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Merritt–Putnam Symposium | Tumor-Associated Epilepsy and Epilepsy-Associated Tumors: Exploring the Bidirectional Crosstalk Between Tumors and Seizures

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Abstract

Links between cancerous and noncancerous brain tumors and epilepsy have long been recognized. However, recent clinical and preclinical studies emphasize that not only do tumors impinge on surrounding brain tissue in ways that promote hyperexcitability and epileptogenesis, but that neural activity also influences tumor progression. In this review, inspired by the Merritt–Putnam Symposium of the 2025 meeting of the American Epilepsy Society, we present a cross-disciplinary dialog between cancer and epilepsy research, including discussion of tumors and epilepsies that are more prominent in pediatric versus adult populations. First, we discuss the neuropathology, genetics, and surgical outcomes of epileptogenic brain tumors, and associated mechanisms of epileptogenesis. Second, we evaluate tuberous sclerosis complex as a model disease for clinical and mechanistic investigation of tumor–epilepsy relationships. Third, we review recent evidence for somatic gene mutations as underlying factors in hypothalamic hamartomas. Lastly, we present evidence for bidirectional relationships between gliomas and neuronal activity.

Keywords

brain tumor, epileptogenesis, glioma, hypothalamic hamartoma, somatic mutation, tuberous sclerosis complex

Introduction

Brain tumors are commonly associated with seizures and epilepsy, with a high degree of heterogeneity based on the location, size, and structure of the tumor(s), and the age at which the tumor and seizures present. The heterogeneity of tumor presentationand features is accordingly reflected in multiple types of tumor-associated seizure semiologies. Both cancerous and noncancerous (i.e., nonproliferating) tumors can promote seizures. However, recent clinical and preclinical studies emphasize that tumors and similar lesions not only impinge on surrounding brain tissue in ways that promote hyperexcitability and epileptogenesis, but that neural activity also influences tumor progression.

In this review, inspired by the presentations in the Merritt–Putnam Symposium at the 2025 meeting of the American Epilepsy Society, we present a cross-disciplinary assessment

incorporating cancer and epilepsy research, discussing multiple forms of tumors and epilepsies that are more prominent in pediatric versus adult populations. Particular focus is placed on neuroepithelial tumors, low-grade epilepsy-associated tumors, tuberous sclerosis complex (TSC), hypothalamic hamartomas (HHs), and gliomas. We discuss the role of multiple signaling pathways implicated in tumor development, such as the mechanistic target of rapamycin (mTOR), mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK), and Sonic hedgehog (SHH) signaling pathways, and the roles of germline and somatic mutations in tumorigenesis.

The Neuropathology, Genetics, and Surgical Outcomes of Epileptogenic Brain Tumors

Low-grade epilepsy-associated brain tumors are uniquely positioned at the intersection of neuropathology, neurogenetics, and neurosurgical practice. Unlike high-grade gliomas or metastatic lesions, these tumors often present with chronic seizures as the primary symptom.[1] For many patients—especially children and young adults—surgical resection results in seizure freedom, which translates directly into improved cognitive, psychological, and social outcomes.[2] Recent advances in neuropathological classification, molecular genetics, and surgical approaches have begun to transform how these tumors are understood and managed.

Tumor Classification: Beyond Morphology

Histopathology has long provided the foundation for classifying epileptogenic tumors, with gangliogliomas, dysembryoplastic neuroepithelial tumors (DNETs), and low-grade gliomas comprising the most common subtypes.[3] Traditionally, diagnosis relied on morphology, identifying neuronal and glial components, dysplastic neurons, or multinodular growth patterns. However, tumor morphology is highly heterogeneous and reliance on morphology alone has resulted in cases of ambiguity.[4]

The most recent WHO classification of central nervous system tumors has emphasized integrated diagnosis, combining histological criteria with molecular signatures.[5] This framework has been particularly illuminating in epilepsy-associated tumors, where morphologic subtleties may obscure biologically distinct entities. For instance, the recognition of "polymorphous low-grade neuroepithelial tumor of the young" (PLNTY) reflects the integration of unique histopathology with molecular correlates, such as MAPK pathway alterations.[6]

Mechanisms of Epileptogenesis

Molecular genetics has dramatically reshaped the understanding of epileptogenic tumors. One of the most striking discoveries is the high frequency of MAPK pathway alterations across multiple tumor types. BRAF V600E mutations, for instance, are common in gangliogliomas and pleomorphic xanthoastrocytomas, whereas FGFR1 alterations are often found in DNETs and PLNTYs.[7] These mutations not only drive tumorigenesis but may also contribute directly to epileptogenicity, for example through altered neuronal excitability or dysregulated signaling in peritumoral networks.

