depressed in cell model [135] and AD brain [136]

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 TFEB (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 dendritic 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 mTORC1 and C2, respectively, showed appropriate inhibitions. Still puzzling, everolimus, an allosteric mTOR inhibitor, had no effect [298, 299].

In an interesting application using a Drosophila model HD model, Lithium was used to activate mTOR-independent autophagy. This along with co-treatment with rapamycin to limit the undesirable side effect of GSK3β-mediated mTOR activation, resulted in enhanced mutant Htt clearance [302, 303]. But here too, there is evidence to the contrary in another rodent model of mutant-Htt, wherein mTOR activity was impaired. Reconstituted mTOR activation by constitutive Rheb proved cytoprotective [304]. In post mortem HD putamen, mHttQ111 transgenic mice, and in mHtt-bearing rat primary neurons, REDD1 (RTP801) is also upregulated and mediates cell death, as the case in PD [285]. Accordingly, downregulation of RTP801 prevented motor learning deficits in the mice. However, contrary to PD, Akt was hyperactivated, from increased Rictor action, 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, RTP801 silencing proved to normalize the Akt hyperphosphorylation by reducing Rictor and enhancing synaptic protein synthesis [285]. Although rapamycin was not tested in these last 3 citations, the HD-PD movement disorders axis demonstrates the duality of PI3K/Akt/mTOR pathway involvement in various neurodegenerations and the need to tailor treatment if this is to be targeted.

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].

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 and autophagy needs boosting by other mechanisms [311, 312]. Progranulin (GRN) mutations resulting in haploinsufficiency also cause familial FTD, and in GRN genetic models Trehalose, is also found to be neuroprotective [312].

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 surprising 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 phopsho-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 downregulated, 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 hAPPJ20 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 triple 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

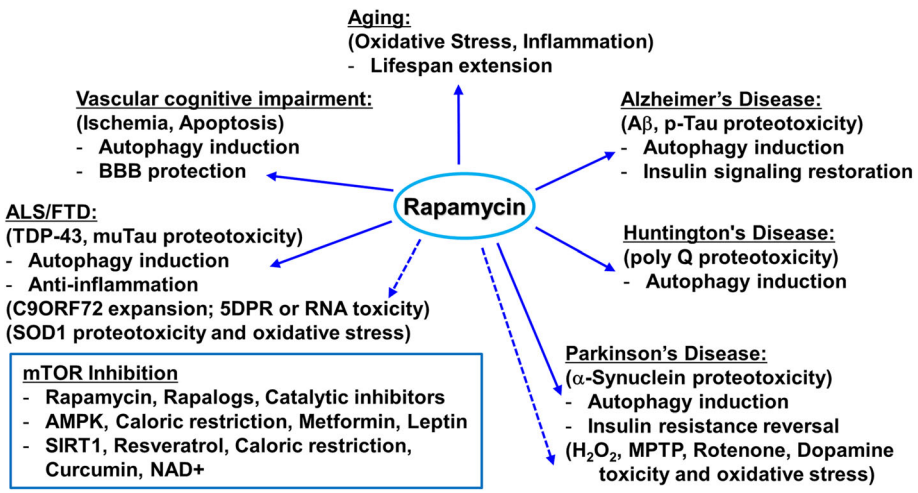


Fig. 4 mTOR inhibition in neurodegenerative disorders. As a nutrient sensor, mTOR has important homeostatic functions to regulate energy metabolism and support neuronal growth and plasticity. However, in Alzheimer's disease (AD), mTOR alternately plays important pathogenic roles by inhibiting both insulin signaling and autophagic removal of beta amyloid and Tau aggregates. Overactive mTOR also abets the cerebrovascular dysfunction of AD. Some of the other neurodegeneration conditions, discussed herein, have similar proteotoxic mechanisms (indicated in parentheses). The beneficial actions of mTOR inhibition with rapamycin are shown as arrows to the corresponding bulleted effects. Dashed arrows indicate unproven actions on those proteotoxic processes

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

[366], glucose intolerance via IRS-1 feedback inhibition [47] and learning impairment [330].

If the focus however is on alleviating proteotoxicity, the goal is to stimulate autophagy and protein removal. As mentioned, most studies would recommend mTOR inhibition and autophagy induction for neuroprotection, for instance in AD [119]. Still, there are other conditions for which mTOR activation would appear therapeutically beneficial. These may include where ischemia/apoptosis or stroke is the overriding pathology [363, 367, 368] noting that mTOR has anti-apoptosis properties, or where oxidative stress is of higher concern such as in certain PD and ALS models [259, 309]. Finally, the timing of mTOR inhibitor treatments can affect mTORC1 and C2 complexes differentially [369, 370]. Thus, it is plausible that an individualized balance between mTORC1 and C2 manipulations would need to be reached for each of the proteinopathies [135, 299].

The 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].

Abbreviations

AD: Alzheimer's disease; Akt: Protein kinase B; ALS: Amyotrophic Lateral Sclerosis; AMPK: AMP-activated protein kinase; Atg: Autophagy-related gene/protein; BCAA: Branch-chain amino acids; BDNF: Brain-derived neurotrophic factor; DJ1 (PARK7): Deptor, domain-containing mTOR-interacting protein; 4E-BP1: 4E-binding protein-1; FTD: Frontotemporal dementia; GSK-3β: Glycogen synthase kinase-3β; HD: Huntington's disease; HIF1-α: Hypoxia-inducible factor 1-α; IGF: Insulin-like growth factor; IRS-1: Insulin receptor substrate 1; LTD: Long-term depression; LTP: Long-term potentiation; MCI: Mild cognitive impairment; mLST8: Mammalian lethal with SEC13 protein 8; mSIN1: Mammalian stress-activated map kinase-interacting protein 1; mTOR: Mechanistic target of rapamycin; NO: Nitric oxide; NOS: Nitric oxide synthase; PARK7: Parkinson's disease protein 7; PD: Parkinson's disease; PDK1/2: Phosphoinositide-dependent kinase 1/2; PI3K: Phosphoinositide 3-kinase; PP2A: Protein phosphatase 2A; PRAS40: Proline-rich Akt substrate of 40kDa; p-tau: Phospho-tau; Protor: Protein observed with Rictor; PTEN: Phosphatase and tensin homolog; p70S6K1: p70 ribosomal S6 protein kinase 1; Rags: Ras-related GTP binding proteins; Raptor: Regulatory-associated protein of mTOR; Rheb: Ras homolog enriched in brain protein; Rictor: Rapamycin-insensitive companion of mTOR; SGK-1: Serum and glucocorticoid-regulated kinase 1; SIRT1: Sirtuin 1; TSC1/2: Tuberous sclerosis protein-complex; T2DM: Type II diabetes mellitus; ULK1: Unc-51-like kinase 1; Vps: Vacuolar protein sorting-associated protein

Authors' contributions

The author(s) read and approved the final manuscript.

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Competing interests

Authors declare that there is no conflict of interest.

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