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Commentary

Loss-of-function mutations in a single allele of the gene encoding DEP domain–containing 5 protein (DEPDC5) are commonly linked to familial focal epilepsy with variable foci; however, a subset of patients presents with focal cortical dysplasia that is proposed to result from a second-hit somatic mutation. In this issue of the *JCI*, Ribierre and colleagues provide several lines of evidence to support second-hit *DEPDC5* mutations in this disorder. Moreover, the authors use in vivo, in utero electroporation combined with CRISPR-Cas9 technology to generate a murine model of the disease that recapitulates human manifestations, including cortical dysplasia–like changes, focal seizures, and sudden unexpected death. This study provides important insights into familial focal epilepsy and provides a preclinical model for evaluating potential therapies.

DEPDC5 takes a second hit in familial focal epilepsy

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Familial focal epilepsy with variable foci

When first described, autosomal dominant familial focal epilepsy with variable foci (FFEVF) was initially puzzling, as family members with this disorder had seizures originating from different cortical regions (1). This presentation is unlike other genetic partial epilepsy disorders, such as autosomal dominant lateral temporal lobe epilepsy (ADLTE), which arises from leucine-rich glioma-inactivated 1 (*LGI1*) mutations, which are characterized by seizures with symptoms (auditory auras in ADLTE) suggestive of more limited seizure initiation sites. Subsequently, mutations of DEP domain–containing 5 (*DEPDC5*) were shown to underlie FFEVF (2, 3); however, the molecular mechanisms responsible for the variable foci were unclear. Subsequently, it was determined that in a subset of patients, the seizure foci contains areas of cortical dysplasia (4, 5). As DEPDC5 is part of the GATOR1 complex, which negatively regulates mammalian target of rapamycin complex 1 (mTORC1) (6), the stage was set for a second-hit mechanism of cortical dysplasia, as has been found for cortical tubers that result from mutations of the tuberous sclerosis (*TSC*) gene. Like the DEPDC5-containing GATOR1 complex, the TSC complex (TSC1/2) also inhibits mTORC1. A second-hit somatic mutation in TSC1/2 in cortical neuron progenitors explains the variable sites of cortical dysplasia that generate seizure foci as in tuberous sclerosis.

DEPDC5 takes a second hit in focal seizures

In this issue, Ribierre et al. (7) present a tour-de-force study that provides strong evidence for a germline and second allele somatic hit (nonsense loss-of-function mutation) of *DEPDC5* in familial focal epilepsies with focal cortical dysplasia. The authors evaluated cortical resection specimens from *DEPDC5* heterozygous subjects with focal epilepsy. In addition to the genetics, mTORC1 signaling was hyperactive, as evidenced by increased neuronal soma size and elevated phosphorylated S6 in the dysplastic neurons of the human seizure resection specimens. These detailed genetic and biochemical correlations in the human tissues then led them to design tests of causality in a mouse model, in which they reconstituted many features of the human disorder. Together, the results of Ribierre et al. provide compelling evidence to support the conclusion that focal epilepsy arising from *DEPDC5* heterozygous mutations occurs through a second-hit loss of function of the second allele, as occurs in tuberous sclerosis.

The mouse model developed by Ribierre and colleagues allowed for further investigation into the cellular and molecular mechanisms of *DEPDC5* mutation–driven focal epilepsy (7). The authors used an elegant approach of in vivo, in utero electroporation to deliver a CRISPR-Cas9 vector that allowed targeted homozygous deletions of *Depdc5* alleles in cortical neuronal progenitor cells of the subventricular zone of fetal mouse brains. This targeted deletion led to deficits in neuronal migration, which were rescued by the treatment of pregnant dams with the mTORC1 inhibitor rapamycin. Moreover, neurons with homozygous *Depdc5* inactivation had elevated levels of phosphorylated S6, which is indicative of mTORC1 activation, and increased soma size. These observations in the murine neurons recapitulated the findings in the human seizure resections (Figure 1). Importantly, mice with focal cortical mosaic homozygous deletions of *Depdc5* suffered seizures, recorded by EEG, with tonic-clonic posturing in some cases and sometimes ending in seizure-related spontaneous death (a potential focal seizure–induced sudden death in epilepsy [SUDEP] model).