Equally intriguing is the overlap between tumor genetics and cortical malformations. mTOR pathway activation, for example, is implicated in both focal cortical dysplasia and certain glioneuronal tumors, suggesting a shared developmental origin of tumor formation and seizure susceptibility. In preclinical studies, the biological context of a genetic alteration in terms of developmental timing and cell lineage appears to contribute to the ultimate neuropathological and clinical manifestation.[8]

Clinically, these genetic insights have important implications. First, they refine diagnoses, as molecular characteristics can distinguish histologically similar lesions in some cases. Second, they open the door to targeted therapies. BRAF inhibitors, FGFR inhibitors, and mTOR pathway modulators are under active exploration, offering potential adjuncts to surgery in patients with incomplete resections or recurrent tumors. While these therapies remain largely experimental in the epilepsy context, they hold potential for future clinical use.

Surgical Outcomes: Seizure Control and Prognosis

Surgical resection remains the cornerstone of treatment for epileptogenic brain tumors. The goals are maximal safe tumor removal and seizure freedom. Numerous studies have demonstrated that gross total resection is the single most important predictor of postoperative seizure outcome.[2] Complete excision of both tumor and associated epileptogenic cortex markedly improves seizure control.

Seizure freedom rates after surgery for these tumors often exceed 70%, a figure far higher than for resective surgery in nonlesional epilepsy.[2] Importantly, even when tumors are histologically low-grade and carry a favorable oncologic prognosis, seizure burden can be profoundly disabling; thus, surgery addresses both the tumor and quality-of-life. Early surgery, particularly in pediatric patients, is associated with better seizure control and reduced neurocognitive sequelae, supporting the argument for timely intervention rather than prolonged trials of ineffective medications.

Summary

The intersection of neuropathology, genetics, and surgery represents a rapidly advancing area in the management of epileptogenic tumors. Combined morphology, immunohistochemistry, and molecular testing is improving diagnosis and prognostic stratification. These areas will continue to advance with new knowledge of tumor biology based on the shared developmental pathways implicated in tumors and epilepsy. Fortunately, many patients achieve long-term seizure freedom with surgical treatment, highlighting the

importance of timely referral and multidisciplinary evaluation.

TSC: A Model Disease for Investigating the Clinical and Mechanistic Relationship Between Tumors and Epilepsy

TSC is a genetic disorder due to mutation of the *TSC1* or *TSC2* gene and features both tumors and epilepsy as major phenotypes.[9] TSC-related tumors involve a spectrum of benign tumor types in multiple organs. Subependymal giant cell astrocytomas (SEGAs) in the ventricles of the brain start as small subependymal nodules and grow progressively throughout childhood. Other tumors are better classified as hamartomas, including the classic cortical tubers, which show minimal growth but are akin to developmental malformations with disorganized tissue and atypical cell types. Pathologically, SEGAs exhibit an abundance of large, undifferentiated proliferating cells referred to as giant cells.[10] In comparison, tubers have a range of abnormal cells, including dysplastic or cytomegalic neurons, reactive astrocytes and giant cells.[11] Clinically, SEGAs are often asymptomatic, but with progressive growth may cause obstructive hydrocephalus with acute neurological symptoms, such as headaches and seizures. Cortical tubers have been strongly associated with chronic epilepsy.

Epilepsy affects 80% to 90% of TSC patients and typically starts early in life. Infantile spasms occur in about one-third of TSC patients, and multiple seizure types in at least half patients, including focal seizures.[12] While spasms often resolve with vigabatrin, chronic seizures in TSC are often intractable to medications, with a majority meeting the definition of drug-resistant epilepsy. Some TSC patients are candidates for epilepsy surgery, such as tuberectomy, as well as neurostimulation and dietary therapy, but many TSC patients are still left with life-long intractable seizures despite available treatments.

