In Basic Science

Commentary

The dentate gyrus (DG) is thought to serve as a “gate,” limiting the flow of excitation through the hippocampus. During epileptogenesis, adult-generated granule cells (DGCs) form aberrant neuronal connections with neighboring DGCs, disrupting the dendate gate. Hyperactivation of the mTOR signaling pathway is implicated in driving this aberrant circuit formation. While the presence of abnormal DGCs in epilepsy has been known for decades, direct evidence linking abnormal DGCs to seizures has been lacking. Here, we isolate the effects of abnormal DGCs using a transgenic mouse model to selectively delete PTEN from postnatally generated DGCs. PTEN deletion led to hyperactivation of the mTOR pathway, producing abnormal DGCs morphologically similar to those in epilepsy. Strikingly, animals in which PTEN was deleted from ≥ 9% of the DGC population developed spontaneous seizures in about 4 weeks, confirming that abnormal DGCs, which are present in both animals and humans with epilepsy, are capable of causing the disease.

Excessive Activation of mTOR in Postnatally Generated Granule Cells Is Sufficient to Cause Epilepsy.


The dentate gyrus is hypothesized to function as a “gate,” limiting the flow of excitation through the hippocampus. During epileptogenesis, adult-generated granule cells (DGCs) form aberrant neuronal connections with neighboring DGCs, disrupting the dentate gate. Hyperactivation of the mTOR signaling pathway is implicated in driving this aberrant circuit formation. While the presence of abnormal DGCs in epilepsy has been known for decades, direct evidence linking abnormal DGCs to seizures has been lacking. Here, we isolate the effects of abnormal DGCs using a transgenic mouse model to selectively delete PTEN from postnatally generated DGCs. PTEN deletion led to hyperactivation of the mTOR pathway, producing abnormal DGCs morphologically similar to those in epilepsy. Strikingly, animals in which PTEN was deleted from ≥ 9% of the DGC population developed spontaneous seizures in about 4 weeks, confirming that abnormal DGCs, which are present in both animals and humans with epilepsy, are capable of causing the disease.

Given the potential significance of this finding, this study was thorough in including a number of control experiments to evaluate for alternative interpretations and mechanisms. The incidental inactivation of PTEN in inhibitory granule cells in

TOR-ing Down the Dentate Gate in Temporal Lobe Epilepsy

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olfactory bulb (which share the same genetic promoter as hippocampal granule cells used to drive PTEN inactivation) had surprisingly little effect on the morphology of these olfactory granule cells, as well as no evidence of abnormal EEG activity in the olfactory bulb. Although mTOR activation in astrocytes can promote epileptogenesis in mouse models of tuberous sclerosis complex (5), there were no significant abnormalities in the number, morphology (e.g., reactive gliosis), or PTEN expression of astrocytes in the \emph{PTEN} knock-out mice in this study. Thus, the source of epileptogenesis in these mice can most likely be localized to the DG granule cells.

Although the findings from this study support the concept that abnormalities in DG granule cells are capable of causing epilepsy, the specific pathophysiological defect(s) in the DG granule cells that promote epileptogenesis in the \emph{PTEN} knock-out mice remains to be determined. Consistent with pathological specimens from human patients and other animal models of temporal lobe epilepsy, a variety of histological abnormalities in DG granule cells were identified in the \emph{PTEN} knock-out mice and could potentially contribute to a breakdown of the DG gate leading to epilepsy. Based purely on the correlative pathological observations in the current and previous studies, it is impossible to distinguish which granule cell abnormalities are more critical for epileptogenesis and which may be compensatory mechanisms or epiphenomena. However, unlike most of the other morphological abnormalities in DG granule cells, the degree of mossy fiber sprouting was poorly correlated with the presence or absence of \emph{PTEN} inactivation. Thus, while mossy fiber sprouting has been a longstanding, leading candidate hypothesized to promote excitatory recurrent circuits in temporal lobe epilepsy, this finding supports other recent studies indicating that mossy fiber sprouting may not be necessary for epileptogenesis in temporal lobe epilepsy (6).

Finally, proving that pathological abnormalities in DG granule cells are sufficient to cause epilepsy does not prove that these abnormalities are necessarily involved in temporal lobe epilepsy, especially in other models or the human condition. More targeted future approaches—selectively reversing specific aspects of DG granule cell dysfunction—will be needed to determine whether and which of these abnormalities are truly necessary for epileptogenesis in this and other models. Similarly, with regard to the involvement of the mTORC1 pathway in epileptogenesis, this and other recent studies provide strong evidence that mTORC1 hyperactivation is sufficient to cause epilepsy (7,8), but further work is needed to determine the conditions under which abnormal mTORC1 activity is necessary for epileptogenesis in acquired temporal lobe epilepsy. mTORC1 may have numerous downstream effects relevant to epileptogenesis and has been implicated in a variety of different models of epilepsy (4). Although in the present study, mTORC1 activation was used primarily as a tool for triggering epileptogenesis and DG granule cell dysfunction, the mechanistic link between mTORC1 and morphological properties of neurons, such as DG granule cells, may be critical for other types of epilepsy beyond the classic mesial temporal lobe epilepsy.

\textit{by Michael Wong, MD, PhD}

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

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If no, enter your name as co-author:

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