Conclusions

The evidence that pathogenic somatic mutagenesis is a cause of neurologic disorders is rapidly growing. Many genes involved in the mTOR and related signaling pathways have now been identified in focal and hemimegalencephaly cortical dysplasia cases (8–12). For many of the identified genes, it remains unclear exactly

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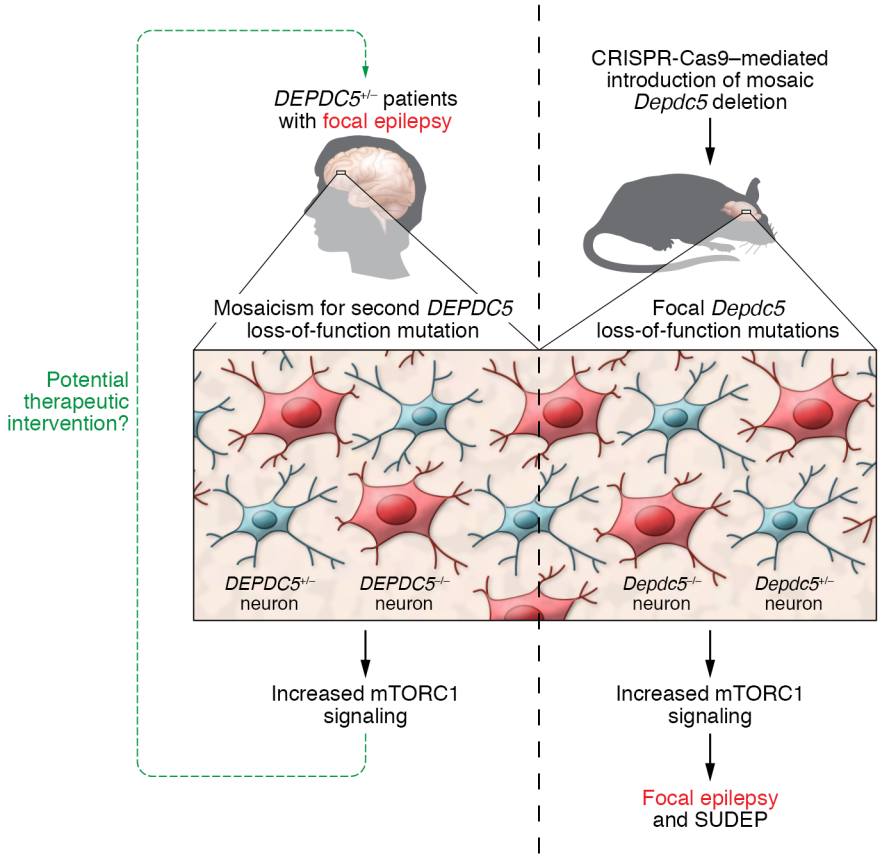

Figure 1. Second-hit *DEPDC5* mutation underlies focal cortical dysplasia in familial epilepsy. In this issue, Ribierre et al. reveal a mosaic pattern of secondary somatic mutations in *DEPDC5* in cortical neurons of *DEPDC5*$^{-/+}$ patients with focal epilepsy. The introduction of mosaic *Depdc5*$^{-/-}$ mutations in a murine model recapitulates the patient phenotype, including magnified mTOR signaling, focal seizures, and SUDEP in some cases.

how these defects lead to epileptiform discharge of the affected neuronal circuits to produce the seizure foci; however, defects in cortical neuron migration, neuronal dendritic and axonal arbor overgrowth, and possibly alteration of the intrinsic excitability of the neurons carrying these mutations may alter the discharge of these dysplastic neuronal circuits. Interestingly, activation of the mTOR signaling pathway, via *Pten* deletion, in just a minor subset of neurons maturing in the adult dentate gyrus is sufficient to generate epilepsy (13).

Beyond mutations in growth and metabolism regulatory genes, loss of one allele of the *Scn1a* sodium channel in the GABAergic neurons is sufficient to promote severe seizures in mouse models of human Dravet syndrome. These seizures are presumably the result of an impaired ability of GABAergic neurons to sustain the high firing rates needed to inhibit circuit activity (14–16). A recent study also found evidence of somatic mutations of *SCN1A* and other genes in autism-epilepsy comorbidity disorders (17, 18). These preliminary results suggest the possibility that genes involved in neurophysiologic functions that would not produce a visible lesion might also underlie some seizure foci.

Considering the now well-established evidence that somatic mutations in neuronal precursor cells can generate hyperexcitable circuits to produce epilepsy, it is readily conceivable that similar strategically placed mutations in neuronal precursors that give rise to circuits important to cognition and behavior could produce an array of episodic behavioral disorders such as panic, aggression, pain, or psychosis (19). Moreover, strategically placed seizure foci might also generate lasting changes in behavior, such as the impaired sociability of autism spectrum disorder, by altering the expression of genes critical to circuit functions (20).

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