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Targeting the Mammalian Target of Rapamycin for Epileptic Encephalopathies and Malformations of Cortical Development

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Abstract

Malformations of cortical development represent a common cause of epileptic encephalopathies and drug-resistant epilepsy in children. As current treatments are often ineffective, new therapeutic targets are needed for epileptic encephalopathies associated with cortical malformations. The mechanistic/mammalian target of rapamycin (mTOR) pathway constitutes a signaling pathway that drives cellular and molecular mechanisms of epileptogenesis in a variety of focal cortical malformations. mTOR inhibitors prevent epilepsy and associated pathogenic mechanisms of epileptogenesis in mouse models of tuberous sclerosis complex and are currently in clinical trials for drug-resistant seizures in these patients. A recent explosion of genetic studies has linked mutations in various genes regulating the mTOR pathway to other cortical malformations, such as focal cortical dysplasia and hemimegalencephaly. Thus, mTOR inhibitors represent promising candidates as novel antiseizure and antiepileptogenic therapies for epilepsy associated with a spectrum of cortical malformations.

Keywords

epilepsy; epileptogenesis; everolimus; malformation of cortical development; mTOR; rapamycin; seizures; tuberous sclerosis

Introduction

The International League Against Epilepsy initially proposed a definition of the term epileptic encephalopathy in 2001,¹ referring to it as “a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function.” In the 2010 revised report of the International League Against Epilepsy Commission on Classification and Terminology,² the term was further refined, with the addition of the concepts that severe cognitive and behavioral impairments are “above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.” Although not included in the definition, key to the concepts set forth by the International League Against Epilepsy is the

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Declaration of Conflicting Interests

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notion that severe epileptic activity during a vulnerable period of brain maturation (e.g., infancy and childhood) has a particularly detrimental and potentially progressive effect on neurological outcome.

Epileptic Encephalopathy as a Common Presentation of Malformations of Cortical Development

Epileptic encephalopathies include a number of age-related syndromes characterized by specific seizure types, electroencephalogram (EEG) patterns, and neurological features. The epileptic encephalopathies are a disparate group of conditions that vary in etiology, treatment, and prognosis. The underlying etiologies are varied even within a particular syndrome, with structural, metabolic, and genetic causes being described. Rapid advances in genetic diagnosis have allowed for the identification of causative genes linked to these devastating forms of epilepsy.³ Furthermore, the advent of modern imaging methods has revealed malformations of cortical development as a leading cause of epileptic encephalopathies. Interestingly, different genetic and/or structural etiologies may lead to similar EEG patterns and clinical phenotypes, which might suggest a common mechanism underlying the disease process in affected individuals.

Ohtahara syndrome, also known as early infantile epileptic encephalopathy with suppression burst, presents during the neonatal or early infantile period. Tonic spasms are characteristic, but other seizure types — including focal motor seizures, hemiconvulsions, and asymmetric tonic seizures — are seen.^{4,5} The characteristic EEG feature is a background suppression-burst pattern, with high-amplitude bursts alternating with nearly isoelectric suppression phases. The etiologies are diverse, but underlying structural abnormalities, including hemimegalencephaly^{6,7} and focal cortical dysplasia,^{8,9} are the most commonly identified causes.⁴

Epileptic spasms, also known as infantile spasms, is an age-dependent epilepsy that typically presents in the first year of life.¹⁰ The characteristic EEG background of hypsarrhythmia consists of chaotic and high-voltage generalized spike and slow-wave activity that typically obscures the normal physiologic EEG background.¹¹ Epileptic spasms are typically, but not always, accompanied by hypsarrhythmia. Epileptic spasms are caused by a variety of etiologies, with a range of cortical malformations implicated in up to one-third of cases.^{12,13} The mainstays of medical treatment of epileptic spasms include corticosteroids and vigabatrin,¹⁴ but surgical treatment has been shown to be effective in those with focal or hemispheric lesions.¹⁵ The long-term prognosis of epileptic spasms is variable, but over half of affected individuals develop other seizure types that are usually resistant to treatment, and more than two-thirds of affected individuals have long-term cognitive and psychological impairments.¹² Prognosis is highly dependent on underlying etiology,¹⁶ but there is some evidence that in individuals with no identifiable underlying etiology, better initial control by hormone treatment may lead to improved developmental outcome.¹⁷ One important etiology of epileptic spasms is tuberous sclerosis complex, with over one-third of individuals with this condition affected by epileptic spasms.¹⁸ Although the underlying pathophysiology is

not entirely clear, cortical tubers in tuberous sclerosis complex are thought play an important role in the development of epileptic spasms.