In investigating the clinical relationship between tumors and epilepsy in TSC, seizures are often thought to originate from cortical tubers. In some cases, focal seizures may be localized to a single tuber, but multiple cortical and subcortical tubers may also form complex epileptogenic networks that make seizure localization difficult. Invasive EEG recordings (eg, stereo-EEG) help localize seizures to individual cortical tubers.[13,14] Most evidence suggests the ictal onset zone is directly within tuber tissue, but in some cases, seizures may arise from the surrounding perituberal region. The best evidence that individual tubers can cause seizures is that tuberectomy may lead to seizure-freedom in select TSC patients.

Mechanistic overlap exists between tumorigenesis and epileptogenesis in TSC. On the cellular level, cytomegalic neurons within tubers have increased excitability with stimulation,[15] but a definitive spontaneous generator for epileptiform activity has not been identified. On the molecular level, while ion channels and neurotransmitter receptors have been implicated in TSC-epilepsy, recent focus has been on upstream signaling pathways, particularly the mTOR pathway, which may overlap both tumors and epilepsy.[16] mTOR is a ubiquitous protein kinase that regulates a number of functions, such as cell growth, proliferation, metabolism, and protein synthesis. The *TSC1* and *TSC2* proteins inhibit mTOR, normally dampening down excessive cell growth and proliferation. Mutation of the TSC genes leads to hyperactivation of the mTOR pathway and increased cell growth and proliferation, promoting tumorigenesis in TSC. Clinical trials have shown that mTOR inhibitors decrease tumor growth in TSC patients, leading to FDA approval of mTOR inhibitors for various tumors in TSC, including SEGAs.[17]

In terms of epilepsy, while tubers don't proliferate like typical tumors, mTOR has other downstream functions that affect neuronal excitability and seizures, such as synaptic plasticity, neurogenesis, inflammation and protein synthesis of ion channels. Thus, similar to tumors, mTOR inhibitors represent a rational, targeted therapy for epilepsy in TSC. Preclinical studies support the efficacy of mTOR inhibitors in preventing or inhibiting seizures in TSC mouse models, as well as megalencephaly, astrogliosis, and abnormal expression of inflammatory cytokines and glutamate transporters, which may all contribute to epileptogenesis.[18] Clinical trials demonstrated an mTOR inhibitor decreases focal seizures in TSC patients with intractable epilepsy, leading to FDA approval for this indication.[19] Therefore, mTOR inhibitors are established in clinical practice to be effective treatments for both tumors and epilepsy in TSC and likely involve overlapping mTOR-mediated mechanisms. As mTOR inhibitors still have incomplete antiseizure efficacy for intractable epilepsy in TSC, future studies have shifted to earlier treatment, starting in infancy, to attempt to prevent epilepsy as an antiepileptogenic effect, rather than waiting to treat intractable epilepsy. An early, preventative approach has the best chance of inhibiting epileptogenesis and tumorigenesis, thus maximizing efficacy against both tumors and epilepsy in TSC.

Somatic Variation in HHs

HHs are rare, noncancerous lesions of the hypothalamus that arise during embryonic development. HH is estimated to occur in 1 in 50 000 to 100 000 children.[20] HH can be classified into intrahypothalamic lesions that occur in the posterior hypothalamus and are associated with gelastic seizures ("laughing seizures"), and parahypothalamic lesions in the anterior hypothalamus that are more typically associated with precocious puberty.[21] Beyond the hallmark lesion, HH often leads to debilitating neurological and developmental complications, including multiple seizure types, cognitive delays, and psychiatric conditions. Treatment often involves surgical interventions that can include surgical resection of the tumor. While most cases are sporadic, approximately 5% of HH can occur as part of syndromic conditions such as Pallister-Hall syndrome, caused by autosomal dominant germline loss-of-function

variants in *GLI3*, and Orofacial Digital syndrome (OFD), associated with X-linked dominant variants in *OFD1*.[22,23]

