Probing Tumor Microenvironment Using Diffusion Tensor Spectroscopy and Imaging

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INTRODUCTION: Past studies have established elevated levels of choline (Cho) metabolites as markers of malignancy[1]. However, the mechanisms in the active transport and diffusion of choline across cellular membranes are not fully understood. The goals of this study are to measure the diffusion characteristics of choline in an attempt to understand the characteristics of tumor microenvironment and the transport of metabolites. In particular, we have used diffusion tensor spectroscopy (DTS)[2,3,4] and imaging (DTI) to: 1. measure diffusion of Cho and water in a tumor animal model, and 2. compare our finding to pathology maps. We present our preliminary results.

MATERIALS AND METHODS: Approximately 2-3x10^6 R3327 malignant human prostate cell lines were harvested and injected subcutaneously into the thigh of three male Copenhagen rats. The rats were imaged 16 and 23 days after injection on a 1.5T GE MR scanner using a homemade four-turn radiofrequency solenoid coil. The rats were subsequently sacrificed and pathology maps of the tumor were obtained. The DTS sequence consisted of a modified PRESS sequence with diffusion weighted gradients inserted before the first and second refocusing pulses. Aquisition parameters were: TR/TE = 1264/144 ms, 16 NEX, 512 repetitions, scan duration/direction = 10:57 min., single-voxel PRESS excitation region ~ 1-2 cm^3, 2 b-values (0 and 1761.4 s/mm^2) along 6 directions (x,y,z): (1,0,0), (0,1,0), (0,0,1), (0.707,0.707,0), (0.707,0, 0.707), and (0, 0.707, 0.707) were obtained. The control group consists of the adjacent thigh muscle of each rat. T2w imaging was used to localize the tumor. In addition, DTI images along six directions were obtained to map the spatial distribution of water diffusion. A similar study was performed to evaluate gradient linearity and sensitivity of the sequence on a BRAINO phantom containing 12.5 mM choline.

RESULTS AND DISCUSSION: Fig 1 shows spectra with no diffusion gradient (b=0) and with diffusion weighing along 6 directions. The ADC trace/3 and FA for rat #2 of Cho are listed below. Unlike water, the Cho ADC and FA values remain stable as the tumor grows and becomes necrotic. Low ADC's of metabolites such as Cho are typically attributed to the viscosity of the cytoplasmic microenvironment[2]. We hypothesize the greater increase in water ADC values (and simultaneous decrease in FA) as compared to Cho are due to the decrease in cell density brought about by necrosis. This results in an increase in water mobility. Since Cho is primarily confined to the intracellular space, its diffusion values are not significantly affected. Fig 2a and 2b are T2w images obtained 16 and 23 days after injection. The boxes show the location of the PRESS selective excitation. The tumor has clearly become necrotic. Fig 2c and 2d are the trace/2 ADC map and FA, respectively, obtained from DTI images. Recently, Pfeuffer *et al.*[2] presented diffusion measurements of {^{1}H-^{13}C}-lactate and {^{1}H-^{13}C}-alanine. Their study highlights the importance of characterizing diffusion properties of metabolites in a tumor model. Our study presents preliminary results of ongoing investigation, demonstrating feasibility of DTS and DTI as a potential probing tool. Monitoring tumor microenvironment can have important implications in terms of efficacy of drug treatment delivery.

Days	ADC (H_20) x10^{-3} [mm^2/s]	ADC (Cho) x10^{-3} [mm^2/s]	FA (H_20)	FA (Cho)
16	0.467	0.367	0.958	0.954
23	0.674	0.384	0.856	0.949

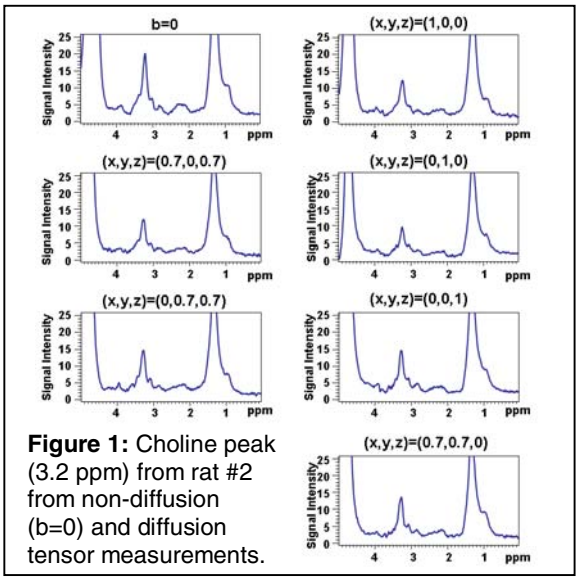

Figure 1: Choline peak (3.2 ppm) from rat #2 from non-diffusion (b=0) and diffusion tensor measurements.

References:[1] Aboagye E *et al.* Cancer Res 1999; 59:80. [2] Pfeuffer, J. *et al* J Magn Reson. 2005 Nov;177(1):129-38. [3] Hakumaki, JM. *et al.* Cancer Res 1998; 58:3791-3799. [4] Posse *et al.* Radiology 1993; 188:719-725.

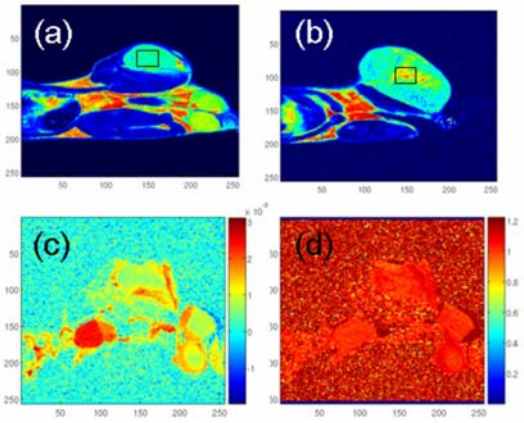

Figure 2: T2w images(a) 16 days, and (b) 23 days after injection. (c) Trace/3 ADC, and (d) Fractional anisotropy (FA) map.