Monitoring Prostate Cancer Progression in A Transgenic Murine Model Using 3T Hyperpolarized ^{13}C MRSI

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Introduction

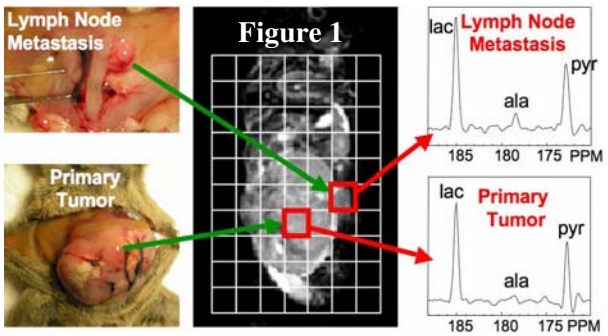
Hyperpolarized ^{13}C-1 pyruvate via dynamic nuclear polarization (DNP) has allowed the acquisition of high spatial and temporal resolution ^{13}C MRSI data when injected into rats (1) and transgenic murine models of prostate cancer (2). The Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model is particularly useful for studying the metabolic changes that occur with prostate cancer evolution and progression since TRAMP mice demonstrate histopathologic disease progression (3) and associated metabolic changes (4) that mimic human disease. While both ^{1}H and ^{13}C MRSI take advantage of the unique metabolism of healthy prostate epithelial cells and changes in cellular bioenergetics that occur with prostate cancer evolution and progression (5), hyperpolarized ^{13}C MRSI potentially offers several exciting advantages. These include a larger chemical shift range resolving more metabolic intermediates, a reduction in background signals from normal prostate metabolism that can mask the presence of prostate cancer, a dramatically shorter acquisition time for spectroscopic data, and the ability to monitor metabolic kinetics. The goal of this study was to quantify the changes in hyperpolarized ^{13}C-1 pyruvate metabolism that occur with prostate cancer progression in TRAMP mice.

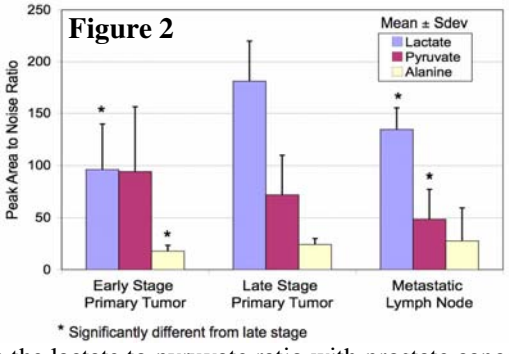
Methods

All studies were approved by the UCSF Animal Care Committee. Jugular vein catheters were placed in the TRAMP mice and mice were anesthetized with 1-1.5% isoflurane and maintained at 37ºC. MRI/MRSI studies were performed on a GE 3T scanner using a custom built dual-tuned proton-carbon T/R coil. ^{1}H MR images were acquired in sagittal, axial and coronal views using a T_2-weighted fast spin echo sequence with a 6 cm FOV, 128 x 128 matrix, 1.5 mm slice thickness with no inter-slice spacing, and TE=102 ms/TR=4 s. A double spin-echo pulse sequence with a small flip-angle excitation, adiabatic refocusing, and a flyback echo-planar readout trajectory was used to acquire *in vivo* 3D hyperpolarized ^{13}C MRSI data 12 seconds after 300-350 µL of hyperpolarized (~20%) ^{13}C pyruvate was injected into the jugular veins of six TRAMP mice (1 normal, 3 early and 3 late stage) (1-2). 3D MRSI data were acquired from the entire mouse using a TE/TR of 140/215, a 8x8x16 matrix, a 40x40x86.4mm FOV (0.135cc resolution), and an acquisition time of 14 seconds. The MRI and ^{13}C MRSI data were processed and aligned using custom software and correlated with pathology identified at dissection. The peak area to spectral noise ratios for lactate, alanine, and pyruvate were determined for voxels within regions of cancer. Metabolic changes between early and late stage primary disease and late stage and metastatic disease were statistically compared using a student's t-test with a Holm correction for multiple comparisons, with $p < 0.01$ considered significant.

Results

Figure 1 shows a pathologically identified large primary tumor and a region of lymph node metastases within a TRAMP mouse with advanced prostate cancer (left side). The regions of primary and metastatic cancer can be clearly seen on the corresponding T_2 weighted coronal image (center) and representative hyperpolarized ^{13}C spectra from the 3D ^{13}C MRSI data set (white grid) taken from within the primary tumor (bottom right) and lymph node metastasis (top right). Figure 2 shows a bar plot summarizing the metabolic changes between early stage, late stage, and lymph node metastases. Both lactate and alanine were significantly higher in the late as compared to early stage tumors. Also the lactate to pyruvate ratios in late stage tumors were significantly higher than early stage (3.2 vs. 1.2), and early stage tumor ratios were higher than normal (1.2 vs. 0.5). Although lactate and pyruvate were lower in metastatic lymph nodes as compared to late stage tumors, the lactate to pyruvate ratios were similar (3.2 vs. 3.5).





Discussion and Conclusions

In summary, during prostate cancer progression from early to late stage primary disease there was a significant increase in pyruvate metabolism to lactate and alanine. In going from late stage primary disease to metastases, the conversion of pyruvate to lactate was similar based on the lactate to pyruvate ratio. Interestingly, there was an overall reduction of lactate and pyruvate levels in metastatic disease, which could be due to an overall reduction in vascularity. These findings suggest that there are significant increases in lactate and alanine production and an increase in the lactate to pyruvate ratio with prostate cancer progression. More studies are necessary to confirm these findings.

References

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