Molecular subgroups of medulloblastoma identification by MR Spectroscopy

Stefan Bluml[1,2], Ashley Margol[3,4], Ashok Panigrahy[5], Richard Sposto[3,6], Rebekah Kennedy[3], Marvin D Nelson[1], and Shahab Asgharzadeh[3,4]

[1]Children's Hospital Los Angeles/USC, Los Angeles, CA, United States, [2]Rudi Schulte Research Institute, Santa Barbara, CA, United States, [3]Children's Hospital Los Angeles and Saban Research Institute, Los Angeles, CA, United States, [4]Department of Pediatrics, Keck School of Medicine, University of Southern California, CA, United States, [5]Children's Hospital of Pittsburgh, Pittsburgh, PA, United States, [6]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, CA, United States

Introduction: Medulloblastomas are the single most prevalent malignant brain tumor in pediatrics. Recently, analysis of tumor specimen identified four molecular subtypes, with "WNT" and "sonic hedgehog (SHH)" subtypes carrying significantly lower risk for disease dissemination and poor outcome than "Group 3" or "Group 4"[1], albeit age and additional genetic mutations need to be considered as well. In this retrospective study we reviewed medical records of 30 patients to compare the metabolic features, obtained non-invasively by in vivo MR spectroscopy (MRS) prior to tumor resection, with their molecular signatures.

Methods: MR spectra of 30 patients with confirmed medulloblastoma were compared with molecular features obtained by gene expression profiling (12 SHH, 17 Group 3/4, 1 WNT). All spectra were acquired on a GE 1.5T clinical scanner with single voxel PRESS sequence (TE = 35 ms, TR = 1.5s, 128 averages) and processed with fully automated LCModel (version 6.3-1c) software. Twenty-eight individual measures were screened for their ability to discriminate between Group 3/4 and SHH using a Wilcoxon rank-sum test. Those with $p \leq 0.05$ were included in a linear discriminant analysis (LDA) to distinguish Group 3/4 from SHH tumors. Correct classification rates were estimated *via* complete leave-one-out internal cross validation (LOOCV).

Results: Among the metabolites measured by MRS, five (aspartate, creatine, myo-inositol, tau, and lip13a) were significantly different between Group 3/4 and SHH patients and were included in the LDA. The most significant were creatine and myo-inositol (both $p<0.001$) which were both higher in the SHH group (**Fig. 1,left**). Overall, *lower* values of aspartate, creatine, myo-inositol, and tau, and *higher* values of lipids, were associated with SHH tumors. A principal component analysis using the concentration levels of these 5 measures in medulloblastoma tumors further delineated SHH and Group 3/4 tumors, with one WNT sample that could not be clustered with the other tumors (**Fig. 1, right**). As estimated by LOOCV, 26 of 29 (90%) SHH and Group 3/4 tumors were correctly classified by the LDA.

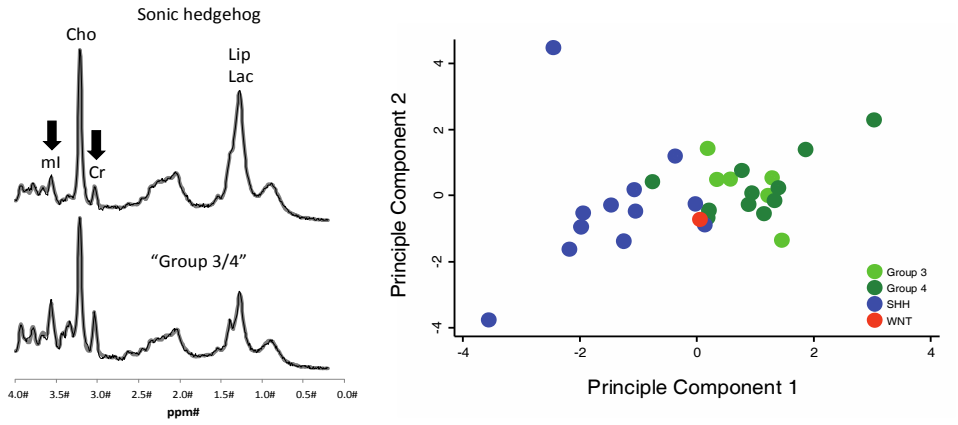

Fig. 1, left: *Typical MR spectra of "Group 3/4" medulloblastoma and Sonic Hedgehog (SHH). "Group 3" and "Group 4" are clinically equivalent and were thus combined. Overall, spectra have a similar appearance with prominent choline (Cho), lipid (Lip) and lactate (Lac) peaks. A detailed analysis, however, shows that SHH tumor could be distinguished from "Group 3/4" tumors by their lower creatine (Cr) and myo-inositol (mI) levels.* ***Right:*** *Shown is the result of a mathematical more involved analysis where metabolic features are combined to generate "Principle Components" that distinguish the different subtypes.*

Discussion: The ability to assign molecular subtypes prior to resection could potentially lead to new treatment strategies. Specifically more conservative treatment approaches with fewer long-term side effects could be considered for a subset of pediatric patients with the SHH (or WNT) subtype.

Acknowledgment: Rudi Schulte Research Institute, Ian's Friends Foundation American Cancer Society, Alex's Lemonade Stand Foundation, NIH T32 CA009659-18.

References: 1. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. Apr 2012;123(4):465-472.