Comparative Metabolic Fingerprinting Employing Hyperpolarized Diethylsuccinate in Two Cancer Models In Vivo.

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Background: Parahydrogen Induced Polarization (PHIP) can offer 50,000 fold increase in MR signal under the right conditions. Diethyl 1-13C 2,3-d2 succinate is generated through the hydrogenation of diethyl 1-13C 2,3-d2 fumarate and hyperpolarization increases the 13C signal by 5000 fold. We have previously employed hyperpolarized diethyl succinate to image and observe real time metabolism in normal mice. Using 13C MRS, metabolism of diethyl succinate in the Tricarboxylic Acid Cycle (TCA cycle) was observed in normal animals 5 s after a 10 μmol tail vein injection [1]. The biodistribution of the compound can be observed using 13C FISP imaging. We have furthered our work by injecting 10-20 μmol of hyperpolarized diethyl succinate via tail vein injection into subcutaneous tumor bearing mice. Hyperpolarized succinate and diethyl succinate are biomedically interesting as the compounds can potentially assess the in vivo activity of succinate dehydrogenase (SDH), the enzyme that was recently tagged as an oncogene due to its crucial role in cell energetics [2] and its role in modulating the Hypoxic Inducing Factor (HIF1α) protein [3].

Purpose: The goal of the research is to apply hyperpolarized diethyl succinate for imaging cancer in two different subcutaneous tumor models in mice and compare their fingerprinting of the downstream metabolites in the TCA cycle in real time in vivo.

Methods: We utilized PHIP to hyperpolarize diethyl 1-13C 2,3-d2 succinate in a home-built polarizer and the hyperpolarized solution in near physiological concentrations (10-20 μmol) is injected via the tail vein of a BALB/c mice bearing a breast (4T1) (N=5) or renal tumor (RENCA) (N=9). A 1H/13C dual resonance volume coil (Doty Scientific, Inc., Columbia, SC) is utilized for 13C hyperpolarized in vivo imaging and CSI spectroscopy. 13C FISP with a flip angle of 60°, FOV 6 or 7 cm, and slice thickness of 15.2 mm was used. 13C CSI (1 ms gauss pulse, 200 ms TR, 8 x 8 or 16 x 16 matrix, FOV ranging from 2.6 cm to 4 cm, slice thickness of 8 to 12 mm). CSI was processed using 3DiCSI software (Columbia University, Qui Zhao). The flux rate of the compound within the tumor was determined using a 4 cm ID solenoid volume coil and a simple pulse and acquire 13C sequence. All 13C imaging and spectroscopy was done on a horizontal bore Bruker Avance 4.7T animal scanner.

Results: A different biodistribution of the diethyl succinate is observed in the two types of tumors. The compound is taken up in the RENCA mice model of cancer while it’s not as specific in 4T1 breast cancer model as revealed in sub-second 13C FISP images. The distribution of the hyperpolarized molecule reveals the regions of tumor heterogeneity in renal tumor like regions of necrosis and metabolically active domains. Real time 13C MRS and 13C CSI of the hyperpolarized metabolites in vivo show different ratios of the metabolites corresponding to the two different tumor types. Measurement of the relative flux-rates of the downstream metabolites as well as the ratios of the metabolites to the hyperpolarized diethyl succinate signal in vivo will be crucial in establishing the dynamics of the TCA cycle in these cancer models as well as their variability. Immuno-histopathological and Western blot correlation are underway to better understand the biochemical basis of the different metabolic fingerprinting as expressed in renal and breast tumors.

Acknowledgements: We thank the following for funding: Tobacco Related Disease Research Program 16KT-0044, NIH/NCI R01 CA 122513, James G. Boswell Fellowship. We thank Dr. Alan Epstein (USC) for help with the animal models.

References: