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Mammalian Target of Rapamycin (mTOR) Pathways in Neurological Diseases

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Abstract

The mammalian target of rapamycin (mTOR) pathway is an essential cellular signaling pathway involved in a number of important physiological functions, including cell growth, proliferation, metabolism, protein synthesis, and autophagy. Dysregulation of the mTOR pathway has been implicated in the pathophysiology of a number of neurological diseases. Hyperactivation of the mTOR pathway, leading to increased cell growth and proliferation, has been most convincingly shown to stimulate tumor growth in the brain and other organs in the genetic disorder, tuberous sclerosis complex (TSC). In addition, mTOR may also play a role in promoting epileptogenesis or maintaining seizures in TSC, as well as in acquired epilepsies following brain injury. Finally, the mTOR pathway may also be involved in the pathogenesis of cognitive dysfunction and other neurological deficits in developmental disorders and neurodegenerative diseases. mTOR inhibitors, such as rapamycin and its analogs, may represent novel, rational therapies for a variety of neurological disorders.

Keywords

rapamycin; epilepsy; seizure; tuberous sclerosis; neurodegenerative disease

Introduction

The mammalian target of rapamycin (mTOR) is a ubiquitous serine-threonine protein kinase that regulates a number of important physiological functions, including cell growth, proliferation, metabolism, protein synthesis, and autophagy. mTOR is also critical for a number of brain-specific mechanisms, such as synaptic plasticity, learning, and cortical development. Significant advances have been made in understanding the complicated upstream and downstream components and regulation of the mTOR pathway and have been reviewed elsewhere.⁽¹⁻³⁾ Briefly, mTOR participates in the formation of at least two functional complexes, mTORC1 and mTORC2. mTORC1 consists of mTOR itself, the regulatory protein raptor, and several other binding proteins. mTORC2 is composed of mTOR, the regulatory protein rictor, and other binding proteins. mTORC1 primarily exerts its functional effects via regulation of ribosomal biogenesis and protein synthesis through controlling the ribosomal protein S6 or the translation initiating factor, eIF4E, which secondarily can influence a variety of processes, including cell growth, proliferation, and metabolism. mTORC1 is inhibited by rapamycin and other rapamycin analogs. In contrast, mTORC2 acts primarily through regulation of a number of other protein kinases and interactions with cytoskeletal elements of cells. While mTORC2 is relatively insensitive to

rapamycin inhibition, mTORC2 can be inhibited by mTOR inhibitors after prolonged exposure in certain cell types.

The mTOR pathway may respond to a variety of physiological stimuli and environmental conditions via modulation by a number of upstream signaling pathways (Fig. 1). Hamartin and tuberlin, proteins encoded by the tuberous sclerosis complex 1 and 2 genes, form a complex that normally inhibits the mTOR pathway via inhibition of the intermediary GTP-binding protein Rheb (Ras homolog enriched in brain). Multiple upstream pathways activate or inhibit the mTOR pathway either directly or by interacting with the hamartin-tuberlin complex. For example, in conditions of energy or nutrient surplus, growth factors, such as insulin, may stimulate the phosphoinositide-3 kinase (PI3K)/Akt pathway, which then activates the mTOR pathway and promotes increased cell growth and metabolism. In contrast, states of energy or nutrient deprivation may trigger other upstream pathways, such as the LKB1/AMPK pathway, which ultimately inhibits mTOR activity and limits cell growth and metabolism.

While physiological regulation of the mTOR pathway is essential for normal cellular function, dysregulation of the mTOR pathway may promote the development or progression of disease under pathological conditions. Given the ubiquity of mTOR in various cell types throughout the body, mTOR may be involved in the pathogenesis of a number of systemic disorders, such as diabetes, cancer, and cardiovascular disease.^(3,4) In addition, abnormal mTOR signaling has also been implicated in a variety of neurological diseases (Fig. 2).^(5,6) In this review, I will highlight the most recent scientific findings and clinical applications of the mTOR pathway in neurological disorders, including tuberous sclerosis complex (TSC), brain tumors, epilepsy, autism/neurodevelopmental disorders, and neurodegenerative diseases. In parallel, I will discuss the potential therapeutic utility of mTOR inhibitors for these disorders (Table 1).

