IDH1-Mutated Gliomas Induce Epileptogenesis Through Alterations in Neuronal Metabolism

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Gliomas are a heterogeneous group of brain tumors that commonly manifest with seizures. Seizures occur in up to 90% of patients with low grade gliomas and are a major contributor to brain tumor morbidity. Given the clinical complexity of TRE, the current understanding of how gliomas disturb the neural circuitry is insufficient.

Within low grade gliomas, 80% of the tumors contain mutations of the metabolic enzyme isocitrate dehydrogenase-1 (IDH-1). Although the mechanism is unclear, IDH-1 mutations have been shown to be an independent contributing factor to epileptogenesis. The neomorphic enzymatic activity of IDH\(^{R132H}\) that converts alpha-ketoglutarate (a-KG) to 2-hydroxoglutarate (2-HG) is a key feature in its pathogenesis (Figure 1). The effects of 2-HG may have heretofore unknown effects on the peritumoral environment. To this end, we demonstrate that 2-HG alters the peritumoral cortex neuronal metabolism and is a putative mechanism for epileptogenesis.

![Figure 1: IDH\(^{1R132H}\) resulting in accumulation of 2-HG.](image-url)
Methods

- **Microelectrode Array with Transwell Inserts**
  - To study the effect of IDH1-R132H glioma cells and the oncometabolite 2-hydroxyglutarate on neuronal activity, we utilized a mixed rat cortical cell culture model on a microelectrode array (MEA) and a CT-2A rodent glioma cell line on transwell inserts.

- **Clinical data and human tissue acquisition**
  - Five participants with IDH1 mutant gliomas and epilepsy underwent staged intracranial monitoring followed by resection of tumor and epileptogenic zone.
Results

- Raster plots from MEA recordings showing bursting activity of cortical culture from a single electrode following 7 days of interaction with IDH$^{WT}$ or IDH$^{R132H}$ CT-2A cells.

- Normalized bursting rate (NBR) of the cortical culture is increased following interactions with IDH$^{R132H}$ compared to IDH$^{WT}$ across 10 biological replicates.
Results

- \(\text{IDH}^{R132H}\) cells treated with AG-120 (\(\text{IDH}^{R132H}\) inhibitor) reduces the NBR to \(\text{IDH}^{WT}\) rates.
- \(\text{IDH}^{R132H}\) has increased production of D-2-hydroxyglutarate (2-HG) compared to \(\text{IDH}^{WT}\), but is decreased following treatment with AG-120.
- 2-HG treated cortical culture increases NBR.
- These results are across three biological replicates.
Results

Mapping was performed for all patients to identify the epileptogenic zone, followed by resection of the tumor and the region. All patients are seizure free after 1 year.

Multiplex fluorescence IHC demonstrates increased LDHA expression in the epileptic cortex compared to the peritumoral nonepileptic cortex.

Table 1: Patient Demographics and Outcomes

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Pathology</th>
<th>Engel Outcome (12mos)</th>
<th>KPS: preop</th>
<th>KPS: 12mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>M</td>
<td>Anaplastic Astrocytoma (WHO grade III)</td>
<td>1a</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>Anaplastic Astrocytoma (WHO grade III)</td>
<td>1a</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>Astrocytoma (WHO grade II)</td>
<td>1b</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>Astrocytoma (WHO grade II)</td>
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<td>80</td>
<td>70</td>
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<tr>
<td>40</td>
<td>M</td>
<td>Anaplastic Oligodendroglioma (WHO grade III)</td>
<td>1b</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Mean: 31</td>
<td>3M / 2 F</td>
<td>4 Astro / 1 Oligo</td>
<td><strong>100% Engel I</strong></td>
<td>Mean: 80</td>
<td>Mean: 86</td>
</tr>
</tbody>
</table>

*KPS: Karnofsky Performance Scale; WHO: World Health Organization
• Treating the cortical culture with isosafrole (ISO) and 2-deoxyglucose (2DG) reduces the NBR of IDH$^{R132H}$ to rates of IDH$^{WT}$.

• 2DG and ISO inhibits glycolysis and LDHA, respectively.
Our small series demonstrates that invasive EEG monitoring for tumor related epilepsy can safely facilitate mapping of epileptogenic and eloquent cortex in the setting of low grade gliomas. Moreover, our *in vitro* MEA transwell model, which mimics the brain-glioma microenvironment, displays the peritumoral environment of IDH^{R132H} gliomas have increased bursting activity compared to IDH^{WT} gliomas. Inhibition of IDH^{R132H} via AG-120 as well as direct treatment of cortical culture with 2-HG increases bursting activity, establishing 2-HG as a causal agent in epileptogenesis. Furthermore, epileptic foci *in vivo* demonstrates an upregulation of LDHA compared to the peritumoral nonepileptic cortex, indicating a hypermetabolic state. To this end, by inhibiting glycolysis and LDHA, bursting activity is corrected to baseline rates, signifying that the hypermetabolic state may be a putative mechanism for epileptogenesis in tumor related epilepsy and can ultimately be a therapeutic target.
Summary Points

• Invasive EEG monitoring for tumor related epilepsy can safely map epileptogenic and eloquent cortex in the setting of low-grade gliomas.

• IDH$^{R132H}$ gliomas cause increased epileptic activity in a 2HG-dependent manner.

• Epileptic foci in vivo from TRE demonstrate upregulation of LDHA and presumably increased metabolic activity.

• Inhibition of LDHA and glycolysis corrects bursting activity to baseline rates, demonstrating that hypermetabolic state is a putative mechanism and potential therapeutic target.

References: