Detection of Radiation Response of Prostate Cancer in TRAMP with Hyperpolarized ^{13}C MRSI

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Introduction

The ^{13}C magnetic resonance spectroscopic imaging (MRSI) of hyperpolarized [1–^{13}C]pyruvate (Pyr) has been viewed as a promising molecular imaging technique in oncology[1,2]. For instance, the transient changes of [1–^{13}C]Pyr and its metabolic product [1–^{13}C]lactate (Lac) were correlated with the diagnosis and tumor progression in a preclinical prostate cancer model[2]. In fact, the first clinical trial for evaluating the clinical use of this methodology targeting prostate cancer is ongoing[3]. Ionizing radiation is a commonly used therapeutic intervention for localized prostate cancer; however, the response of prostate cancer to radiation is patient specific and may take months to be detected by conventional imaging techniques. Here we investigate whether the tumor response to radiation in transgenic mouse model of prostatic adenocarcinoma (TRAMP) can be detected with hyperpolarized [1–^{13}C]Pyr MRSI.

Method

The TRAMP mouse model used in this study develops an autochthonous tumor in the prostate at the onset of puberty. The progression of tumors was volumetrically monitored by T_2 weighted ^{1}H MRI (FSE sequence with TE = 26 ms, TR = 4 s, 0.34-0.5 mm slice thickness, 192×320 matrix in coronal FOV of 3×5 cm^2) at 7 T. All mice (n = 8) were imaged with hyperpolarized ^{13}C MRSI in two groups, treated and untreated. The treated group (n = 5) received localized x-ray radiation (200 kV, 20 mA, 1.21 cGy/s) doses up to 10 Gy in two daily fractions to the tumor 4 days before ^{13}C MRSI. The treated group was compared to the untreated group (n = 3) that was imaged with hyperpolarized ^{13}C MRSI when the tumor reached a baseline size of ~1200 mm^3.

Pyr was polarized using dynamic nuclear polarization (DNP) technique at 1.4 K and 3.3 T with the irradiation of 94 GHz microwaves. The polarized substrate ([1–^{13}C]pyruvic acid, trityl radicals, and Gd^{2+}) was quickly dissolved in Tris/EDTA and NaOH at 37 °C, yielding 80 mM Pyr solution at pH 7.4 that injected intravenously into each anesthetized mouse via tail vein. The ^{13}C spectra were acquired at 3 T repeatedly with a volumetric acquisition encompassing the tumor (2.7×2.7×3 mm^3 nominal resolution) following a bolus injection (300 µL of 80 mM Pyr over ~20 s) of hyperpolarized Pyr. To optimize the signal-to-noise ratio (SNR) of metabolites, a spiral-3D time-resolved spectroscopic pulse sequence[4] was utilized with multiband excitation[5] (Pyr/Lac flip angle of 2°/8°) scheme.

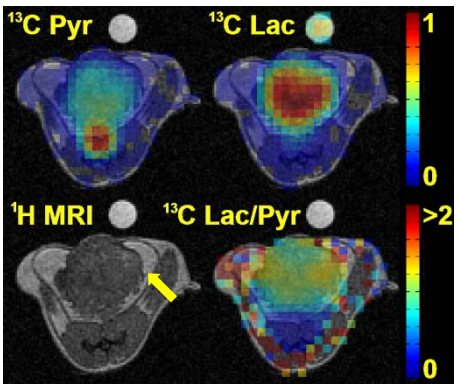

Figure 1: Representative data of a treated mouse (tumor size 1100 mm^3). Pyr and Lac are individually normalized. Tumor is marked with an arrow on the ^{1}H MRI.

The MRSI spectra were reconstructed as described in ref 4. The time-resolved metabolic maps of ^{13}C-labeled Pyr and Lac were obtained by peak integration. The average intensities (proportional to concentration) of metabolites were measured in the regions of interest (ROI) in the tumor slices selected using proton MRI anatomical references. Metabolic activity in treated versus untreated groups was quantified as the time-averaged Lac/Pyr ratio ($= \sum_t \mathrm{Lac}(t)/\sum_t \mathrm{Pyr}(t)$). Wilcoxon rank sum test for unpaired samples was used to assess the statistical significance.

Results

Based on MRI volumetry, the TRAMP tumors grew with tumor doubling time of 6±2 days and rapidly shrank in response to localized irradiatiosn with 50%-size reduction time of 4±1 days. Upon the Pyr injection, three metabolites, Pyr and Lac with high SNR and alanine with low SNR, were observed in the tumor (Figure 1). There was no apparent correlation between the Lac/Pyr ratios and the tumor sizes in both groups (Figure 2). The treated group displayed lower Lac/Pyr ratios than the untreated group (P = 0.036).

Discussion and Conclusions

Our resolution allowed visualizing higher concentration of metabolites in the dorsal aspect of the tumor due to higher vascularization than the ventral portion. The observation of the Lac/Pyr ratio being uncorrelated with tumor size appears to be in agreement with previous work[2], which indicated that this ratio better correlates with histological grade than the tumor size. This permits the tumor size to be ignored in comparing the two groups. Nevertheless, the Lac/Pyr ratio was markedly different between the groups with similar tumor sizes around 1200 mm^3. The statistically significant difference (P < 0.05) of the Lac/Pyr ratio between the treated and untreated groups may indicate the metabolic response to the radiation treatment. Our preliminary data, therefore, suggest the feasibility of using ^{13}C MRSI for detecting therapeutic response of prostate cancer to radiation in TRAMP mice. Further investigations are underway to acquire additional data for assessing the best metabolic metrics correlating with radiation response in prostate cancer.

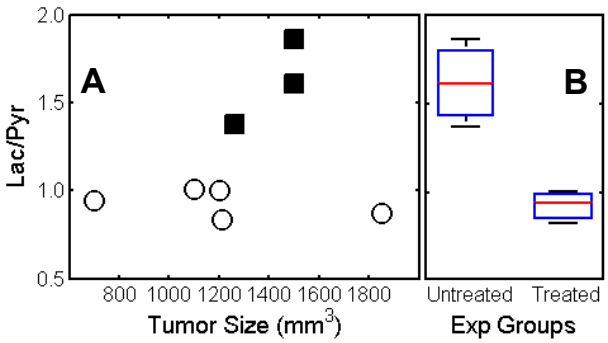

Figure 2: (A) Lac/Pyr ratio versus tumor size of treated (open circles) and untreated (filled boxes) mice. (B) Box plot, showing the separation of Lac/Pyr ratios between the experimental groups (P = 0.036).

References: [1] Golman K *et al.* Cancer Res **66**, 10855 (2006). [2] Albers MJ *et al.* Cancer Res **68**, 8697 (2008) [3] http://clinicaltrials.gov/ct2/show/NCT01229618 [4] Mayer D *et al.*, Magn Reson Med **62**, 557(2009). [5] Larson P *et al.* J Magn Reson **194**, 121 (2008).

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