Early genetic studies using chromosomal microarray and targeted sequencing identified somatic alterations in *GLI3*, including loss of heterozygosity and point mutations, suggesting a role for somatic mosaicism in HH pathogenesis.[24,25] Two subsequent exome sequencing studies of paired blood and hamartoma tissue expanded this understanding. These 2 studies identified somatic variants in *GLI3*, *OFD1*, *PRKACA*, among other genes and several large structural variants the majority of which were enriched in genes encoding proteins involved in the SHH signaling pathway.[26,27] Later investigations identified bi-allelic "two-hit" models, implicating genes such as *DYNC2H1, DYNC2I1, SMO,* and *IFT140,* establishing HH as a ciliopathy.[28,29] Somatic variants were also found in *PTPN11* suggested a potential link to MAPK signaling,[28] and possible links to mesial temporal lobe epilepsy[30,31] and epilepsy-associated tumors. Further linking HH to epilepsy,[32] recent work found a novel loss-of-heterozygosity event in *TNK2*, a gene previously associated with infantile spasms.[33] Somatic variants arising during embryonic development and bi-allelic 2-hit variants, comprising a germline variant in combination with a second somatic variant, collectively explain between 34% and 77% of sporadic HH cases.[27,28,33,34] Disease presentation as either sporadic or syndromic HH likely depends on variant burden and tissue localization.[35,36]

Despite the recent advances in our understanding of the genetic landscape of HH, approximately 35% of sporadic HH cases remain genetically unexplained. Future research directions aim to overcome current limitations in somatic variant detection, including long-read sequencing technologies that will allow for the identification of structural variants missed by exome sequencing and improved tissue sampling strategies could reduce reliance on surgical resections and allow for further explorations the full landscape of somatic variants in tumors not eligible for resection. New single-cell sequencing approaches that enable identification of precise identification of cells harboring the somatic variants and determining cell-type-specific signaling changes will also be key to further advancing our understanding of HH pathophysiology and potential therapeutic strategies.

Mechanistically, SHH signaling plays a central role in hypothalamic development by regulating GLI protein activity through primary cilia. Variants in HH-associated genes are thought to likely impair SHH signaling and lead to transcriptional repression, although there are also some variants that may activate the pathway and lead to activated transcription.[35] Interestingly, SHH dysregulation has also been reported to be involved in cancer biology, where it contributes to stem cell maintenance, proliferation, epithelial–mesenchymal transition, angiogenesis, and metastasis.[37] These shared mechanisms suggest that understanding the role of SHH across cancerous and noncancerous tumors may illuminate aspects of pathophysiology and inform treatment approaches.

The link between HH and epileptogenesis is not fully understood. While early speculation suggested a more indirect role, there is now clear evidence for that HH lesions are intrinsically epileptogenic.[38–40] Additional work is needed to fully understand the primary and secondary roles of HH in epileptogenesis, particularly additional studies of *ex vivo* analysis of human tissue resections and establishing animal models of HH.

Bidirectional Relationships Between Gliomas and Neuronal Activity

Over the past decade the interrelationship between brain tumors and resident neurons has emerged as a key facet of tumor progression and tumor-associated changes in network activity.[41] Seminal work in the field of cancer neuroscience has shown that brain tumors hijack activity-dependent neuronal mechanisms to support tumorigenesis, proliferation, tissue microenvironment (TME) remodeling, and survival. These mechanisms include direct neuron to tumor depolarizing synaptic connections, neuron-derived paracrine factors, and neuron-derived neuromodulators. These interactions enable tumors to release paracrine factors that remodel neuronal synapses toward hyperactivity, which can culminate in glioma related epilepsy. This subsequent elevation of neuronal activity causes the release of factors and enhanced synaptic connections with tumors, which promote tumor progression. This vicious cycle of bidirectional, self-amplifying communication between brain tumors and neurons is a unique component of the brain TME which contributes to both malignant progression and the milieu of neurological endophenotypes associated with brain tumors. In the following sections we will summarize studies that defined many of the mechanisms associated with tumor–neuron interactions, focusing on glioma.

Tumor-to-Neuron Signaling

The first studies to demonstrate that glioma can influence neuronal activity involved mechanisms associated with glutamate release. It was shown that gliomas directly secrete glutamate to induce hyperactivity and tumor growth, where glioma cells utilize the xCT transporter (SLC7A11) system to significantly elevate extracellular glutamate, lowering the threshold for peritumoral neuronal hyperexcitability.[42] Treating de novo murine and patient-derived xenograft glioma models with the xCT antagonist sulfasalazine lowered extracellular glutamate and subsequently reduced hyperexcitability.[43] Together these studies demonstrate how tumors increase the tone of excitability in neurons by altering the synaptic constituency or increasing the opportunity for firing, by increasing the availability of glutamate.