Tuberous Sclerosis Complex (TSC)

TSC probably represents the prototypical disease related to abnormal mTOR signaling. TSC is an autosomal dominant genetic disorder involving tumor or hamartoma formation in multiple organs, including the heart, kidney, lungs, eyes, skin, and brain.^(7,8) While symptoms may occur as a result of tumors and other abnormal lesions in any of these organs, neurological involvement, including epilepsy, developmental delay, mental retardation, behavioral disorders, and autism, often constitutes the most common and disabling manifestations of TSC. The pathological hallmark of TSC is the cortical tuber, a focal malformation of cortical development, which is histologically identical to certain types of isolated focal cortical dysplasia. Epilepsy may be directly triggered by cortical tubers, although intracranial recordings suggest that seizures actually originate from the regions surrounding the tubers.⁽⁹⁾ The pathophysiology of cognitive deficits and autism is even less understood, but may relate to the disruption of normal cortical circuits by tubers or to tuber-independent cellular and molecular defects of neurons and glia. In addition to tubers, subependymal nodules, consisting of small collections of dysplastic neurons and glia, commonly align the ventricular walls. While subependymal nodules are asymptomatic, subependymal giant cell astrocytomas (SEGAs) may grow progressively and constitute a substantial risk for obstructive hydrocephalus, a neurosurgical emergency. Besides the neurological manifestations of TSC, tumor growth in other organs may also cause significant clinical problems. In particular, enlarging renal angiomyolipomas (AMLs) may lead to hypertension, bleeding, and renal failure. The interstitial lung disease, lymphangiomyomatosis (LAM), may occur particularly in adult women with TSC and cause progressive dyspnea, pneumothoraces, and respiratory insufficiency. Until the recent

emergence of mTOR inhibitors, all treatments for manifestations of TSC have involved symptomatic therapy or surgical resection of tumors.

Mutations in two different genes, *TSC1* and *TSC2*, which encode the proteins hamartin and tuberlin, respectively, have been identified to cause TSC.^(10,11) A similar phenotype may result from a mutation in either of these two genes because hamartin and tuberlin bind together to form a single functional complex. As the hamartin-tuberlin complex normally inhibits the mTOR pathway, mutation of either *TSC1* or *TSC2* leads to abnormal disinhibition of the mTOR pathway. This hyperactivation of the mTOR pathway may result in increased cell growth and proliferation, which can promote tumorigenesis in TSC patients, as well as other downstream functional effects.

The relevance of the mTOR pathway in the pathophysiology of TSC was first suggested in simplified biological systems, such as drosophila and yeast, in which hamartin and tuberlin were shown to inhibit mTOR signaling.^(12–15) Demonstration of this basic interaction immediately indicated that mTOR inhibitors, such as rapamycin, could be of strong therapeutic value in TSC. The potential utility of mTOR inhibitors for tumors in TSC was first established for renal tumors in mouse models of TSC.⁽¹⁶⁾ Subsequently, rapamycin was also shown to decrease the abnormal proliferation of astrocytes in other TSC knock-out mice, suggesting that mTOR inhibitors may represent an appropriate treatment for SEGAs.⁽¹⁷⁾

Several clinical trials of mTOR inhibitors for tumor growth in TSC patients have been conducted in recent years. First of all, rapamycin or the rapamycin analog, everolimus, has been shown to decrease SEGA growth in TSC patients.^(18,19) These studies have led to the official regulatory approval of the mTOR inhibitor, everolimus, for treatment of SEGAs in TSC in the United States. Although mTOR inhibitors clearly reduce SEGA size, one important caveat is that the tumors tend to grow back if the drug is discontinued, indicating that long-term treatment may be necessary to maintain effectiveness. In addition to SEGAs, clinical trials also support the efficacy of mTOR inhibitors for renal AMLs and pulmonary LAM,^(20,21) and official approval for AMLs has just occurred. Another potential use of rapamycin that is under clinical trials is topical administration for facial angiofibromas.⁽²²⁾ Thus, there appear to be multiple promising therapeutic applications of mTOR inhibitors for treating various tumor phenotypes in TSC.

Non-TSC-related Brain Tumors

In addition to SEGAs in TSC, the mTOR pathway has been implicated in the pathophysiology of other brain tumors unrelated to TSC, particularly other types of gliomas. Active expression of upstream and downstream mTOR pathway markers, such as Akt, S6K, and S6, occurs in human gliomas and correlates with the malignancy grade.^(23,24) Furthermore, specific genetic mutations have been found in gliomas that could lead to downstream activation of the PI3K/Akt/mTOR signaling, such as in the epidermal growth factor receptor (EGFR) and phosphatase and tensin homolog on chromosome 10 (PTEN) genes.^(25–27) mTOR inhibitors have been reported to inhibit growth of tumor cells in xenografts of human gliomas implanted into mouse models.^(28–30) The mechanism of the antitumor effects of rapamycin against gliomas is still being investigated, but may involve direct cytotoxic and antiproliferative effects, inhibition of vascular endothelial growth factor and angiogenesis, decreased invasive propensity, and increased sensitivity to radiation.^(30,31)

Based on the encouraging basic science and preclinical findings, a couple of clinical trials have been conducted testing the effect of mTOR inhibitors on patients with gliomas. Phase II trials of the mTOR inhibitor, temsirolimus (CCI-779), in patients with glioblastoma

multiforme have reported good tolerability and modest effects on radiographic or other clinical criteria in a subset of patients, but overall did not demonstrate efficacy in primary endpoints of time to tumor progression and survival.^(32,33) Possible reasons for poor efficacy include pharmacokinetic issues and blood-brain barrier penetration. However, much attention is now focused on the complex role of parallel and feedback signaling mechanisms in tumorigenesis. In particular, primary or feedback activation of Akt with mTOR inhibition may lead to alternative pathway activation that may cause resistance to mTOR inhibitors and persistent tumor growth. Newer research strategies have focused on inhibiting multiple mTOR-related signaling mechanisms, such as using dual PI3K-mTOR inhibitors, mTORC1/mTORC2 inhibitors, and other combination therapies.^(34,35) However, unlike the established efficacy of rapamycin in treating SEGAs in TSC patients, targeting the mTOR pathway as anti-tumor treatments for non-TSC-related gliomas is clearly more complicated and awaits further investigations before establishment in clinical practice.

Epilepsy

While the role of the mTOR pathway in tumorigenesis and the associated utility of mTOR inhibitors for treating tumors in TSC is firmly documented, the importance of mTOR in the common, disabling neurological symptoms of TSC, in particular epilepsy, autism, and cognitive deficits, is not as well established. These neurological manifestations of TSC typically are not directly related to tumor growth per se. Even if epilepsy is caused by cortical tubers, tubers are developmental malformations that do not grow progressively like tumors. Other cellular and molecular abnormalities, not directly related to cell growth and proliferation, likely promote epileptogenesis, such as aberrant circuit formation and dysregulated neurotransmitter receptors or ion channels.⁽³⁶⁾ Given the known role of the mTOR pathway in regulating such functions as protein synthesis and synaptic plasticity, it is reasonable to hypothesize that mTOR is also involved in mechanisms of epileptogenesis in TSC. However, whether mTOR inhibitors represent a rational treatment for seizures and neuropsychiatric symptoms in TSC patients has not been definitively established at this point.

Although the specific downstream mechanisms of epileptogenesis are still uncertain, animal models of TSC do indicate that the mTOR pathway is important for the pathophysiology of epilepsy in TSC and that mTOR inhibitors may represent appropriate treatments to either prevent epilepsy (antiepileptogenic) or inhibit existing seizures (antiseizure).^(37,38) Several mouse models of TSC, involving conditional inactivation of *Tsc1* or *Tsc2* in neurons, glia, or brain progenitor cells, have been documented to have epilepsy. Early treatment with rapamycin prior to the onset of seizures can prevent the development of epilepsy, as well as many of the pathological and molecular changes in the brain that likely promote epileptogenesis in these mice.^(17,39–42) In addition, later treatment of mice that already have epilepsy can decrease seizure frequency. mTOR inhibitors may also improve cognitive deficits in mouse models of TSC.⁽⁴³⁾ Similar to the reversible effects on tumor growth in TSC patients, unfortunately the beneficial effects of rapamycin on seizures do not persist if rapamycin is stopped.

Data on the utility of mTOR inhibitors for epilepsy in TSC patients are more limited. A couple of case reports suggest that mTOR inhibitors may decrease seizure frequency in TSC patients being treated for SEGAs.^(44,45) In larger clinical trials primarily testing the effect of everolimus on SEGA growth, seizures were examined as a secondary measure and a significant decrease in seizure frequency was reported with everolimus.⁽¹⁹⁾ However, these previous reports could have been confounded by an indirect effect of everolimus on seizures related to decreased SEGA growth and hydrocephalus. Another clinical trial is currently ongoing, examining the effect of everolimus on seizure frequency as the primary outcome

measure, independent of SEGAs. Preliminary results from this uncontrolled study also support that mTOR inhibitors may decrease seizure frequency in TSC patients with established epilepsy.⁽⁴⁶⁾ However, larger, placebo-controlled trials are still needed to definitively establish whether mTOR inhibitors are an effective treatment for epilepsy in TSC.

Beyond symptomatic treatment of ongoing epilepsy, perhaps a much more significant question is whether mTOR inhibitors can actually prevent epilepsy when started prior to the first seizure.^(37,38) While current seizure medications simply suppress seizures as symptomatic therapy, it has been recognized for a while that novel treatments are needed that have disease-modifying or “antiepileptogenic” properties to prevent the development or progression of epilepsy. TSC patients may represent a very appropriate population to develop and test a preventative/antiepileptogenic therapy for a couple of reasons. While many patients with epilepsy present with seizures unpredictably without any previously known risk factors, some TSC patients can be identified at a young age before the onset of epilepsy due to non-neurological findings of TSC. Thus, it is feasible to identify and start a preventative treatment on this subset of TSC patients. Furthermore, TSC patients are at high risk (~80–90%) of developing epilepsy. Therefore, it can be justified to start a neurologically-asymptomatic TSC patient on antiepileptogenic therapy as a preventative measure. However, despite the evidence for antiepileptogenic effects of mTOR inhibitors in animal models of TSC, designing and conducting antiepileptogenic clinical trials are extremely difficult and at this point, there are no human data indicating whether mTOR inhibitors have antiepileptogenic properties to prevent epilepsy in TSC patients.

