An in-vivo 1H MRS study of metabolic correlation in IDH1 vs. IDH2 mutated gliomas

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Target audience: Neuro-oncologists/-radiologists, and MR spectroscopists in brain tumors.

Purpose: A high fraction of gliomas contain mutations in isocitrate dehydrogenases (IDH) 1 and 2 [1,2]. IDH1 and IDH2 catalyze the NADP$^+$ dependent conversion of isocitrate to α-ketoglutarate in the cytosol and mitochondria, respectively. The mutations in these enzymes induce a neomorphic enzyme activity, resulting in the production of 2-hydroxyglutarate (2HG) [3,4]. Given the cellular difference between IDH1 and IDH2, the tumor metabolism may differ between IDH1- and IDH2-mutated gliomas. To date there is no report comparing the impact of an IDH1 *vs.* IDH2 mutation directly in patients. Here we report an *in-vivo* ^{1}H MRS analysis focusing on metabolic differences between IDH1- and IDH2-mutated gliomas.

Methods: *Patient enrollment*: Thirty-three patients with IDH-mutated gliomas (median age 36, range 20 - 62) were enrolled in the study. Of the 33 gliomas, 28 were IDH1 mutated and 5 were IDH2 mutated. Patients were scanned at multiple time points (3 - 7 scans; time intervals 1 - 10 months). The data obtained prior to treatment (chemotherapy and/or radiation) only were used for IDH1 *vs*. IDH2 group comparison since metabolic profiles could be altered due to therapy [5]. *MR experimental*: The MR scan protocol included T_2w-FLAIR and single-voxel MRS at 3T. Metabolites were measured using a previously-reported 2HG-optimized PRESS method (TE = 97 ms) [6]. The voxel size was 3 - 8 mL, depending on the tumor size. For large tumor mass, single-voxel MRS data were acquired from 2 - 3 locations within the tumor. Data acquisition parameters included TR = 2 s and NEX = 64 - 512. Following LCModel fitting, metabolite levels were estimated with reference to water at 42 M. One hundred fifty spectra with singlet linewidth < 6 Hz were selected for subsequent analysis for metabolic comparison between IDH1- and IDH2-mutated tumor groups. The group comparison was performed in terms of the correlation and linearity between metabolite concentrations. Two-tailed t-test was conducted for comparison between the groups.

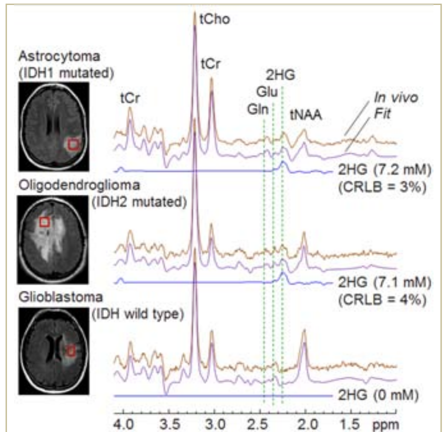

FIG 1. *In vivo* spectra from three glioma patients are shown together with spectral analysis result of 2HG. Dashed lines are drawn at 2.25, 2.35 and 2.45 ppm. The singlet linewidths of the spectra were 4 - 5 Hz.

Results: **Figure 1** shows examples of *in-vivo* detection of 2HG in patients with IDH1- and IDH2-mutated gliomas in comparison to a glioblastoma with IDH wild type. With the use of PRESS TE = 97 ms at 3T, the 2HG signal was clearly discernible at 2.25 ppm in the IDH mutated gliomas while in the glioblastoma with IDH wild type, the spectral region at ~2.25 ppm was essentially null. 2HG in IDH-mutated gliomas was measured with good precision (CRLB of 3-4%). The neighboring resonance (2.35 ppm) of glutamate (Glu) showed small signals in the tumor patients. For the 33 patients with IDH-mutated gliomas, 2HG was detected in all spectra (150 spectra; 118 and 32 spectra from IDH1-mutated (*IDH1m*) and IDH2-mutated (*IDH2m*) glioma groups, respectively). For each IDH group, an 8×8 correlation matrix, which was calculated from the concentration estimates of 8 metabolites from the spectra, was color mapped (**Fig. 2**). The metabolic correlation was somewhat greater in *IDH2m* than in *IDH1m*, the coefficient ranging from –0.48 to 0.73 and from –0.61 to 0.80, respectively. The correlations of 2HG with tCho (total choline), tNAA and Glu were notable. The 2HG level increased with increasing tCho in both groups, and the correlation was higher in *IDH2m* than in *IDH1m* (0.79 *vs*. 0.42) (**Figs. 2**). The slope of the tCho-to-2HG linearity was significantly larger in *IDH2m* than in *IDH1m* (0.51 *vs.* 0.22; $p = 3\times10^{-4}$) (**Fig. 3**). The 2HG level was inversely correlated with tNAA in both groups. The correlation was also stronger in *IDH2m* than in *IDH1m* (–0.61 *vs*. –0.29), but the tNAA-to-2HG slope was not significantly different between the groups (–0.48 *vs*. –0.36; p = 0.5). An inverse correlation of 2HG with respect to Glu was prominent in *IDH2m*, stronger than in *IDH1m* (–0.47 vs. –0.21), but the Glu-to-2HG slope was similar (–0.25 *vs*. –0.15; p = 0.39). For the pairs of metabolites other than 2HG, strong positive correlation was present between Glu and tNAA in both IDH groups (0.7 - 0.8) (**Fig. 2**), with Glu-to-tNAA slopes of 0.4 - 0.5 (**Fig. 4**). The correlations between tCr and tNAA and between Glu and tCr were strong in *IDH2m* (~0.7), while the correlations being moderate in *IDH1m* (0.1 - 0.3). For The IDH group difference in the slope of linearity was significantly different between glutamine (Gln) and tCho and between Glu and tCr (3×10^{-4} and 8×10^{-3}, respectively) (**Fig. 4**).

