Examining the Effects of Molecular Aberrations on Metabolic Tumor Environment

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Introduction

The tumor microenvironment is metabolically susceptible to both genetic and environmental effects.

- Assessed gliomas characterized by the following genetic mutations: isocitrate dehydrogenase (IDH) mutation, 1p/19q co-deletion, and methylguanine methyltransferase promoter mutation.
- Tumors with the aforementioned mutations have shown better prognosis, response to targeted therapies, and overall survival.
- These genetic mutations act as predictive biomarkers that correspond to patient outcomes and enable more accurate tumor classification.
- In this study, we explored the neurochemical metabolites found in gliomas with the aforementioned mutations and their potential role in treatment monitoring and tumor identification.
- We hypothesized that the genetic mutations will result in different metabolite microenvironments between the tumor genotypes.

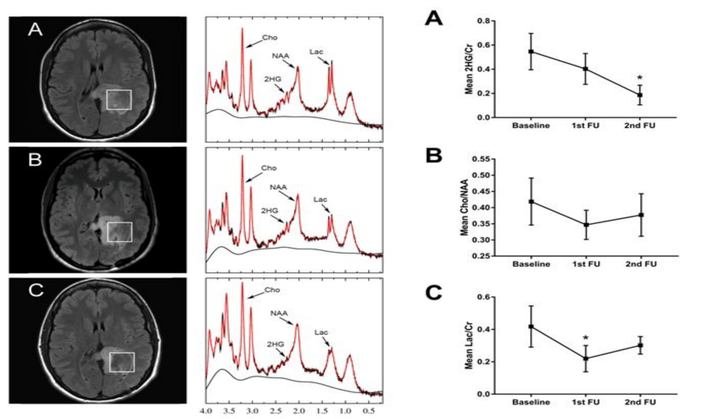

Fig 1. Example of treatment monitoring using MRS in an IDH1-mutant glioma. Left panel: A. MRS acquired at baseline. B) MRS acquired at 3 months after starting treatment. C) 6 months after treatment is completed. Right panel: Longitudinal changes in A) 2HG, B) Choline, and C) lactate.

- Magnetic resonance spectroscopy (MRS) is a non-invasive analytical technique that utilizes nuclear magnetic resonance (NMR) on clinical MRI scanners to identify, distinguish and quantify chemical metabolites *in vivo*.

Methods

- 515 single-voxel MRS scans were acquired using point resolved spectroscopy (TE=97ms) in 183 patients under IRB.
- Data pre-process was performed with OpenMRSLab and metabolites were quantified with LCModel.
- Clinical data for each patient (e.g. tumor type, WHO grade and treatment at time of scan) was collected from EPIC clinical records.
- Statistical analysis was performed using the Mann-Whitney U test with $\alpha = 0.05$.

Discussion and Conclusion

- Decreased glutamate in an IDH mutation patient as compared to an IDH WT patient. Tumors of this mutation are less aggressive and thus, display less glutamate (tumor aggressiveness indicator).
- Potential use of glutamate as a co-biomarker to 2HG, to optimize IDH1 glioma identification.
- Lipids are necrosis indicators and tumors display high necrosis when they are aggressive.
- Creatine levels were higher for UM and WT patients (novel finding). Aggressive tumors have higher infiltrative activity meaning they use more energy to continue expanding.
- Higher levels of mI for unmethylated patients; higher levels of mI are associated with more aggressive tumors.
- Robust variation of metabolites. Favorable for further investigation into the potential incorporation of alternative metabolites in treatment monitoring and tumor identification.

Results

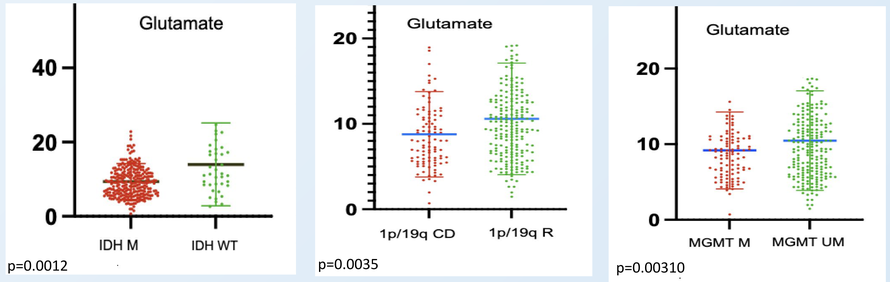

Fig A. Variation in glutamate between IDH mutant (M) and wild-type (WT), 1p/19q co-deleted (CD) and retained (R) and MGMT methylated (M) and unmethylated (UM).

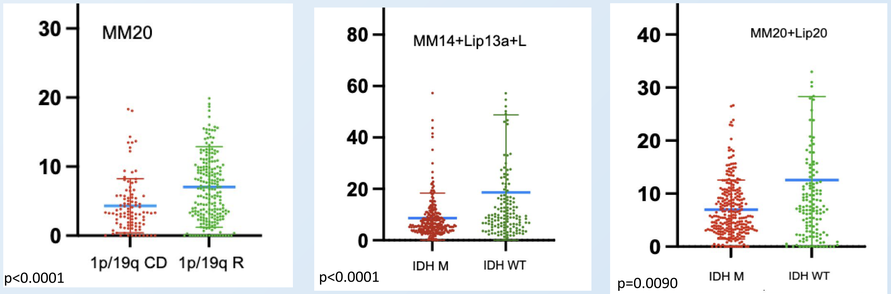

Fig B. Lower MM20 (p<0.0001), MM14+Lip13a+L (p<0.0001), MM20+Lip20 (p<0.0090)

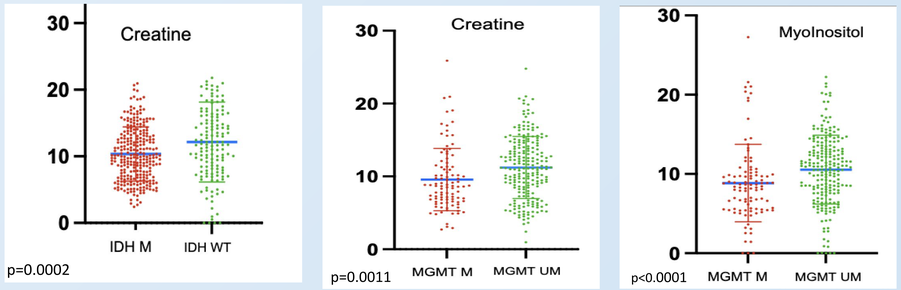

Fig C. Lower creatine (metabolic activity indicator) in MGMT M and IDH M compared to WT.

Fig D. Lower myo-inositol(mI)- glial marker in MGMT M compared to UM

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