Similar to TSC, several other, relatively rare genetic disorders involve dysregulation of the mTOR pathway and an increased risk for tumors and epilepsy. Pten is a tumor suppressor gene that regulates growth via modulation of the phosphatidylinositol-3 kinase (PI3K)/AKT pathway which is an upstream activator of the mTOR pathway (Fig. 1). Pten knock-out mice exhibit neuronal hypertrophy, megalencephaly, and seizures, and treatment with mTOR inhibitors decreases the pathological abnormalities and suppresses seizures.^(47–49) In one Pten mouse model, rapamycin not only decreased seizures, but also reversed deficits in social behavior suggestive of autism.⁽⁵⁰⁾ Similar to the TSC models, seizures return within weeks of cessation of rapamycin therapy, although subsequent intermittent rapamycin treatment is able to maintain a long-term antiseizure effect.⁽⁴⁹⁾ The link between mTOR and epilepsy is further supported in patients with a rare disorder known as polyhydramnios, megalencephaly, and symptomatic epilepsy syndrome (PMSE), in which deletions in the *STRADA* gene cause dysregulation of mTOR signaling via a reduction in the LKB1/AMPK pathway.⁽⁵¹⁾ Finally, genetic polymorphisms and biochemical markers of mTOR activation have been identified in patients with isolated focal cortical dysplasia, a common etiology of intractable epilepsy.^(52–60) While mTOR inhibitors may represent rational therapies for seizures in these other types of epilepsy, such clinical use has not yet been reported.

While genetic epilepsies affecting the mTOR pathway are relatively rare, there is increasing interest as to whether the mTOR pathway may be involved in other, more common types of epilepsy, such as following acquired brain injury. In animal models, mTOR signaling is abnormally increased following traumatic brain injury or status epilepticus that leads to chronic epilepsy.^(61–65) The mTOR pathway is also activated by hypoxia or toxin-related insults that acutely induce neonatal seizures or infantile spasms.^(66,67) mTOR inhibitors can decrease pathological abnormalities that are associated with epileptogenesis, in particular mossy fiber sprouting.^(61–64) Rapamycin may decrease behavioral and cognitive deficits in animal models of traumatic brain injury.⁽⁶⁸⁾ There is some evidence that mTOR inhibitors can inhibit existing seizures or prevent epilepsy in some animal models of acquired epilepsy,^(62–64,66,67) although other studies have found negative results.^(69–71) Variability

among different studies in effectiveness for epilepsy may depend on a number of factors, such as dose, timing, and animal model. Even when found to be effective, whether mTOR inhibitors primarily have antiepileptogenic/preventative effects or traditional seizure-suppressing effects is still debated. With a number of issues still to be resolved on a basic science and animal model level, mTOR inhibitors have not been tested in patients with acquired brain injury or post-injury epilepsy.

Other Neurodevelopmental Disorders and Autism

In addition to TSC, there are a number of other genetic disorders characterized primarily by neurodevelopmental disabilities, such as autism, mental retardation, and other cognitive deficits, as well as epilepsy. Interestingly, abnormal mTOR signaling has also been implicated in many of these diseases, including Fragile X syndrome, Down syndrome, and Rett syndrome.⁽⁷²⁾ The potential involvement of dysregulated mTOR signaling in multiple neurological disorders characterized by cognitive deficits should not be surprising, as the mTOR pathway has been implicated in mediating physiological mechanisms of learning and memory. In particular, experience-dependent forms of synaptic plasticity, such as long-term potentiation and depression, largely rely on protein synthesis activated by the mTOR pathway.^(73,74) Furthermore, changes in dendritic morphology may represent a structural substrate for memory and can be regulated by the mTOR pathway,^(75,76) whereas abnormalities in dendritic morphology have been demonstrated in these neurogenetic syndromes, including TSC, Fragile X, Down, and Rett syndromes.⁽⁷⁷⁾

Fragile X syndrome is one of the most common causes of inherited mental retardation and autism. In this disease, abnormal trinucleotide repeat expansion of the *Fragile X mental retardation 1 (FMR1)* gene on the X chromosome leads to loss of expression of the corresponding protein (FMRP). FMRP is an RNA binding protein that normally prevents protein synthesis via binding of messenger RNA. In addition, the mTOR pathway has been found to have increased activation in a *Fmr1* KO mouse and in pathological brain specimens from Fragile X patients.^(78,79) Although the biochemical link between FMRP and mTOR is not entirely clear, there is some evidence that FMRP may normally inhibit the PI3K/Akt pathway and that loss of FMRP function would then lead to hyperactivation of PI3K/Akt and subsequently the mTOR pathway.⁽⁷⁸⁾

