

Metabolic Differences between Oligodendroglial Brain Tumors with and without 1p19q Deletion

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Introduction: The loss of chromosomal heterozygosity of the 1p and 19q arms has been linked to increased sensitivity to chemotherapy and is the strongest prognostic indicator for oligodendroglial tumors irrespective of treatment^{1,2}. The biological basis of the disparity in prognosis with respect to 1p19q is not known. Using High Resolution Magic Angle Spinning (HRMAS) we examined the spectroscopic profiles of metabolites within Grades 2 and 3 oligodendroglioma (OD) and oligoastrocytoma (OA) tumors with and without the deletion to determine if a co-deletion in 1p and 19q has an effect on metabolism in tumors.

Methods: We performed pre-operative MRI/MRSI studies on 29 newly-diagnosed patients with non-enhancing brain lesions that were subsequently diagnosed as OD (18 Grade 2, 1 Grade 3) or OA (9 Grade 2, 1 Grade 3). Biopsy locations were selected from areas containing the highest choline to NAA ratio from the patients' preoperative MRI multivoxel MRS sequence. During resection the surgeon was able to view the target locations in real time, displayed on the BrainLab navigation screen, and extract biopsies from the selected areas. Biopsies were frozen in liquid nitrogen and later analyzed using HRMAS in a 500MHz Varian spectrometer equipped with a GHX nanoprobe. The samples were spun at 2250Hz at 1°C and spectra acquired using a 1D presaturation

sequence. Concentrations were determined using ERETIC and in house HRQUEST software having units of mmol/L⁵. Eleven metabolites, Alanine (Ala), free Choline (Cho), total Creatine (tCre), Glycerophosphocholine (GPC), Glutathione (GSH), Glutamine (Gln), Glutamate (Glu), N-Acetyl Aspartate (NAA), Phosphocholine (PC), Taurine (Tau) and Myo-Inositol (mI) were interrogated. Statistical analysis of the data was done by first performing a Wilcoxon model to determine differences between the groups and then a more stringent linear mixed model, with "patient" as the random effect was used to account for multiple biopsies originating from a single patient. Significance was defined as p=0.05.

Results: Forty-eight biopsies were collected, 30 biopsies contained the 1p19q deletion and 18 did not.

OA tumors made up 23% of 1p19q-deleted tumors and 55% of the tumors that had intact 1p19q, OD represent 77% of 1p19q deleted tumors and 45% of tumors with intact 1p19q. Using the Wilcoxon model, we found significant differences in tCre (p=0.001), GPC (p=0.007), GSH (p=0.02), Gln (p=0.004) and mI (p=0.01) between the 1p19q-deleted and 1p19q-intact tumors. When controlling for multiple comparisons only tCre (p=0.01) and Gln (p=0.02) remained significant. Since more than 50% of 1p19q intact samples originated from the OA group we also used the mixed model to test for differences between tumor type (OA vs OD) and none were found.

Discussion: The source of the lower levels of Gln and tCre in the 1p19q-deleted tumors is not clear. tCre reflects creatine and phosphocreatine that is often utilized as an alternate energy source for glycolytic tissues such as brain tumors. Glutamine is the metabolic substrate for generating the neurotransmitter, glutamate, in the glutamate-glutamine cycle. Such strong differences in tCre and Gln between tumors with and without the 1p19q deletion indicates that 1p19q may be involved with cell metabolism. Further studies are needed to understand the role 1p19q chromosomal status plays in metabolism and response to chemotherapy.

References: 1) C. Hartmann et al *Cancer Research*, 2009, Volume 171, I, 25-49 2) Smith JS et al *J Clin Oncol* 2000; 18: 636-45 3) McKnight, Ph.D. et al *JNS*; 2007: 660-666 4) Yevgeny et al *J. Nutr.*, 2000; 130: 1026 5) Ratiney et al *NMR Biomed* 2010; in press

Figure 1: Relative Cre levels in 1p19q deleted (top) and intact (bottom)

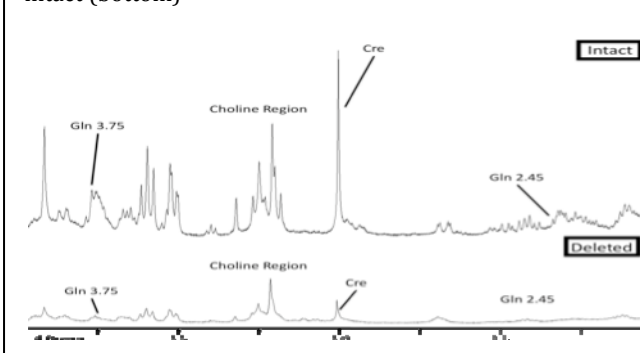


Figure 2: Creatine and Glutamine within tumors with and without 1p and 19q deletion s.

