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

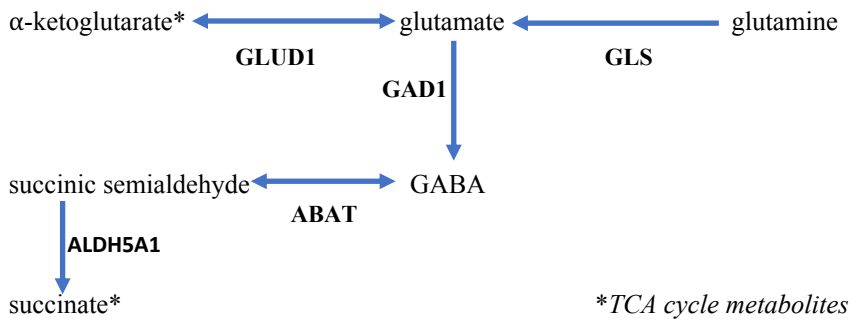
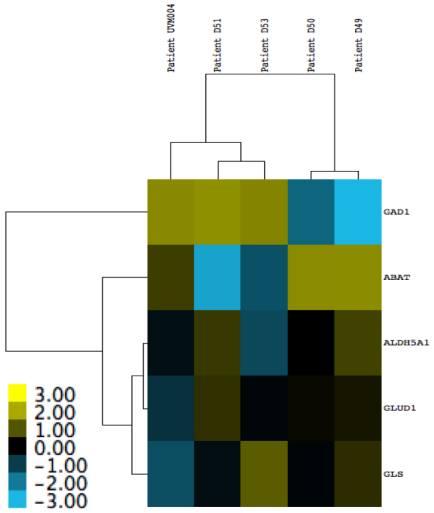


Figure 2: Expression Patterns in 5 Patient GBM Tissue Samples



- **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

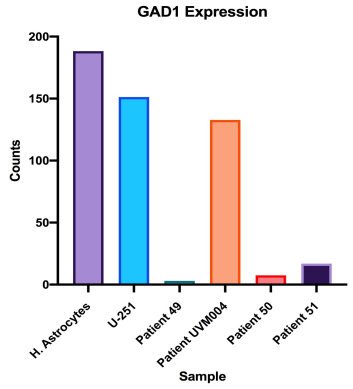
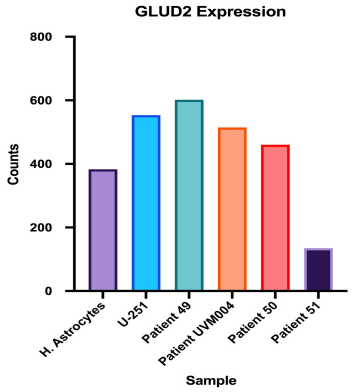


Figure 4: GLUD2 as Mystery Glutamate Source in GBM tissue



- 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 tumorigenesis in glioma patients

References

1. Thakkar, Jigisha P et al. "Epidemiologic and Molecular Prognostic Review of Glioblastoma." *Cancer epidemiology, biomarkers & prevention* 23.10 (2014): 1985–1996. Web.
2. Hujber, Zoltan et al. "GABA, Glutamine, Glutamate Oxidation and Succinic Semialdehyde Dehydrogenase Expression in Human Gliomas." *Journal of experimental & clinical cancer research* 37.1 (2018): 271–271. Web.