Similarly, in a mouse model of Down syndrome, the most common genetic cause of mental retardation, there is also evidence for increased mTOR pathway activity, which may relate to increased levels of brain-derived neurotrophic factor.⁽⁸⁰⁾ In contrast, in a mouse model of Rett syndrome, another common genetic cause of mental retardation and autism, the mTOR pathway shows signs of decreased activation.⁽⁸¹⁾

Overall, these findings suggest the possibility of using mTOR modulators to treat many of these neurogenetic causes of mental retardation and autism associated with mTOR hyperactivation. In a mouse model of TSC, rapamycin reversed deficits in spatial learning and long-term potentiation.⁽⁴³⁾ Effects of rapamycin on cognitive deficits in mouse models of Fragile X and Down syndrome are currently under investigation.⁽⁷²⁾ While no clinical reports of the effects of mTOR inhibitors on autism or cognitive measures presently exist in people, there is currently at least one ongoing clinical trial investigating effects of mTOR inhibitors on cognitive outcomes in TSC patients (NCT01289912, clinicaltrials.gov).

Neurodegenerative Diseases

On the opposite end of the developmental spectrum, classic neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's disease, are characterized by accumulation of abnormal misfolded or toxic proteins and associated neuronal death. As the

mTOR pathway is involved in regulation of cell death and survival mechanisms, it makes sense that mTOR has also been implicated in the pathophysiology of these neurodegenerative disorders.⁽⁶⁾ In particular, mTOR signaling may modulate mechanisms of apoptotic cell death. Furthermore, the mTOR pathway normally inhibits autophagic mechanisms, which help degrade and clear aggregated or accumulated proteins. Thus, mTOR inhibitors may represent a rational therapy for this group of diseases by inducing autophagy or directly regulating neuronal death mechanisms.

Alzheimer's disease involves progressive cognitive dysfunction and memory loss associated with development of both extracellular plaques containing amyloid-beta aggregates and intracellular neurofibrillary tangles composed of hyperphosphorylated microtubular protein tau. Increased mTOR activity is seen in mouse models of Alzheimer's disease and correlates with the progression of abnormal amyloid-beta levels and tau pathology.⁽⁸²⁾ Furthermore, mTOR and its downstream signaling kinases promoting phosphorylation are abnormally increased in neurofibrillary tangles from Alzheimer's brains and may contribute directly to hyperphosphorylation of tau.⁽⁸³⁾ The relationship between amyloid-beta and mTOR is more complex, as amyloid-beta itself can increase mTOR activity,⁽⁸²⁾ but conversely rapamycin can reduce amyloid-beta levels.⁽⁸⁴⁾ Thus, mTOR inhibitors may represent rational therapy for Alzheimer's disease by reducing the hyperphosphorylation of tau, decreasing amyloid-beta levels, and inducing autophagy. In fact, mTOR inhibitors have been reported to reverse cognitive deficits in mouse models of Alzheimer's disease.^(82,84)

Huntington's disease, an autosomal dominant disorder, involves relatively selective neurodegeneration in the basal ganglia and cortex, related to trinucleotide repeat expansion of polyglutamine on the huntingtin protein. Mutant huntingtin protein is not effectively cleared from neurons, leading to accumulation of toxic intracellular aggregates and associated neuronal death. In mouse models and human brains of Huntington's disease, mTOR has been shown to be sequestered in polyglutamine aggregates. mTOR inhibitors can enhance autophagy and consequently reduce huntingtin accumulation and associated neuronal death in cellular and animal models of Huntington's disease.^(85,86) Furthermore, rapamycin can improve motor deficits in mouse models of Huntington's disease.⁽⁸⁵⁾

Finally, Parkinson's disease is characterized by a progressive movement disorder related to loss of specific populations of central and peripheral neurons, including dopaminergic cells in the substantia nigra. The mTOR pathway may regulate cell death mechanisms in Parkinson's disease via interaction with a stress response protein RTP801, which is activated by oxidative stress and induces apoptotic cell death. Rapamycin has been reported to inhibit expression of RTP801 and correspondingly protect against neuronal death in in vitro and in vivo models of Parkinson's disease.⁽⁸⁷⁾ Alternatively, dopaminergic neuronal death in Parkinson's disease has been hypothesized to be related to oxidative stress-induced lysosomal depletion and a resulting accumulation of undegraded autophagosomes. By inducing autophagy, rapamycin was shown to restore normal lysosomal levels and attenuate dopaminergic neuronal death in a cellular model of Parkinson's disease.⁽⁸⁸⁾ Although the mechanisms may vary, cumulative evidence supports that mTOR inhibitors are neuroprotective in animal models of a variety of neurodegenerative diseases. At this point, however, no clinical trials have been conducted testing the effect of mTOR inhibitors on patients with these neurodegenerative disorders.