Lennox-Gastaut syndrome is an epileptic encephalopathy of childhood characterized by the triad of multiple seizure types, including tonic, atonic, and atypical absence seizures, as well as cognitive and behavioral abnormalities and a characteristic EEG pattern consisting of paroxysms of fast activity and slow generalized spike-wave discharges.¹² Approximately 50% of children with epileptic spasms progress to Lennox-Gastaut syndrome, and of individuals with the condition, approximately 12% have been shown to have a history of epileptic spasms.¹⁹ Although the etiologies of Lennox-Gastaut syndrome are diverse, malformations of cortical development are increasingly being identified as a cause,²⁰ with resective surgery a potential treatment option in such cases.²¹ Overall prognosis for patients with Lennox-Gastaut syndrome is poor, with almost all affected individuals having severely impaired cognition and behavior.²²

Malformations of Cortical Development

Malformations of cortical development designate a group of developmental disorders that are common causes of developmental delay and epilepsy. Malformations of cortical development have long been recognized as a cause of drug-resistant epilepsy.²³ Rapid advances in the fields of molecular biology, genetics, and neuroimaging prompted a revision to the classification scheme,²⁴ but the general framework has remained unchanged in that attempts at classification are based upon the earliest developmental step at which the developmental process is perturbed. Additionally, when possible, the associated genetic abnormality has been included in the classification scheme. Very broadly, the malformations are divided into 3 groups, with Group I being secondary to abnormal neuronal or glial proliferation or apoptosis, Group II being secondary to abnormal neuronal migration, and Group III being secondary to abnormal postmigrational development. Although the malformations lie on a wide spectrum, ranging from focal cortical dysplasias to diffuse megalencephalies, they are similar in that they often present as intractable seizures and/or as an epileptic encephalopathy during infancy or childhood.

Tuberous Sclerosis Complex

Tuberous sclerosis complex is an autosomal dominant disorder caused by mutations of the *TSC1* (encoding tuberin) or *TSC2* (encoding hamartin) genes.^{25,26} The disease was initially named by the French neurologist Bourneville for the cortical malformations (tubers) he discovered in the brains of affected individuals. The clinical features of tuberous sclerosis complex are widely variable, with multisystem involvement and a clinically evolving phenotype that changes with age.^{27, 28} Tuberous sclerosis complex is characterized by widespread hamartoma development affecting virtually any organ system in the body, with the major tumors including but not limited to cortical tubers of the brain, angiomyolipomas of the kidneys, and rhabdomyomas of the heart.²⁷ Neurological manifestations account for much of the disability associated with tuberous sclerosis complex, with nearly 80% to 90% of individuals developing epilepsy during their lifetime.²⁹ In one single-center series of tuberous sclerosis complex patients with epilepsy, over half of the affected individuals had

epileptic spasms and over a quarter had Lennox-Gastaut syndrome.³⁰ Other single-center series¹⁸ have shown an association between epileptic spasms and poorer neurological outcomes, including an increased risk for refractory epilepsy and cognitive impairment. In addition to epilepsy, individuals with tuberous sclerosis complex are at high risk for other neuropsychiatric disorders, particularly autism, which has been reported to affect nearly 50% of these individuals.³¹

Although the pathophysiology of epilepsy is not entirely understood, cortical tubers are hypothesized to play a key role in the development of epilepsy. Cortical tuber resection has been shown to be highly effective in the treatment of epilepsy in tuberous sclerosis complex,^{32,33} but intracranial EEG monitoring has also implicated perituberal tissue in cortical hyperexcitability and possibly seizure onset.³⁴ Pathologically, cortical tubers show abnormalities of cellular proliferation and are characterized by a loss of the 6-layered structure of the cortex, with prominent abnormalities including dysplastic neurons, giant cells, and bizarrely shaped astrocytes.^{35,36}

Other Malformations

Focal cortical malformations classified with the cortical hamartomas of tuberous sclerosis complex include diffuse cortical dysgenesis associated with polyhydramnios, megalencephaly, symptomatic epilepsy syndrome; hemimegalencephaly; and focal cortical dysplasia. These malformations demonstrate histopathologic similarities, specifically a disruption of the 6-layer organization of the cortex, loss of radial neuronal orientation, and presence of bizarre, dysmorphic neurons and other cytomegalic cells.³⁷

Polyhydramnios, megalencephaly, symptomatic epilepsy syndrome is an autosomal recessive neurodevelopmental disorder caused by mutations in the STE20-related kinase alpha (*STRADA*) gene.³⁸ The clinical features of this disorder include polyhydramnios, history of preterm labor, distinctive craniofacial features, macrocephaly, infantile-onset multifocal seizures, and global developmental delay. Histopathological features are characterized by megalencephaly and cytomegaly with enlarged and dysmorphic neurons.³⁸

Hemimegalencephaly may occur sporadically or as part of several neurocutaneous syndromes such as hypomelanosis of Ito or linear nevus syndrome.^{39,40} The typical clinical presentation consists of intractable epilepsy, severe psychomotor retardation, and contralateral hemiparesis.³⁹ Epilepsy is often the most severe neurologic manifestation, with presentations typically including tonic seizures in the newborn (Ohtahara syndrome), epileptic spasms in the young infant, or Lennox-Gastaut syndrome in the young child.³⁹ The neuropathology is notable for hemispheric enlargement, disruption of the normal 6-layered structure of the cortex, dysmorphic neurons, and balloon cells.⁴⁰

Focal cortical dysplasias are localized regions of abnormal cerebral cortex that can be seen in any brain region but are most often identified in extratemporal regions.⁴¹ The clinical symptoms are heterogeneous, with refractory seizures beginning in childhood being the most common clinical manifestation.⁴² The histopathologic hallmark of focal cortical dysplasias is dyslamination of the neocortex, with focal cortical dysplasia type I referring to

lesions limited to dyslamination and focal cortical dysplasia type II referring to lesions displaying dysmorphic neurons without (type IIa) or with balloon cells (type IIb).^{43,44} The balloon cells identified in focal cortical dysplasia type IIb dysplasia show pathologic similarities to the giant cells identified in the cortical tubes of tuberous sclerosis complex,³⁷ suggestive of a shared pathogenic pathway.

Need for New Antiseizure Therapies and Treatment Targets

Treatments for epileptic encephalopathy caused by malformations of cortical development are far from ideal. Epilepsy surgery can help some patients, but surgery has significant risks and many patients are not good surgical candidates. Conventional antiseizure medications are often ineffective in controlling the seizures or altering the neurocognitive outcomes seen in individuals with epileptic encephalopathies. Currently available antiseizure medications are relatively nonspecific in their mechanisms of action, acting to decrease neuronal excitability by targeting ion channels and neurotransmitter systems. Despite the current availability of more than 20 antiseizure drugs used in the treatment of epilepsy, none of the newer second-generation agents has been proved to be exceptionally superior to older first-generation agents.⁴⁵ Rather, we still use some of our oldest and most nonspecific agents such as corticosteroids¹⁴ in the treatment of epileptic encephalopathies such as epileptic spasms. Malformations of cortical development commonly present with epileptic encephalopathy,¹⁰ and recent discoveries implicating the mechanistic/mammalian target of rapamycin (mTOR) pathway in various brain malformations, including tuberous sclerosis complex, focal cortical dysplasia,⁴⁶ hemimegalencephaly,^{47,48} and megalencephaly associated with polyhydramnios, megalencephaly, symptomatic epilepsy syndrome,⁴⁹ have generated excitement about potentially novel therapies targeting this pathway. Such therapies could potentially alter the course of epileptic encephalopathy in individuals with brain malformations, and if successful, be applied more broadly to epileptic encephalopathies as a whole.

mTOR Pathway as Novel Therapeutic Target

The mTOR signaling pathway (Figure 1) processes a variety of environmental cues to regulate cellular growth and homeostasis, with aberrations of the mTOR pathway being implicated in a number of diverse conditions, including epilepsy (genetic and acquired), neurodegeneration, cancer, obesity, and type 2 diabetes.^{50–52} mTOR is a serine/threonine protein kinase that belongs to the phosphoinositide 3-kinase (PI3K)-related kinase family and forms 2 distinct complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2). mTORC1 stimulates protein synthesis, allowing for cellular growth and proliferation, whereas mTORC2 is primarily involved in cytoskeletal organization.⁵⁰ mTORC1 is sensitive to rapamycin, whereas mTORC2 is relatively insensitive to rapamycin treatment, at least in the acute phase.

The mTOR pathway consists of a number of upstream regulatory pathways and downstream mediators. *TSC1* (encoding hamartin) and *TSC2* (encoding tuberlin) form a heterodimer complex that plays a central role in the mTOR pathway. The TSC1-TSC2 complex negatively regulates mTORC1 by converting Rheb (Ras homolog enriched in brain) from its

active GTP-bound state into its inactive GDP-bound state.⁵³ Downstream cellular processes are mediated by kinases such as S6 kinase 1 (*S6K1*) and elongation factor 4E binding protein 1 (*4EBP1*), which carry out processes such as protein synthesis, lipid synthesis, and inhibition of autophagy.⁵⁰

Under physiologic conditions, mTORC1 activity is influenced by extracellular and intracellular cues, including growth factors, stress, energy status, oxygen, and amino acids, which are relayed via various kinases that act upstream of the TSC1-TSC2 complex.⁵⁰ Key upstream messengers include but are not limited to *PI3K*, *Akt* (also known as *PKB*, protein kinase B), *STRADα* (STE20-related kinase adapter alpha), *AMPK* (AMP kinase), and *DEPDC5* (DEP domain-containing 5) (Figure 1). The *PI3K/Akt* pathway is activated in anabolic states (e.g., by growth stimulating signals such as insulin) and negatively regulates the TSC1-TSC2 complex, allowing for increased mTORC1 activity and ultimately cellular growth and proliferation.⁵⁴ The *STRADα/AMPK* pathway is activated during catabolic states (e.g., nutrient deprivation) and allows for increased activity of the TSC1-TSC2 complex, leading to negative regulation of mTORC1 and a decrease in cellular growth and proliferation.⁵⁵ *DEPDC5* is an upstream negative regulator of mTORC1 that forms part of the GATOR1 complex, which is activated under conditions of amino acid deprivation and acts as a negative regulator of the mTORC1 pathway.⁵⁶

Many of the upstream and downstream components of the mTOR pathway have now been identified as having genetic mutations in association with various malformations of cortical development, collectively referred to as “mTORopathies” (Figure 1). This common mechanistic defect found in multiple cortical malformations suggests the possibility of using mTOR inhibitors as a novel therapeutic approach for epileptic encephalopathy and drug-resistant seizures in this group of disorders.

mTOR and Tuberous Sclerosis Complex

Tuberous sclerosis complex is the prototypical disease in which mTOR has been implicated in epileptogenesis. As the *TSC* genes normally inhibit TOR, mutation of the either *TSC1* or *TSC2* leads to dysregulation of the mTOR pathway. Hyperactivation of the mTORC1 pathway stimulates increased cell growth and proliferation, which represents a rational mechanistic explanation for tumor growth in tuberous sclerosis complex. The use of mTOR inhibitors, such as sirolimus (rapamycin) and everolimus, thus constitutes a rational treatment for tumors associated with tuberous sclerosis complex. In fact, clinical trials have proven their efficacy for brain (subependymal giant cell astrocytomas),⁵⁷ kidney (angiomyolipomas),⁵⁸ and lung (lymphangiomyomatosis)⁵⁹ tumors in tuberous sclerosis complex, leading to FDA approval of everolimus (subependymal giant cell astrocytomas, angiomyolipomas) or sirolimus (lymphangiomyomatosis) for these indications.

