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Understanding epilepsy in IDH-mutated gliomas: towards a targeted therapy

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Epileptic seizures are very frequent in diffuse gliomas: the majority of patients with astrocytomas, oligodendrogliomas, and glioblastomas will experience brain tumor-related epilepsy during the course of their disease. It is not only an unpleasant complication for patients that reduces quality of life and causes considerable morbidity. It is also likely that tumor-related neuronal hyperexcitability (that underlies epilepsy) can create a vicious cycle that ultimately drives brain tumor growth.[1,2] We know today that this also includes neuron-glioma synapses that are of the AMPA receptor subtype and that can be specifically targeted with the antiepileptic drug perampanel; since brain tumor-produced glutamate is also known to be involved in neuronal hyperexcitability, this approach emerged as a particularly promising single therapeutic approach for these two related diseases.[1,2] Of note, neuron-glioma synapses were detected not only on adult glioblastomas but also on IDH-mutated astrocytomas.[3]

Nevertheless, it has been clear for several years that something must be special about epileptogenesis in IDH-mutated gliomas. Although the clinical disease course is much more favorable than in IDH wild-type tumors, it is now well established that the IDH mutation is clearly associated with a more severe tumor-related epilepsy, meaning more and more pharmacoresistant seizures. This seemingly contradictory fact cannot solely be explained by a higher cumulative incidence of epileptic seizures over many years in patients suffering from these slow growing tumors: it is even evident when determined over fixed periods of time.[4] It is unlikely that this can be primarily attributed to invasion patterns or other anatomical factors, which seem to be quite similar between IDH mutant astrocytomas and wild-type astrocytomas/glioblastomas, which includes the formation of neuron-interacting membrane tube extentions of glioma cells.[3,5] One suggested explanation was that the oncometabolite D-2-Hydroxyglutarate (D-2-HG) that is produced by the mutant IDH enzyme bears similarities to glutamate, the main excitatory neurotransmitter.[6] This seemingly plausible explanation has recently been challenged, and open questions about alternative factors and downstream mechanisms remained.

In this issue of *Neuro-Oncology*, Mortazavi and co-workers[7] provide an alternative, at least additional explanation for the particularly high frequency of seizures in IDH-mutated gliomas, and for their particularly high resistance to current antiepileptic drugs. This explanation also fits very well to recent discoveries in molecular epileptology and is based on solid cell culture and electrophysiological data from patient tissue. First, they investigated how genetically modified IDH^{R132H} vs. IDH^{WT} glioma cells influence the electrical activity of neurons in a co-culture model. Here, this clinically most frequent IDH mutation was associated with a higher firing rate and burst number of spiking in neurons, which argues for induction of neuronal hyperexcitability. Ivosidenib, an inhibitor of the mutant IDH that can normalize D-2-HG levels, reversed that phenomenon, arguing for a role of this oncometabolite in neuronal hyperexcitablity.

Next, the authors investigated how D-2-HG exerts its action on neurons. They demonstrate distinct metabolic changes in the neuron-glioma coculture system under D-2-HG treatment, with increases in maximal glycolytic rate and mitochondrial respiratory activity. Importantly, they can even find indications of this metabolic reprogramming by D-2-HG in resected brain tissue from the infiltration zone of five IDH mutant gliomas, with increased expression of lactate dehydrogenase A in neurons, similar to what was seen in the co-culture system. Of note, this was only evident in cortex areas that had been intraoperatively defined as epileptic by electrode recordings, but not in cortex areas where no hyperexcitability was evident in the patient.

The next question was: how exactly is this metabolic reprogramming making neurons more prone to epileptic activity? Here, a master regulator of cellular metabolism, but also other tumor-related functions (including in gliomas) appeared

plausible: the mTOR pathway. Indeed, by a set of carefully planned experiments and control investigations, the authors demonstrate that the oncometabolite D-2-HG is indeed driving mTOR pathway activation in the co-culture system treated with D-2-HG, and also in patient tissue samples. Importantly, the mTOR inhibitor rapamycin was able to reverse these changes. Further experiments revealed that the metabolic programming by D-2-HG was not simply due to its stimulatory effects on neuronal spiking, but an independent effect.

A final set of experiments addressed the chicken-and-egg question: which is first, mTOR pathway activation or metabolic reprogramming? Here, D-2-HG, but also another activator of the mTOR pathway, both produced the characteristic metabolic changes, but also neuronal bursting activity—which was successfully inhibited by rapamycin in both cases. Together, this suggests that D-2-HG primarily activates the mTOR pathway, through a molecular mechanism that still needs to be defined. The resulting metabolic shift is one plausible explanation of increased epileptogenesis in the context of the IDH mutation.

The translational implications of this study are significant. One is to providing an explanation why inhibitors of mutant IDH might exert antiepileptic effects in patients, as suggested by a recent case report.[8] This could be independent of the potential cytostatic or cytotoxic effects of this drug class on tumor cells, and due to the lowering of D-2-HG concentrations in the brain. More importantly, a second class of drugs is suggested for targeted antiepileptic treatment in IDH mutant gliomas: mTOR inhibitors, like rapamycin, everolimus or temsirolimus. While these drugs are well known to Neuro-Oncologists for their good antiepileptic effects in subependymal giant cell astrocytomas in tuberous sclerosis,[9] the current study by Mortazavi et al. adds IDH mutant gliomas to the basket of brain tumor diseases that can specifically profit from mTOR inhibition. This would also be supported from an increasing body of evidence outside the field of Neuro-Oncology that, at least under certain molecular circumstances that are associated with an activation of the mTOR pathway, mTOR inhibitors can act as effective antiepileptic drugs.[10] It will be exciting to learn whether those patients suffering from IDH^{mut} brain tumor-related epilepsy that are not responding well to approved antiepileptic drugs can indeed profit from mTOR inhibitors.

Moreover, the study of Mortazavi et al. sets the stage for similar research in glioblastoma, where epileptogenesis is still incompletely understood and predictive molecular markers are missing. In this respect, the new study by Ricklefs et al.[11] where the RTK II subclass was found to be associated with seizure development provides important hints. Future studies can build on these findings and unravel whether the mTOR pathway, or other specific ones, are involved in epileptogenesis in glioblastoma, too.

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