Serial Hyperpolarized ^{13}C 3D-MRSI Following Therapy in a Mouse Model of Prostate Cancer

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Introduction: The development of retaining highly polarized spins in solution via DNP has enabled the study of real time metabolism *in vivo* using pre-polarized ^{13}C label substrates (1). Using hyperpolarized ^{13}C MRS, tumor cell response to chemotherapy has been detected ex vivo (2). Also, a prior study detected significant changes with disease progression in a transgenic mouse prostate cancer model using hyperpolarized ^{13}C 3D-MRSI (3). The goal of this study was to use hyperpolarized ^{13}C 3D-MRSI to serially study prostate cancer response to androgen deprivation therapy in this murine model.

Methods: Animals: All animal experiments followed institution approved protocol. Eight TRAMP mice at various disease stages were included in the study. ^{1}H MR imaging and hyperpolarized ^{13}C MRSI were performed on each animal prior to androgen deprivation therapy as well as at three, five, seven days or different combinations of those durations following therapy.

Hardware and pulse sequence: All studies were performed using GE 3T scanner (GE Healthcare, Waukesha, WI) using a custom build dual-tuned quadrature ^{13}C/^{1}H mouse coil. T2-weighted FSE pulse sequence was used (TE/TR = 102ms/5s) to acquire ^{1}H MR images in all three planes. A double spin-echo pulse sequence with small tip-angle excitation, adiabatic refocusing and flyback echo-planar readout trajectory (4) was used to acquire *in vivo* 3D hyperpolarized ^{13}C MRSI data in 14s from TRansgenic Adenocarcinoma Mouse of Prostate (TRAMP) mice (5) after the animals were injected with hyperpolarized $^{13}C_1$ pyruvate. 3D MRSI data were acquired with an 8x8x16 matrix and a 40mmx40mmx86.4mm FOV (0.135cc resolution).

Results and Discussion: Representative images and hyperpolarized ^{13}C MRSI data from a TRAMP mouse before and after hormone deprivation therapy are shown in Figure 1. In the region of prostate cancer, elevated ^{13}C lactate was observed prior to therapy. In mice demonstrating a reduction in tumor volume, also demonstrated a reduction in ^{13}C lactate after therapy (Figure 1 and 2A). Higher lac/pyr ratios at the baseline studies were observed in non-responding cancers (N=4, tumor volume increased) and lac/pyr did not reduce post therapy (Figure 2B). For the mice with lower lac/pyr ratio at baseline studies (N=4), reduction of lactate was observed in the post-therapy studies and survival times were longer, an indication of androgen sensitive disease.

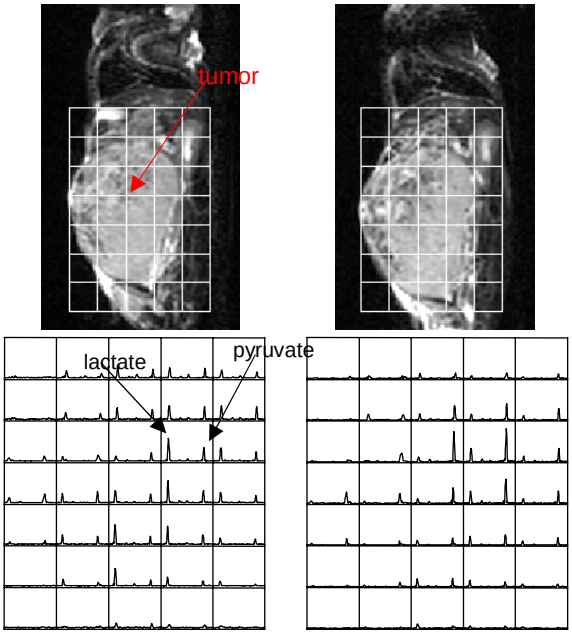

Figure 1. Sagittal FSE images and the corresponding hyperpolarized ^{13}C 3D MRSI data from a TRAMP mouse before (left) and 5 days following complete hormone deprivation therapy (right). High ^{13}C lactate (lac/pyr ratio = 1.8) was observed in the primary tumor pre-therapy, and it was greatly reduced (lac/pyr = 0.7) after the animal responded to hormone therapy.

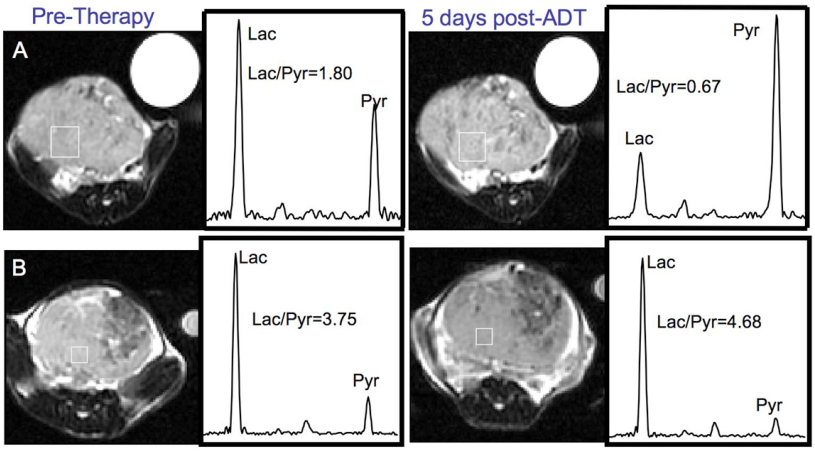

Figure 2. Magnitude of lactate signals in pre-treated TRAMP tumors predicted response to anti-androgen therapy as measured by continued tumor growth. The TRAMP tumor shown in A, has lower levels of pre-treatment hyperpolarized lactate than the tumor shown in B. At 5 days after therapy there was a reduction in hyperpolarized lactate and tumor volume In the study shown in A, while there was an increase in hyperpolarized lactate tumor volume in TRAMP B.

Conclusions: This study demonstrated the feasibility of using pre-polarized ^{13}C MRSI to serially monitor metabolic changes in a preclinical prostate cancer model following therapy *in vivo*. In this preliminary study, lower tumor Lac/Pyr ratios at baseline were associated with a reduction in Lac/Pyr after therapy and a positive response to therapy as measured by tumor growth and/or survival. In agreement with the prior disease progression study (3), pre-treatment lactate levels appeared to be indicative of less advanced, more androgen sensitive cancers, and more studies are ongoing to further investigate this possible correlation.

References:

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