Aberrant Glutamate and GABA Metabolism in Glioblastoma
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Introduction

• Glioblastoma (GBM) remains perhaps the most challenging type of neoplasm to treat (1). As a consequence, continued research in pursuit of understanding GBM pathogenesis is crucial for paving the way for novel therapeutics.

• Exploration of metabolic insult in glioma may provide the most compelling avenue. This raises the question: What if genomic instability in glioma is downstream of an initial metabolic insult?

Background

• Most debated mutation in glioma is a metabolic one: mutation in isocitrate dehydrogenase (IDH) is known to confer better survival prognosis through unclear mechanisms.

• Astrocytes and neurons play roles in maintenance of glutamate and GABA neurotransmitter pools, and astrocytes catabolize both glutamate and GABA.

• In 2018, Hujber et al. publish data demonstrating increased cellular respiration in IDH mutant and increased GABA oxidation and proliferation in IDH wild type (2).

• This inspired my primary research question to be: what are the origins of excess glutamate/GABA in glioblastoma?

Methods

• Using RNA-Seq and mRNA Nanostring data of DHMC and UVM GBM patient samples – first obtained by the Gaur lab – we conducted a preliminary analysis of the key human genes and enzymes in glutamate and GABA metabolism while comparing their presence in GBM to healthy human astrocytes.

Results

Figure 1: Direct Metabolic Pathways for Glutamate and GABA

<table>
<thead>
<tr>
<th>α-ketoglutarate*</th>
<th>GLUD1</th>
<th>glutamate</th>
<th>GAD1</th>
<th>glutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>succinic semialdehyde</td>
<td>ABAT</td>
<td>GABA</td>
<td></td>
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*GLUD1 and GLS, which continues to highlight the importance of searching for a more unifying source of excess glutamate in GBM

Figure 2: Expression Patterns in 5 Patient GBM Tissue Samples

- GAD1 and ABAT have inverse expression trends, which may suggest a straightforward inhibitory pathway as GABA accumulates.
- The absence of a clear expression trend amongst glutamate producers GLUD1 and GLS, which continues to highlight the importance of searching for a more unifying source of excess glutamate in GBM.

- Note close clustering of ALDH5A1 and GLUD1. A strong correlation between GLUD1 and GABA oxidation could once again reinforce why IDHm might be protective.

Results and Conclusions

Figure 3: Decreased GAD1 Expression in GBM tissue

Figure 4: GLUD2 as Mystery Glutamate Source in GBM tissue

- Based on this preliminary patient data, the inhibition of GAD1 and GABA oxidation together may present an aberrant metabolic pathway specific to GBM patients.
- Glutamate dehydrogenase 2 (GLUD2) should be further studied to establish its role in the excessive glutamate that could be the originator of tumorgenesis in glioma patients.

References