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Linking brain tumors and epileptic seizures

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Abstract

Mutationally activated BRAF^{V600E} influences the behavior of different types of cells in the brain and leads to promotion of seizures as well as brain tumors, indicating how both can be pharmacologically targeted in the clinic.

Intractable epilepsy is an important medical challenge about which there is poor understanding—it is not known why 25% of patients with epilepsy fail to respond to combinations of antiepileptic drugs (AEDs)¹. Patients with intractable epilepsy are at an increased risk of early death, trauma, and psychosocial difficulties, and their overall quality of life is poor. These patients frequently require invasive therapies, such as neuromodulation or surgery that attempts to control synaptic transmissions or remove the underlying cause of the seizures². The underlying cause of epilepsy in many such patients is a brain tumor; this phenomenon is known as a long-term epilepsy-associated tumor (LEAT) and results in complications for therapy for both the seizures and the tumor. One approach to address intractable epilepsy is to customize the combination of AEDs used for the various types of epilepsy¹. Alternatively, understanding the underlying cause of these seizures may lead to new and improved therapeutic interventions. For example, activation of the PI3K–mTORC pathway by mutations is associated with cortical malformations (but interestingly, not tumor formation)³, which has led to successful clinical deployment of everolimus, an mTORC1 inhibitor, for the treatment of epilepsy in a molecularly defined subset of patients, with relatively modest side-effects⁴. In this issue of *Nature Medicine*, Koh et al.⁵ report a mechanistic link between the activity of the BRAF^{V600E}-mutant oncoprotein kinase, commonly expressed in gangliogliomas (GGs), and intractable epilepsy and show evidence that BRAF^{V600E} could be a therapeutic target for epilepsy.

LEATs are typically detected in the neocortex of younger patients and are generally slow-growing, low-grade tumors comprising cells of glial and neuronal differentiation. LEATs are also often associated with focal cortical dysplasia (FCD)². GG and dysembryoplastic neuroepithelial tumors (DNT) are the most common LEATs in pediatric patients who

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Competing interests

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ultimately require surgery for intractable epilepsy. However, it remains unclear why these tumors are capable of inducing intractable epileptic seizures. Although previous studies have suggested an association between BRAF^{V600E}, LEAT and FCD adjacent to the tumors, it is unclear how these associations may be related to epileptogenicity^{6,7}.

In their study, Koh et al.⁵ confirmed in 56 patients with LEAT that *BRAF*^{T1799A} (encoding BRAF^{V600E}) was the most common mutation and was carried by 50% of patients. Deeper analysis of five patients with GG-associated LEATs revealed that 60% of them expressed the mutated *BRAF*^{T1799A} gene, and no other significant mutations were identified. The authors also demonstrated that mutationally activated BRAF^{V600E} was expressed in both the neuronal and glial components of the tumor, suggesting that *BRAF* mutation is an early event in tumorigenesis. Importantly, using mouse models, the authors showed that BRAF^{V600E} expression in neural progenitor cells resulted in dysmorphic and epileptogenic neurons, whereas BRAF^{V600E} expression in glial cells resulted in tumorigenic cells that did not produce seizures (Fig. 1). The identification of glial cells as the origin of tumor cells provides a deeper understanding of tumor development. Indeed, these observations complement the recent findings of Lee et al.⁸, who concluded from their analysis of both patients with glioblastoma and genetically engineered mice that it is the neural stem cells in the subventricular zone of the brain that are the cells of origin of that tumor.

Koh et al.⁵ also demonstrated that in BRAF^{V600E}-driven brain tumor cells, there is decreased expression of mRNAs encoding proteins involved in synaptic transmission, nervous system development and regulation of synaptic plasticity compared with normal neurons. The authors propose that elevated expression of RE1-silencing transcription factor (REST, also called neuron-restrictive silencer factor (NRSF)) is a key upstream event associated with this mRNA expression pattern. REST is a member of the Kruppel-type zinc finger transcription factor family typically associated with suppression of neuronal-associated genes in nonneuronal tissues, and its expression was significantly increased in BRAF^{V600E}-driven GG specimens through the action of c-MYC, another key transcriptional regulator. These data are compatible with previous observations that REST contributes to seizure activity through transcriptional repression of genes involved in normal neuronal function⁹. Indeed, the authors found that either genetic or pharmacological inhibition of REST expression in mice with BRAF^{V600E}-driven tumors resulted in a significant delay in the development and frequency of seizures. More notably, intraventricular administration of vemurafenib, a Food and Drug Administration (FDA)-approved BRAF^{V600E} inhibitor, to mice with BRAF^{V600E}-driven tumors led to decreased REST expression and a significant decrease in the frequency of seizures. With respect to the frequency of *BRAF* mutations in brain tumors, these data have important implications for the use of BRAF^{V600E} inhibitors, such as dabrafenib, encorafenib or vemurafenib, in both the treatment of *BRAF*-mutated brain tumors and the intractable seizures associated with these tumors¹⁰.

The authors' research raises several important clinical considerations before such an approach to control seizures in patients with BRAF^{V600E}-driven brain tumors might be implemented. Of note, oral administration of vemurafenib to mice was unsuccessful in reducing seizure burden in the authors' study, necessitating an invasive infusion of the drug directly into the ventricles. This likely reflects the low brain penetrance of vemurafenib in

mice with an intact blood–brain barrier¹¹. However, intraventricular drug administration is not a viable clinical option for patients with BRAF^{V600E}-driven brain tumors. Moreover, clinical trials have previously demonstrated the effectiveness of orally administered BRAF^{V600E} inhibitors against *BRAF*-mutated brain tumors, indicating sufficient penetration of such drugs in humans¹².

To become eligible for BRAF^{V600E} inhibitor therapy, a patient would need pathologic confirmation of the *BRAF*^{T1799A} mutation, and such testing is becoming more routine for brain tumors. Although BRAF^{V600E} inhibitors are FDA-approved, the standard of care for GG remains maximal safe resection. Indeed, total tumor resection is achieved in approximately 70% of patients who receive this surgery, and many LEAT patients have a significant chance of being seizure-free following surgery and thus requiring no further AED therapy². Hence, the use of BRAF^{V600E} inhibitors for seizure control would not alter the goal of surgical control of the tumor, which remains the standard of care, whenever possible. However, the use of BRAF^{V600E} inhibitors for combined tumor and seizure control may be useful in the adjuvant setting in patients unable to achieve complete tumor resection or those with persistent postsurgical seizure activity and known to be BRAF^{V600E} positive in the residual FCD.

Finally, there is a concern as to when a decision to stop pathway-targeted BRAF^{V600E} inhibition might be made if it was being used as a seizure-controlling medication in children as opposed to a tumor-directed therapy. Studies are still ongoing in pediatric patients, and the effects of long-term use of such drugs in children remains unknown. This is particularly important given the risk of retinopathy and the development of secondary tumors associated with single-agent BRAF^{V600E} inhibitors. However, this might be circumvented by the use of combined vertical inhibition of both BRAF^{V600E} and its downstream targets MEK1 and MEK2, as is now common in the treatment of *BRAF*-mutated melanoma and lung cancer and is currently being investigated for the treatment of *BRAF*-mutated brain tumors¹⁰. Regardless of the complexities of the clinical translation of the findings by Koh et al.⁵, their elegant research has opened the door to a deeper mechanistic understanding of how oncogene activation in brain tumors contributes to the emergence of intractable epileptic seizures and suggests avenues of future research that might improve outcomes for this group of patients.

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Fig. 1 |. The role of BRAF^{V600E} signaling and REST in GG-associated intractable epilepsy. Koh et al.⁵ find that expression of mutationally activated BRAF^{V600E} in neural stem cells during early brain development results in dysplastic, non-neoplastic, epileptogenic neurons. By contrast, BRAF^{V600E} expression in cells that develop along the glial differentiation pathway results in neoplastic but nonepileptogenic cells. BRAF^{V600E}-driven GG-associated LEAT seizures are driven by constitutive BRAF^{V600E} → MEK → ERK signaling that drives expression of c-MYC that in turn promotes elevated expression of REST. Elevated REST expression leads to transcriptional repression of mRNAs associated with neuronal function resulting in the development of intractable epileptic seizures.