Future Directions

A number of issues need to be addressed in order to optimize the current use of mTOR inhibitors and to expand the clinical indications in various neurological diseases. With regard to the present indication for SEGAs in TSC patients, while everolimus has proven

efficacy in decreasing tumor growth, a potential limitation is the ill-defined duration of therapy. Cessation of treatment seems to result in a regrowth of tumors, so mTOR inhibitors are not a cure for tumors in TSC and long-term treatment is likely necessary to maintain efficacy.^(18–20) Since SEGAs often present in early childhood, this potentially would require treatment for decades or longer. Significant side effects that may occur with mTOR inhibitors, including chronic immunosuppression and associated opportunistic infections, make this prospect of long-term treatment less attractive. One potential option to alleviate this concern would be to use “drug holidays” or treatment paradigms with intermittent application of mTOR inhibitors. Animal model data suggest that intermittent use of mTOR inhibitors can maintain efficacy, but reduce risk of side effects, such as immunosuppression.^(49,89–91)

To expand the clinical indications of mTOR inhibitors beyond TSC-related tumors, additional basic and clinical data are needed. For epilepsy, if the encouraging preliminary data from ongoing uncontrolled clinical trials in TSC are confirmed, a placebo-controlled trial of an mTOR inhibitor for intractable epilepsy in TSC patients would be a reasonable, feasible next step. In contrast, testing the potential antiepileptogenic efficacy of mTOR inhibitors for preventing epilepsy is a much more complicated endeavor, involving a number of practical barriers and ethical issues. Some TSC patients can be identified at an early age prior to the onset of seizures due to non-neurological findings and may be appropriate candidates for starting a potential antiepileptogenic therapy. However, while a large proportion of TSC patients will develop epilepsy, a subset will not, thus exposing such patients to an unnecessary treatment with side effects. Ideally, biomarkers could first identify those patients that are at highest risk for epilepsy and the best candidates for an antiepileptogenic therapy. Although such biomarkers for epilepsy have not been definitely established, future studies might establish specific EEG or brain MRI abnormalities as biomarkers for epilepsy in TSC. Beyond TSC, other high-risk populations, such as patients with traumatic brain injury, could be candidates for antiepileptogenic treatment. Furthermore, cognitive deficits and autism from other neurogenetic syndromes with mTOR hyperactivation (e.g., Fragile X, Down syndrome) could be targeted, and neurodegenerative disorders could be considered for neuroprotective trials with mTOR inhibitors. However, expansion to these non-TSC neurological disorders should await more definitive data from animal models.

Summary/Conclusions

There is accumulating evidence that the mTOR pathway may be involved in the pathophysiology of a number of neurological diseases. At this point, this evidence is predominantly derived from basic science and animal model studies. However, these findings are starting to be translated into the clinical arena. TSC is the one disease in which the mTOR pathway has been established as a central component of its pathogenesis and mTOR inhibitors have proven benefit. The rapamycin analog, everolimus, has recently been approved for treatment of SEGA and AML growth in TSC patients, and similar approval for other TSC-related tumors, such as LAM, and angiofibromas, may soon follow. In contrast, for non-TSC-related gliomas, such as glioblastoma multiforme, initial clinical trials have not demonstrated clear efficacy of mTOR inhibitors, and focus is now shifted to dual pathway inhibitors and combination therapies. Preliminary clinical studies suggest that mTOR inhibitors may be beneficial for treating seizures in TSC patients with established epilepsy, but await definitive confirmation from controlled trials. While several studies with TSC mouse models suggest that mTOR inhibitors have antiepileptogenic properties for preventing epilepsy, clinical antiepileptogenic drug trials are difficult to conduct and have not yet been attempted with mTOR inhibitors in TSC patients. Similarly, there is a variety of evidence that mTOR inhibition may also have disease-modifying effects in animal models

of acquired epilepsy and various common neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's disease, but use of mTOR inhibitors have not been tested in patients with these diseases. Overall, considerable progress has been made in demonstrating the potential utility of mTOR inhibitors in a variety of neurological disorders. With ongoing progress in basic and clinical research, there are reasons to be optimistic that the clinical indications of mTOR inhibitors for neurological disease will continue to expand in the future.