By comparison, mechanisms of epileptogenesis are not as well-delineated as tumor growth. Cortical tubers have been strongly implicated in epilepsy in tuberous sclerosis complex, as surgical removal of tumors can sometimes eliminate seizures in some tuberous sclerosis complex patients.³³ However, as tubers may be relatively inexcitable electrically, the perituberal region has also been implicated in directly generating seizures.⁶⁰ Furthermore,

non-lesional regions of the tuberous sclerosis complex brain also could be involved in epileptogenic cellular and molecular mechanisms in some cases. In this regard, mTOR hyperactivation in tuberous sclerosis complex may play a central role in promoting epileptogenesis by a variety of downstream mechanisms that affect neuronal excitability, such as ion channel expression, axonal sprouting, and inflammation.⁶¹ If this is the case, mTOR inhibitors may be a rational treatment for epilepsy in tuberous sclerosis complex.

Animal Models

A number of mouse models have been generated that recapitulate many of the pathological and cellular features of tuberous sclerosis complex and provide strong evidence that mTOR is involved in epileptogenesis in tuberous sclerosis complex.^{62–66} Targeted inactivation of the *Tsc1* or *Tsc2* gene in different brain cell types, including neurons and glia, leads to spontaneous seizures in mice. mTOR activity can be measured and is increased in these mouse models. Treatment of mice with mTOR inhibitors can decrease seizures. Furthermore, early treatment with rapamycin prior to onset of seizures can prevent epilepsy in these mice. Importantly, rapamycin does not simply suppress seizures by decreasing neuronal excitability, like standard antiseizure drugs, but appears to have true antiepileptogenic or disease-modifying effects by preventing the associated cellular and pathological defects causing epileptogenesis. For example, in one tuberous sclerosis complex mouse model primarily affecting glial cells, rapamycin prevents abnormalities in astrocyte proliferation, expression in astrocyte glutamate transporters, and diffuse megalencephaly of the brain that contribute to epilepsy.⁶⁵ In a neuron-specific conditional knock-out mouse, neuronal hypertrophy and myelination defects are corrected by rapamycin, along with the seizures.⁶⁴

It should be noted that rapamycin treatment must be continued indefinitely to maintain effectiveness, as seizures will emerge if rapamycin is stopped. This rebound effect is not surprising given that the genetic defect of *Tsc* inactivation persists and drives mTOR reactivation once rapamycin is discontinued. It has been argued that the lack of persistent effect after drug withdrawal is more consistent with an antiseizure action, not a disease-modifying or antiepileptogenic effect. However, the mechanism of action of mTOR inhibitors is completely different than that of standard antiseizure drugs that directly inhibit neuronal activity in preventing or reversing structural and pathological abnormalities in tuberous sclerosis complex mouse models. In fact, perhaps with genetic diseases like tuberous sclerosis complex in mind, an International League Against Epilepsy committee recently proposed an updated definition of disease-modifying treatment to include those that alters the “development or progression of epilepsy, comorbidities, and also the associated pathology,” without regard to whether the effect was sustained after treatment withdrawal.⁶⁷ On the basis of this definition, mTOR inhibitors do appear to have antiepileptogenic effects in tuberous sclerosis complex mouse models.

Clinical Studies

The preclinical work in tuberous sclerosis complex mouse models has started to be translated into clinical trials. Data from uncontrolled studies suggest that everolimus decreases seizure frequency in patients who have tuberous sclerosis complex and drug-

resistant epilepsy.^{68,69} A large multicenter, placebo-controlled trial is near completion, so definitive data will hopefully be available soon as to whether mTOR inhibitors are effective and safe for treating intractable seizures in these patients. If the results are positive, everolimus may become the first FDA-approved drug for epilepsy with a completely different mechanism of action than standard medications in targeting a cell signaling pathway.

Even if the results with everolimus are negative in drug-resistant epilepsy in tuberous sclerosis complex, the mechanisms of early epileptogenesis versus end-stage intractable seizures are likely very distinct, so there would still be significant hope that a preventive, antiepileptogenic approach could work to prevent epilepsy if started at an early stage. In this regard, mTOR inhibitors may have the largest potential for impact. While current antiseizure medications are known to suppress seizures symptomatically by decreasing neuronal activity, there are no proven antiepileptogenic drugs to prevent epilepsy in high-risk patients. On the other hand, designing, conducting, and justifying antiepileptogenic drug trials are very difficult for a number of reasons. One issue is identifying the appropriate high-risk populations for preventive therapy, in which the benefits of potentially preventing epilepsy in a subset of patients outweigh the risks and side effects of treating the entire population. In this respect, tuberous sclerosis complex may be an ideal population for a preventive therapy,⁷⁰ given that many of these patients are identified at a young age prior to seizure onset due to non-neurological findings,⁷¹ and yet the prevalence of epilepsy in tuberous sclerosis complex is extremely high, close to 90%.¹⁸ Furthermore, predictive biomarkers for epilepsy in tuberous sclerosis complex may be available, as a recent study found that an abnormal EEG in asymptomatic tuberous sclerosis complex patients had a 100% positive predictive value for infantile spasms and other seizure types in the future, thus further narrowing the highest-risk population to be targeted.⁷² Despite these promising features, an antiepileptogenic drug trial of mTOR inhibitors has not yet been conducted, but may be planned in the near future.

mTOR and Other Malformations of Cortical Development

While mTOR has been strongly implicated in epilepsy in tuberous sclerosis complex, the condition is often viewed as a model disease that may share pathophysiological mechanisms with other related disorders. Pathological similarities between tubers of tuberous sclerosis complex and focal cortical dysplasia type IIB, as well as hemimegalencephaly, suggest a common underlying pathophysiological mechanism. For example, dysregulation of cell growth, as evident by cytomegalic, immature cells in these different malformations (e.g., giant cells in tubers, balloon cells in focal cortical dysplasia type IIB) could reflect a common defect in mTOR signaling. In fact, as hypothesized by Crino almost a decade ago, many focal brain malformations do appear to be “mTORopathies.”⁷³ This is supported by abnormal expression of different mTOR pathway markers within these cortical malformations,^{74,75} and most convincingly, by the recent identification of pathogenic mutations in different genes regulating the mTOR pathway, such as *AKT*, *PTEN*, *STRADA*, *DEPDC5*, and *mTOR* itself.^{46–48,76–79}

Animal Models

As animal models involving *Tsc1* or *Tsc2* inactivation in the brain have been instructive in investigating the role of mTOR in epileptogenesis in tuberous sclerosis complex, other mouse models targeting other aspects of the mTOR pathway have similarly been helpful in studying epilepsy in other cortical malformations. *PTEN*, an upstream regulator of mTOR, which is mutated in Cowden syndrome and isolated focal cortical dysplasia,⁸⁰ has been most extensively examined. Analogous to the *Tsc* mouse models, inactivation of *Pten* in neurons and glial lead to pathological and cellular features of some cortical malformations, such as increased mTOR activity, cytomegaly, and megalencephaly, as well as robust epilepsy.^{81–84} Treatment with rapamycin can decrease seizures in these *Pten* knockout mice. Although infantile spasms have not been specifically reported in tuberous sclerosis complex or *Pten* mice, rapamycin has been shown to decrease spasm-like seizures in an acquired injury model of infantile spasms.⁸⁵

One significant limitation of many previous animal models of mTORopathy and epilepsy are a lack of focal lesions, as the pathological and cellular abnormalities tend to be diffuse, leading to generalized megalencephaly. To better recapitulate focal malformations, such as tubers or focal cortical dysplasia, several recent studies have used a specialized method, in utero electroporation, to target gene inactivation in more restricted areas of cortex, leading to the development of focal cortical lesions. The first reported study, related to tuberous sclerosis complex, used this method to generate focal, tuber-like cortical lesions with *Tsc1* gene inactivation.⁸⁶ These mice did not have documented spontaneous epilepsy, but did have a decreased seizure threshold to a convulsant drug. Most recently, in utero expression of mutated genes of *Akt* or *mTOR* itself induced focal cortical areas of cytomegalic neurons and disrupted cortical lamination, as well as spontaneous seizures.^{87,88} Rapamycin was tested in one of these models and reversed the seizure phenotype.

