Monitoring Temporally Selective LDH-A Gene Deletion in Prostate Cancer Using Hyperpolarized Frequency Specific 13C-MRI

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Introduction:

Increased lactate dehydrogenase, isoform A (LDH-A) production has been associated with a wide variety of malignancies. LDH-A expression and activity are known to be increased in prostate cancer [1]. Recently, mice with transgenic constructs have been generated in the TRAMP model for prostate cancer, in which the LDH-A gene can be temporally knocked down. We have initiated proof-of-concept studies in these transgenic mice, using hyperpolarized (HP) ^{13}C frequency specific MRI, after administering $^{13}C_1$-pyruvate to monitor changes in pyruvate metabolism in prostate tumors across time, before and after knock-down of the LDH-A gene.

Methods:

LDH-A-TRAMP were generated in which Cre and Lox-P elements were introduced such that the LDH-A gene could be selectively deleted via administration of a short course of tamoxifen. Adult male LDH-A-TRAMP mice were allowed to develop spontaneous tumors of the prostate, with periodic assessment by T2-weighted proton imaging at 14.1T. On identification of an appropriate tumor lesion, mice underwent high-resolution T2 weighted (T2W) imaging in combination with Diffusion Weighted Imaging (DWI) and 3D-GRASE ^{13}C imaging, following injection of hyperpolarized $^{13}C_1$-pyruvate, as part of a baseline study. After this baseline study, mice were injected with 80µl of tamoxifen in corn oil every day for 4-5 days. A follow up T2/DWI/3D-GRASE study was then conducted several days following completion of the tamoxifen treatment. Three such mice have been studied to date. The experiments were done using a vertical, 14.1T (Agilent) 600WB micro-imaging system equipped with 55mm 1000mT/m gradients and 40mm diameter proton and carbon RF coils. The mice were placed in a temperature controlled animal holder and anesthetized using a mixture of isoflurane/oxygen. An animal monitoring system (SA Instruments) was used to monitor respiration and trigger the scanner during all protocols. The proton coil was used for shimming and anatomical imaging and then the carbon coil was used for ^{13}C imaging. $^{13}C_1$-pyruvate was polarized using an Oxford Hypersense™ DNP instrument and 300µl of the resulting dissolution mixture containing 80mM pyruvate was administered via a tail vein catheter. The GRASE sequence with chemical selective pulses was used to acquire 3D images of lactate (Lac) and pyruvate (Pyr) in 154ms/frequency [2]. The multi-slice, T2W images were used to define the tumor region of interest (ROI) and determine the volume, ADC and Lac/Pyr ratios.

Results:

Three LDH-A-TRAMP mice have been studied to date, with varying initial tumor sizes and varying times of follow up. Data from the animal with the most complete follow up demonstrated a well defined, clearly circumscribed and homogenous tumor by T2 proton imaging, which grew slightly larger over one week after gene knockdown. ADC values also decreased by 30% in the tumor over this period [7.56 (±0.88)x10^{-4} to 5.24 (±0.86)x10^{-4} mm^2 s^{-1}]. No appreciable ADC change was seen in adjacent normal muscle tissue in this animal. Tumor volume increased 13% over this period (from 0.85 to 0.96 cc). In contrast, a reduction of the HP ^{13}C Lac/Pyr ratio was observed in the tumor region (Figure 1), and a statistically significant change of 24.7±12.1% was measured. In two mice with a longer period of follow up (i.e, 2 weeks), tumor volume decreased more substantially - 37 and 85%, respectively.

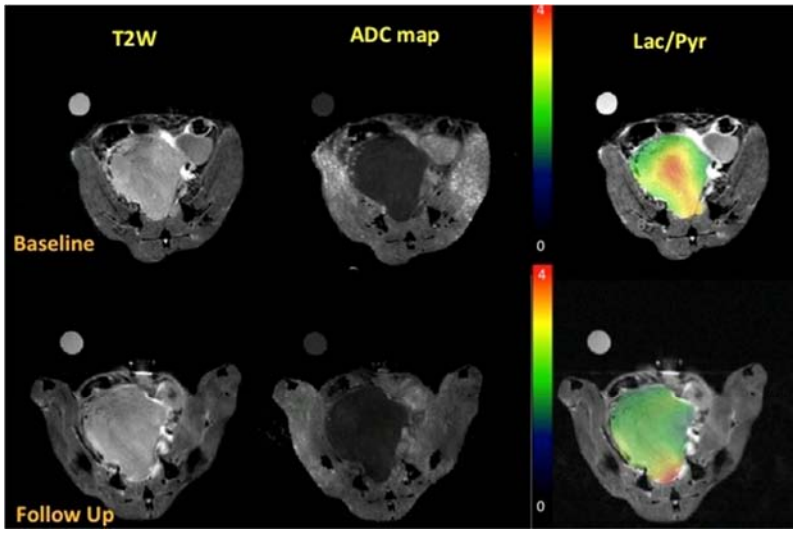

Figure 1. Images from the baseline study (top) and 7 days following gene deletion (bottom) on an LDH-A knockdown mouse with a large prostate tumor. ^{13}C images were obtained 42s after injecting 300µl hyperpolarized $^{13}C_1$ pyruvate into the mouse and the lactate to pyruvate ratios calculated. The T2 weighted spin echo images were used to define the ROI of the tumor.

Conclusions:

These preliminary studies indicate that changes in LDH-A expression and activity can be detected by HP frequency specific ^{13}C MRI (early response in HP Lac/Pyr ratio) in prostate tumors in vivo, following genetic deletion, well before changes in more classical morphometric or diffusion-based parameters occur. At about 1 week following initiation of LDH-A gene knockdown, both tumor size and ADC showed changes consistent with continued progression, while a significant decline in HP ^{13}C Lac/Pyr ratio was already evident. Previous studies on TRAMP tumor models have shown an increase in the HP ^{13}C Lac/Pyr ratio with tumor progression [3]. Longer follow up in the few LDH-A-TRAMP studied to date suggested eventual decrease in morphometric measures and ADC with time. Further studies are underway with this new transgenic model to confirm these findings.

References:

1. Goldman RD , *et. al* , Cancer Res 24:389-399 (1964). 2. Sukumar S, *et. al.* 19th Annual ISMRM Meeting (2011) E-poster #4388. 3. Albers MJ, *et. al.* Cancer Res 68:8607-8615 (2008).

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