Mutational Analysis Reveals the Origin and Therapy-Driven Evolution of Recurrent Glioma

University of California, San Francisco researchers recently reported in Science the mutational profiling of 23 initially low-grade gliomas (LGGs) and associated recurrent tumors and profiled a subset of recurrent tumors in temozolomide-treated patients. Three key findings with potentially important clinical implications for LGG management were demonstrated: (1) LGGs and paired recurrent tumors are highly divergent and often only share a few early mutations, thus partly explaining their differential therapeutic responses; (2) mutant isocitrate dehydrogenase-1 (IDH1) may be critical for LGG formation and is a potential therapeutic target; and (3) temozolomide therapy may contribute to malignant transformation and affect clinical outcome.

Johnson et al. determined the genetic profiles of LGGs and associated recurrences. Mutations that are shared or exclusive to the initial tumor or recurrences were characterized for each of 23 initial tumors and recurrences found up to 11 years later, and tumor phylogenies were mapped via evolutionary analyses. Overall, the paired tumors shared a significant percentage of mutations exclusive to the initial tumors in 43% of cases. These findings suggest that gliomas and recurrent tumors share early tumorigenic mutational origins but diverge afterward in tumorigenesis.

LGG sequencing also revealed that an IDH1 mutation was present and remained unchanged in all paired tumors, highlighting IDH1 as a potentially critical LGG driver mutation. IDH1 mutants produce 2-hydroxyglutarate R-enantiomer, an interesting tumor metabolism product that inhibits histone enzymes and alters gene expression. Recent work highlights a possible LGG-selective therapeutic opportunity because inhibitors of IDH-1 mutant activity selectively reduce tumor growth rate and stimulate glioma differentiation.

This work also reported the effects of temozolomide therapy on mutational profiles of recurrent gliomas, especially given that temozolomide use in LGG therapy is controversial.

Mutational profiles of paired tumors in 10 temozolomide-treated patients were determined. Recurrent tumors from 6 of the 10 patients exhibited hypermutated phenotypes after temozolomide therapy, carrying many more mutations per million base pairs compared with their initial tumors. The hypermutated state is likely caused by the propensity of temozolomide to mutate and compromise DNA mismatch repair pathways. Additionally, the authors characterized the unique hypermutated signature and found significant association with high-grade glioma signaling pathways such as retinoblastoma and protein kinase B–mammalian target of rapamycin signaling (Figure, B). These results suggest that temozolomide therapy may contribute to malignant transformation of LGGs, and further studies are needed to determine whether this alters clinical outcomes.

Ray R. Zhang, BS
Kelli B. Pointer, BS
John S. Kuo, MD, PhD
Robert J. Dempsey, MD
University of Wisconsin
Madison, Wisconsin
Why Glioma Patients Seize: Adding More Pathological GABA to the Glutamate Hypothesis

Patients with primary infiltrative brain tumors frequently have seizures, with epilepsy rates ranging from 60% to 100% in patients with low-grade gliomas and 25% to 60% in patients with high-grade gliomas. Several studies have demonstrated that an imbalance between excitatory glutamatergic and inhibitory gamma-aminobutyric acid (GABAergic) activity may underlie epileptic activity, with excess glutamate release contributing to neuronal death in high-grade tumors. GABA$_A$ receptor expression and synapses are known to be reduced in peritumoral neocortical areas. Furthermore, research on nontumoral mesial temporal sclerosis tissue has implicated pathological GABAergic signaling in human epileptogenesis. The K$^+$/Cl$^-$ cotransporter NKCC1, which transports chloride ions into the cell, is normally expressed at low levels in adult human cerebral tissue, whereas the KCC2 cotransporter, which extrudes chloride ions, is normally expressed at high levels. Decreased neuronal expression of KCC2 in epileptogenic tissue results in increased intracellular chloride. This perturbation in neuronal chloride homeostasis converts GABA$_A$ receptor activation from the normal adult brain hyperpolarizing inhibitory response to a depolarizing excitatory response (Figure 1). A similar mechanism of increased intracellular chloride has also been implicated in promoting glioma cell migration. Recently, 2 studies investigated the role of chloride homeostasis and GABAergic signaling in peritumoral epileptogenesis using human neocortical slices and a mouse glioma model, respectively.

In human peritumoral neocortical slices, Pallud et al. from the University of Paris Sorbonne demonstrated that GABAergic perturbations in peritumoral tissue from both low- and high-grade gliomas contribute to epileptogenicity. Peritumoral specimens exhibited interictal-like discharges, peri-ictal discharges (PIDs), and ictal-like discharges (IDs), whereas control and tumor tissue did not. The authors found that interictal-like discharges were suppressed by inhibition of both glutamatergic AMPA and GABA$_A$ receptors, identifying the role of both neurotransmitters in the generation of these discharges. Furthermore, researchers demonstrated that GABA$_A$ alone can depolarize pyramidal cells and does so at a significantly higher rate in peritumoral tissue than normal tissue. Consistent with prior human epilepsy work, the authors hypothesized that abnormal cellular Cl$^-$ trafficking was responsible. They found that peritumoral pyramidal neurons from epileptogenic tissue expressed increased NKCC1 levels relative to normal tissue and abnormally decreased KCC2 receptor levels (Figure 2), resulting in elevated intracellular chloride. GABA activation of neurons with elevated intracellular chloride induces excitatory depolarization rather than the inhibitory neuronal hyperpolarization that is normally seen in the adult brain in response to GABA$_A$ activation (Figure 1).

The Haberfeld team went on to further clarify the complex pathological interplay that characterizes human peritumoral epilepsy. To examine activity more closely resembling a true seizure, they induced IDs by placing tissues in a proconvulsant environment, allowing the recording of PIDs. PIDs always preceded IDs and increased in frequency during the transition to IDs. However, PIDs were not affected by GABA antagonists. In addition, chloride blockade via NKCC1 cotransporter antagonism abolished interictal-like discharges and IDs but had no influence on the firing of PIDs. During the transition to IDs, PIDs from different foci tended to increase in synchrony, and conduction speed increased. Thus, PIDs appear to contribute to intracellular Cl$^-$ accumulation through recurrent, synchronous activation of pyramidal cells, whereas GABAergic interneurons responsible for interictal-like discharges actually depolarize the pyramidal cells themselves.

REFERENCES