Clinical Studies

In the past few years, there has been a virtual explosion of genetic studies implicating various components of the mTOR pathway in focal cortical malformations and epilepsy. Focal cortical dysplasia and hemimegalencephaly have been linked to germline and somatic mutations in phosphatidylinositol 3-kinase (*PI3K*), *AKT*, *DEPDC5*, and *MTOR*.^{46–48,76–79} While drug-resistant epilepsy and epileptic encephalopathy are common presentations of these cortical malformations, the effect of rapamycin in these other cortical malformations has not yet been reported. The one exception is with the rare genetic syndrome known as polyhydramnios, megalencephaly, and symptomatic epilepsy (also referred to as Pretzel syndrome), which is caused by a mutation in the STE20-related kinase adaptor α (*STRADA*) gene, another regulator of mTOR.⁷⁷ Rapamycin treatment led to a significant decrease in seizure frequency in a small cohort of these patients.

Conclusions and Future Directions

Emergence of the mTOR pathway as a potential treatment target for epilepsy associated with TSC and other related focal cortical malformations has been one of the most exciting advances in epilepsy research in the last decade. Epileptic encephalopathy, including

infantile spasms, is often the presenting symptom of many of these malformations of cortical development, and is frequently resistant to available treatments. As dysregulated mTOR activity may be central in driving downstream cellular and molecular mechanisms of lesion formation and epileptogenesis itself, the potential therapeutic applications of mTOR inhibitors for epilepsy in these “mTORopathies” are tremendous. While current antiseizure medications primarily act by directly decreasing neuronal excitability via modulation of ion channels and neurotransmitter systems, mTOR inhibitors use a completely novel mechanism of action, regulating a variety of cellular and molecular processes, such as cell growth and plasticity, metabolism, and protein synthesis. However, it is possible that once epilepsy is established, especially when caused by structural brain malformations, treatment with mTOR inhibitors may be too late to significantly inhibit or reverse these established processes. In contrast, if administered early in the process of epileptogenesis, mTOR inhibitors may have a much greater potential to prevent epilepsy and other neurological symptoms from developing in the first place.

No proven antiepileptogenic or preventive therapy for epilepsy exists, and a feasible preventive approach depends on being able to identify at-risk patients in the presymptomatic stage prior to epilepsy onset. Some TSC patients can be identified in early infancy due to non-neurological findings; however, seizures are often the presenting symptom of other cortical malformations. The use of biomarkers, such as those that are EEG-derived, or the potential for genetic screening for mTOR-related mutations may allow early diagnosis of these malformations, making early intervention feasible. Overall, mTOR inhibitors hold promise as potentially novel antiseizure and antiepileptogenic drugs for epileptic encephalopathy and drug-resistant epilepsy related to a spectrum of cortical malformations.

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Figure 1.

Simplified schematic depicting the mTOR pathway and associated “mTORopathies.” The mTOR pathway involves 2 complexes, mTORC1 and mTORC2. mTORC1 integrates cellular energy levels via upstream kinases and controls many downstream functions, including transcription and translation, lipid synthesis, cell growth, cell proliferation, cell survival, and cell death. mTORC2 has been less extensively studied, but has downstream functions involved in cytoskeletal organization. mTORC1 is sensitive to rapamycin inhibition, whereas mTORC2 is relatively insensitive to rapamycin (at least during the acute phase). Mutations in different upstream and downstream aspects of the mTOR pathway have been associated with various malformations of cortical development and epilepsy, including tuberous sclerosis complex, focal cortical dysplasia, and hemimegalencephaly. Abbreviations: 4E-BP1, elongation factor 4E binding protein 1; AMPK, 5′-adenosine monophosphate-activated protein kinase; DEPDC5, DEP domain-containing 5; eIF4E, eukaryotic translation initiation factor 4E; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI3K, phosphoinositide-3-kinase; PMSE, polyhydramnios, megalencephaly, symptomatic epilepsy; PTEN, phosphatase and tensin homolog on chromosome 10; Rheb, Rhas-homolog expressed in brain; S6K1, S6 kinase 1; STRADα, STE20-related kinase adapter alpha; TSC1, tuberous sclerosis complex 1 protein; TSC2, tuberous sclerosis complex 2 protein.