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# Commentary: mTOR inhibition suppresses established epilepsy in a mouse model of cortical dysplasia

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## Commentary

Over twenty approved drugs for epilepsy exist, including at least a dozen developed in the last two decades, but the available medications continue to suffer from a couple significant limitations: drug-resistance in about one-third of all epilepsy patients and a lack of preventative, anti-epileptogenic, or disease-modifying treatments for epilepsy. While most current anti-seizure medications act primarily by modulating ion channels or neurotransmitter systems, the search for new drugs to address these shortcomings have increasingly focused on novel mechanisms of action. The mechanistic/mammalian target of rapamycin (mTOR) pathway has recently emerged as an attractive target for new epilepsy drugs.[1] mTOR is a ubiquitious protein kinase involved in regulating a number of important physiological functions, such as cell growth, proliferation, synaptic plasticity, and protein synthesis. mTOR inhibitors, such as rapamycin, may represent a rational treatment for epilepsy, because regulation of the mTOR pathway could not only have direct anti-seizure effects by modulating neuronal excitability, such as through regulation of the expression of ion channels or neurotransmitter receptors, but could also have novel anti-epileptogenic effects in interrupting early molecular and cellular processes of epileptogenesis, such as neurogenesis, axonal sprouting, and neuronal migration.

mTOR inhibitors already show significant promise as novel treatments for epilepsy in the genetic disorder, tuberous sclerosis complex (TSC). TSC is characterized by hamartoma or tumor formation in multiple organs, including the brain, primarily related to dysregulation of the mTOR pathway, which is normally inhibited by the *TSC* genes. mTOR inhibitors are approved, effective therapies for tumors in TSC. Although epilepsy in TSC is not directly related to tumor growth per se, cortical tubers, which represent focal cortical malformations similar to focal cortical dysplasia type IIB, are strongly associated with epilepsy, which occurs in about 80% of TSC patients. In animal models of TSC, rapamycin can both prevent epilepsy when initiated early and decrease existing seizures when started late.[2; 3] Uncontrolled clinical trials indicate that mTOR inhibitors can reduce seizures in TSC

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patients with drug-resistant epilepsy,[4] and initial unpublished results recently released from a large, multicenter placebo-controlled trial also indicate a beneficial effect. The potential for early, preventative treatment in TSC patients prior to the onset of epilepsy is currently being considered, although preventative clinical trials with mTOR inhibitors have not yet been initiated.

TSC may be viewed as a prototypical "mTORopathy" leading to malformations of cortical development and epilepsy, as recent advances in genetic studies have now identified germline or somatic mutations affecting different components of the mTOR pathway in a variety of other cortical malformation, such as hemimegalencephaly and isolated, non-syndromic focal cortical dysplasia.[5] Thus, mTOR inhibitors could also be considered as a potential treatment for epilepsy related to a spectrum of cortical malformations.[6] While TSC can often be diagnosed early before the onset of epilepsy due to non-neurological findings, epilepsy is often the presenting symptom of non-syndromic cortical malformations, such as focal cortical dysplasia. In these cases, despite the theoretical mechanistic potential of mTOR inhibitors as anti-epileptogenic therapies, an early preventative approach is practically not feasible. Thus, there is a continued need to pursue new treatments with novel mechanisms of action that can hopefully suppress or reverse ongoing, drug-resistant epilepsy.

Toward this goal, the study awarded the 2016 Basic Science Epilepsia Prize by Nguyen et al. is very novel and significant in testing whether mTOR inhibition is effective for treating established epilepsy in a mouse model of cortical dysplasia.[7] The authors utilize a conditional knockout (KO) mouse involving inactivation of the phosphatase and tensin homology (PTEN) gene in neurons. As PTEN is an upstream negative regulator of the mTOR pathway, knockout of *Pten* in mice leads to mTOR hyperactivation and cellular features of cortical dysplasia, including neuronal hypertrophy, gliosis, and cortical disorganization, as well as epilepsy. Previous work from this group has shown that early rapamycin, starting at 4 weeks of age, can inhibit epilepsy progression in *Pten*-KO mice.[8] In the present study, the initiation of rapamycin treatment was delayed until 9 weeks of age, when the pathological abnormalities and severe epilepsy are already well-established, as evident by almost continuous subclinical epileptiform activity on EEG and superimposed episodes of motor seizures. Even at this late stage of epileptogenesis, mTOR inhibition caused a dramatic reduction in epileptiform activity and clinical seizures. Rapamycin was also able to decrease the gliosis, indicating that at least some of the pathological abnormalities in these mice were partially reversible by inhibiting mTOR.

These findings are important in indicating mTOR activity contributes to the maintenance of established epilepsy, complementing previous studies implicating mTOR in early epileptogenesis. From a clinical standpoint, this supports the potential of using mTOR inhibitors to treat seizures in the later stages of epilepsy, including possibly drug-resistant epilepsy. A limitation of this study is the model involves relatively diffuse pathological abnormalities throughout the cortex and hippocampus, thus not precisely mimicking the more focal cortical malformations typically seen clinically in many patients. For future studies of mTOR inhibitors, newer modeling techniques, involving spatially and temporally targeted gene inactivation, can generate more focal models of cortical dysplasia and

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epilepsy. On the other hand, the efficacy of rapamycin in a very severe model of epilepsy and cortical dysplasia in the current study indicates that mTOR inhibition would most likely be effective in less extensive cases. Given the expanding number and variety of cortical malformations that have now been reported to be due to mTORopathies, the current study provides tremendous promise and potential clinical applications for targeted treatment of this increasingly common and significant group of epilepsies.

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