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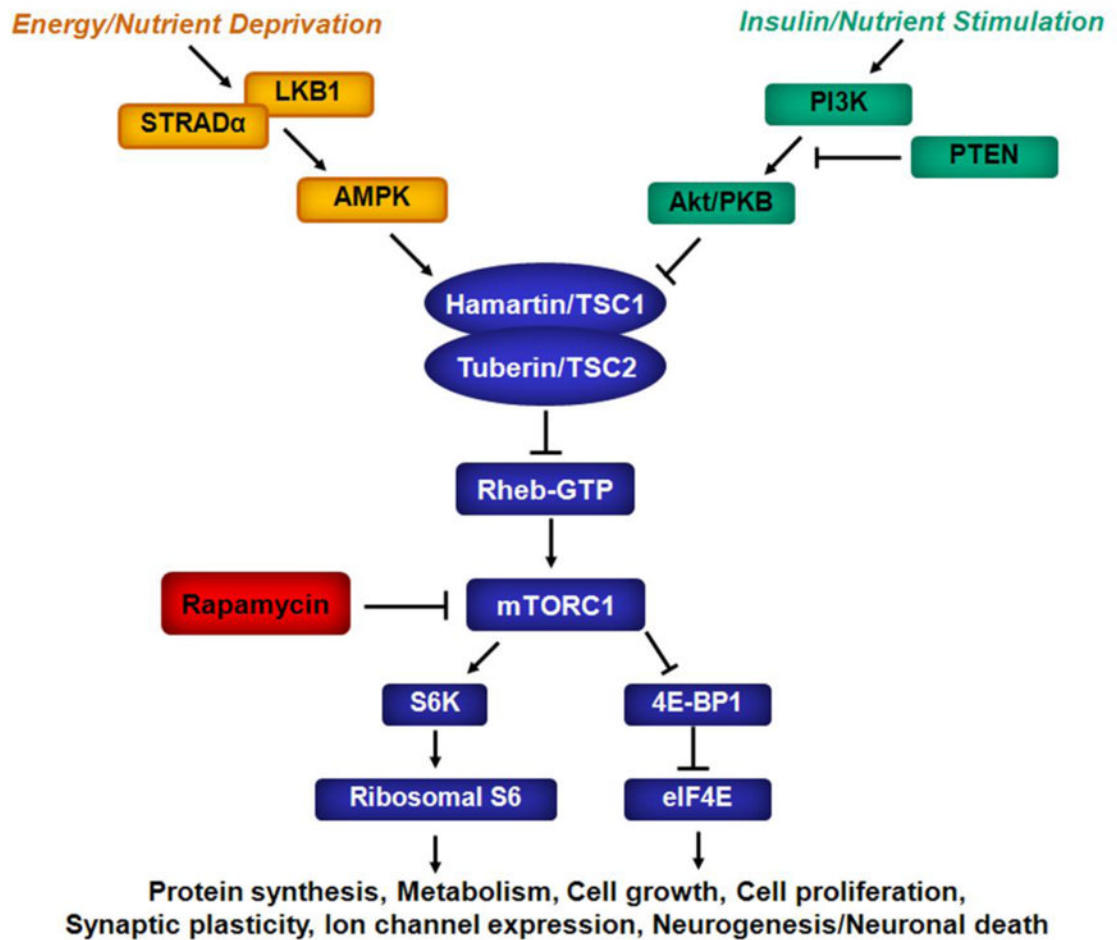


Fig. 1. Physiological regulation of the mTOR pathway. The mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase, which forms two complexes, rapamycin-sensitive mTORC1, and relatively rapamycin-insensitive mTORC2 (not shown). mTORC1 activates downstream signaling mechanisms involved in ribosomal biogenesis (S6K, Ribosomal S6) and protein translation (4E-BP1, eIF4E). Through regulation of protein synthesis and other mechanisms, the mTOR pathway modulates a number of important physiological processes, such as cell growth and proliferation, metabolism, and brain-specific functions (e.g., synaptic reorganization, ion channel expression, neuronal death). In turn, the mTOR pathway may be activated or inhibited by various physiological stimuli via various upstream signaling pathways and intermediary proteins (TSC1, TSC2, Rheb). AMPK - 5' adenosine monophosphate-activated protein kinase; eIF4E, elongation initiation factor 4E; mTOR - mammalian target of rapamycin; PI3K - phosphoinositide-3 kinase; PTEN, phosphatase and tensin homolog on chromosome 10; Rheb - Ras homolog enriched in brain; STRAD α - STE20-related kinase adapter alpha; S6 - ribosomal protein S6; S6K - ribosomal S6 kinase; TSC1 - tuberous sclerosis complex 1 protein; TSC2 - tuberous sclerosis complex 2 protein; 4E-BP1 - elongation factor 4E binding protein 1.

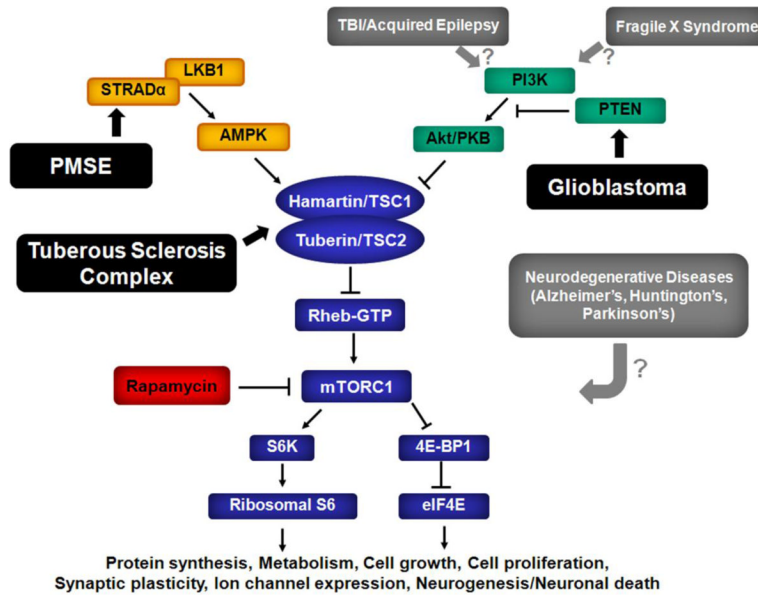


Fig. 2.