Studies from development have found that astrocytes can promote synaptogenesis in the healthy brain via secreted factors including Glypicans and Thrombospondins.[44] Interestingly, glial secretion of glypicans and thrombospondins appears to be a mechanism of synaptogenesis coopted by gliomas to promote growth. In a study screening an allelic series of PIK3CA point mutations, specific driver variants

were capable of altering the synaptic milieu of the TME to promote network hyperexcitability, which was associated with more aggressive tumor growth.[45] In a mechanism parallel to astrocytic promotion of synaptogenesis, these PIK3CA variants increased Glypican 3 production in glioma cells. This Glypican 3 altered the glioma synaptic milieu, which created network hyperactivity and glioma-related epilepsy. Separate studies during lexical retrieval language tasks in humans found that cortical regions not associated with speech behavior were highly active, consistent with elevated neuronal activity throughout the brain. This evidence suggests that the tumor remodeled the surrounding neuronal network to increase this cellular activity in the task-associated activity. Further analysis of these patient tumor cells revealed an enrichment for the THSB1 transcript, encoding the synaptogenic factor Thrombospondin 1.[46] Thus, gliomas release paracrine factors that promote synaptogenesis such as Glypican 3 and Thrombospondin 1, which aberrantly remodel brain network activity.

Neuron-to-Tumor Signaling

The first studies on a neuron-derived mechanism that drives glioma progression identified activity-dependent NLGN3 shedding as a driver of glioma growth in pediatric high grade glioma (HGG) xenografts. Optogenetic stimulation of local cortical neurons led to an increase in pHGG xenograft proliferation in vivo, the first ever direct observation that elevated neuronal activity promotes glioma cell growth. This effect was found to be paracrine in nature, and subsequent studies revealed that NLGN3 activates PI3K-mTOR signaling in glioma cells[47] and that TME-derived NLGN3 is required for tumor growth. Building off of this, parallel studies using chemogenetic approaches for neuronal manipulation demonstrated that neuronal populations in cortical regions contralateral to the primary can drive tumor infiltration throughout the brain.[48] This activity-dependent mechanism utilizes axon guidance-associated mechanisms to facilitate infiltration. Other examples of circuit-specific activity induction of glioma growth include olfaction-induced secretion of IGF-1 from neurons. Olfaction activates Olfactory Receptor Neurons, which induce mitral and tufted cells to secrete IGF-1.[49] IGF-1 then serves as a circuit-specific and activity-dependent glioma mitogen.

In addition to paracrine signaling, direct, electrochemically active neuron to tumor synapses have also been identified and have emerged as key drivers of malignant progression. Ultrastructural electron microscopy identified structures resembling synapses between neurons and glioma.[50,51] To address whether these synapses were functional, tumor cells were first grafted into the CA1 region of the mouse hippocampus[50] and voltage-clamp recordings of tumor cells (in the CA1 regions) recorded inward depolarizing currents characteristic of excitatory postsynaptic current upon CA3 stimulation, supporting the notion that these are functional synapses. Additional studies revealed that these glutamatergic synapses were regulated AMPA receptors rather than NMDA. The use of a dominant negative AMPA receptor in these tumor cells blocked the cell's AMPA responsiveness and slowed glioma growth. These studies highlight that synaptic activity between neurons and glioma contributes to tumor growth.[50,51]

Concluding Remarks

Recent innovations in clinical genetics, preclinical model development and mechanistic investigation, and improved neurosurgical approaches have expanded our insight into the bidirectional relationship between brain tumors and seizures. In the future, precision medicine approaches based on growing molecular genetic knowledge hold promise for patients with incomplete resections or inoperable lesions, though clinical trials focused on seizure outcomes are needed. As the field evolves, the most transformative advances are expected to come from continued cross-disciplinary integration. Continued investigation of these relationships, for example through further model development and advances in single-cell genomics and proteomics, is necessary to promote improved understanding of tumor and epilepsy pathophysiology and identify novel therapeutic avenues, with high relevance for treatment of both brain tumors and epilepsy.

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