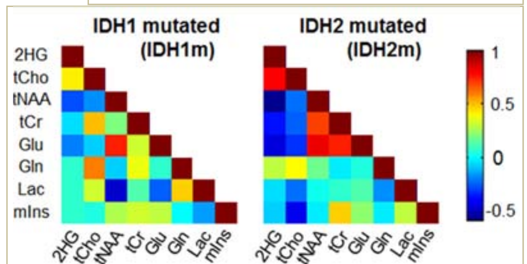

FIG 2. The correlation matrix of 8 metabolites is color mapped for IDH1- and IDH2-mutated glioma groups. For each group, the concentration estimates of 8 metabolites from N data sets were put into an N×8 matrix, from which an 8×8 correlation matrix was calculated using a Matlab command (CORR). The number of data sets, N, was 118 and 32 for *IDH1m* and *IDH2m* groups, respectively.

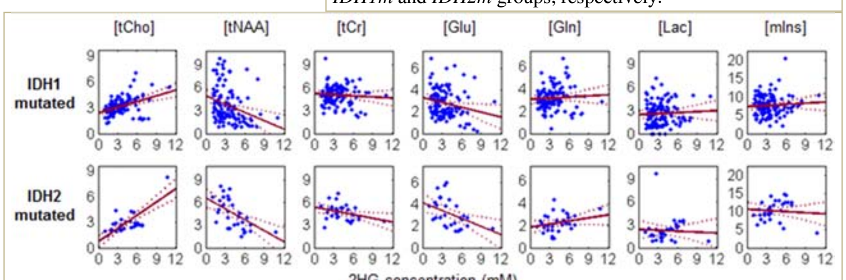

FIG 3. The concentration estimates (mM) of 7 metabolites are plotted versus 2HG concentrations for IDH1-mutated and IDH2-mutated tumor groups. Solid and dotted lines indicate linear fits and 95% confidence intervals of the fits.

Discussion & Conclusion: The present study shows that the 2HG concentration increases with increasing alterations in tCho, tNAA and tCr levels from their normal levels. This observation suggests that a high 2HG level may provide a biomarker of tumor malignancy. The correlation and linearity in several pairs of metabolites were quite different between IDH1- and IDH2-mutated gliomas, suggesting these mutations have different metabolic consequences in the tumor. The trend of stronger inverse correlation of 2HG and Glu in IDH2 than in IDH1 could be related to the fact that IDH2 mutations are confined to mitochondria. Specific inhibitors of the two isoforms are entering clinical trials [7], but enrollment depends on a tissue diagnosis and identification of the mutation. The ability to determine noninvasively which mutation is present would potentially spare the patient a surgical procedure to make the diagnosis. This is of particular importance for those in whom a surgical procedure could have deleterious neurological consequences. Future study will require analysis for patient-specific metabolic difference and potential difference in metabolic response to treatment between IDH1 and IDH2 mutations.

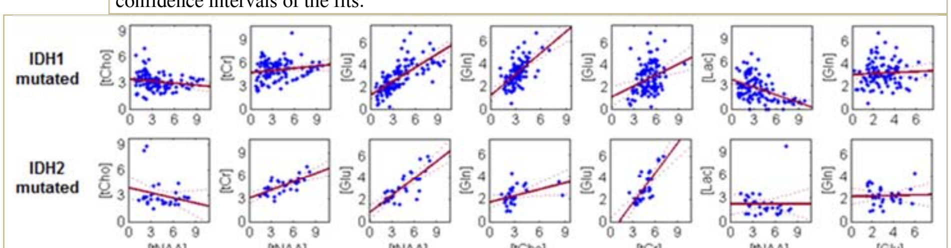

FIG 4. The concentration estimates (mM) and linear regression results are shown, in a similar fashion as in Fig. 3, for seven pairs of metabolites other than 2HG.

References: **1.** Parsons *et al*. Science 2008;321:1807-1812. **2.** Yan *et al*. N Engl J Med 2009;360:765-773. **3.** Dang *et al*. Nature 2009;462:739-744. **4.** Ward *et al*. Cancer Cell 2010;17:225-234. **5.** Choi *et al*. ISMRM 2013. p. 509. **6.** Choi *et al*. Nat Med 2012;18:624-629. **7.** Rohle *et al*. Science 2013;340:626-630.

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