Pathological regulation of the mTOR pathway in neurological disease. Dysregulation of the mTOR pathway has been implicated in the pathophysiology of a variety of different neurological diseases. In some disorders (shown in black boxes), there is convincing evidence of a direct molecular or genetic link between the disease and a specific upstream component of the mTOR pathway, specifically TSC and hamartin/tuberin, polyhydramnios, megalencephaly and symptomatic epilepsy syndrome (PMSE) and STRAD α , and glioblastoma and PTEN. In other disorders (shown in gray boxes), the mechanistic link to the mTOR pathway is not as well established, although there is some evidence that traumatic brain injury (TBI), other acquired epilepsies, and fragile X syndrome may involve activation of PI3K/Akt. The least is known about how neurodegenerative disorders, such as Alzheimer's, Huntington's, and Parkinson's disease, affect the mTOR pathway, although downstream effects likely involve regulation of autophagy, clearance of protein aggregates, and neuronal death mechanisms. See legend to Fig. 1 for other abbreviations.

Table 1**Effects of mTOR Inhibitors in Animal Models and Clinical Studies of Neurological Disease**

Neurological Disease	Effects on Neurological Manifestations	Proposed Mechanism(s) of Action	References
Astrocytomas and Other Tumors in TSC			
Clinical studies in TSC patients	Reduction in volume of SEGAs, as well AMLs and angiofibromas; improvement in pulmonary functions (related to LAM) in TSC patients.	Inhibition of cell growth/proliferation.	18–22
Animal models of TSC	Reduction in renal tumors, brain megalencephaly, neuronal hypertrophy, and astrocyte proliferation in KO mice.	Inhibition of cell growth/proliferation.	16,17,39–42
Other (non-TSC) Brain Tumors			
Clinical studies of patients with glioblastoma multiforme	No effect on primary endpoints of tumor progression and survival.	N/A	32,33
Xenopants of human glioma in mice	Reduction in glioma cell growth	Inhibition of cell growth/proliferation, cytotoxic effects, inhibition of angiogenesis, sensitization to radiation.	28–30
Genetic Epilepsies			
Clinical studies in TSC patients	Reduction in seizure frequency in TSC patients	Unknown.	19,44–46
Animal models of TSC	Prevention of epilepsy (early treatment) and reduction in seizure frequency (late treatment) in KO mice.	Inhibition of cell growth/proliferation, decreased neuronal dispersion, improved myelination and astrocyte glutamate transport.	17,39–42
Animal models with PTEN inactivation	Reduction in seizure frequency in KO mice.	Inhibition of cell growth/proliferation	47–50
Acquired Epilepsies/Seizures			
Animal models of acquired epilepsy/seizures	Reduction in epilepsy following status epilepticus. Reduction in epilepsy following neonatal seizures Reduction in spasms in rats following brain injury.	Inhibition of mossy fiber sprouting, cell death Inhibition of enhanced glutamate EPSCs Unknown	62–64 66 67
Autism/Other Neurodevelopmental Disorders			
Animal models of TSC	Reversal of learning deficits in KO mice	Reversal of deficits in synaptic plasticity	43
Animal models of Fragile X and Down syndrome	Effects of mTOR inhibitors not yet reported, but mTOR pathway is abnormally activated.	N/A	78–80
Neurodegenerative Diseases			
Animal models of Alzheimer's disease	Improvement in cognitive/memory deficits in transgenic mice.	Decreased phosphorylation of tau, decreased amyloid-beta, induction of autophagy.	82–84
Animal models of Huntington's disease	Improvement in motor deficits, decreased neuronal death in transgenic mice.	Induction of autophagy.	85,86
Animal models of Parkinson's disease	Reduction in dopaminergic neuronal death in MPTP-treated mice.	Inhibition of pro-apoptotic protein RTP801, induction of autophagy and lysosomal biogenesis.	87,88

Abbreviations: AML – angiomyolipoma, EPSC – excitatory postsynaptic currents, KO – knock-out, LAM – lymphangioma, N/A – not applicable, PTEN – phosphatase and tensin homolog on chromosome 10, MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, mTOR – mammalian target of rapamycin, SEGA – subependymal giant cell astrocytoma, TSC – tuberous sclerosis complex.