Comparative study of tumor lactate and tumor vasculature in aggressive and indolent prostate cancer animal models by 2D-MR Spectroscopic Imaging and DCE-MRI

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Introduction

The physiologic, biochemical, and growth properties of tumors are heterogeneous, both spatially and with growth. The aim of this study is to compare lactate concentration in an aggressive (R3327-AT) and indolent Dunning H (DH) prostate tumor to determine the potential of lactate as a marker of tumor aggressiveness. High levels of lactate have been reported in head and neck and cervical cancer, have been associated with a high risk of metastasis, and are considered a poor prognosis marker for survival (1,2).

Methods

Animal studies were conducted in compliance with protocols approved by the animal care protocols in MSKCC. R3327-AT cells were subcutaneously implanted in the thigh region of 12 Copenhagen rats. Dunning H tumors were grown by implanting tissue chunks subcutaneously in the thigh region of 6 Fischer-Copenhagen rats. MR lactate determination and perfusion studies were conducted at five tumor sizes (I: 200-400 mm^3, II: 700-810 mm^3, III: 1400-1600 mm^3, IV: 1850-2200 mm^3 and V: 2450- 2850 mm^3) for R3327-AT and (I: 300-420 mm^3, II: 650-800 mm^3, III: 1364-1645 mm^3, IV: 1821-2236 mm^3 and V: 2425- 2858 mm^3) for DH tumors. Rats were anesthetized with Isoflurane (1.0 to 2.5 %) combined with air during catheterization and MR imaging experiments. MRS and DCE-MRI experiments were performed on a Bruker 4.7 T, 40 cm bore animal scanner. A 2 turn volume coil with a 25 mm diameter was used. Frequency selective 15 ms single-lobe Sinc pulses were employed for Sel-MQC editing (4). The ZQ →DQ coherence transfer pathway was selected in Sel-MQC experiments using a phase cycling gradient scheme with g1:g2:g3 = 0:-1:2 with duration $\delta_1 = \delta_2 = 2$ ms, $\delta_3 = 4$ ms, and an amplitude of 24 G/cm. 512 data points were collected with 8 averages, TR=2 s and spectral width of 2500Hz. A matrix size of 16×16, FOV=40 mm (2.5 x 2.5 mm in plane resolution) was used. 2D CSI lactate maps were obtained from a 5 mm slice in the tumor region which was coregistered with a 5 mm thick T2-weighted image. Quantitation of tumor lactate is done by comparing its signal intensity with standard lactate solution by using substitution method (3). Dynamic contrast enhanced (DCE) MR images (3 sagittal slices, 2 mm thickness; 0.2 mm slice spacing, 12 sec temporal resolution, pulse sequence Gradient Echo Fast Imaging (GEFI), TR/TE-50ms/3ms; 128 X 128 matrix, 288 time points, NEX=2), were obtained after injection of Gd-DPTA (0.2 mM/Kg; Magnevist, Berlex Laboratories)) intravenously (2 minutes after start of the scan)). DCE-MRI data were analyzed to evaluate the rate constant "k_{ep}", Ak_{ep} (based on a two-compartment model proposed by Hoffman et al (5)) and the slope of signal change (change in signal/time).

Results and Discussion

Fig 1 (A-D) shows a series of representative lactate 2D-CSI spectra (sagittal slice) from the same R3327-AT tumor, co-registered with the corresponding T2-weighted MR image. Lactate was not detected in tumors less than 350 mm^3. Starting at tumor volumes of 700mm^3, increased lactate was seen with tumor size (p =0.01 comparing to tumors ~2200mm3) until tumors exceeded approximately 2500 mm^3 when a decrease in concentration of lactate were noted – this may be due to necrosis and is being correlated with histopathology data. Figure 2 shows a graph of lactate vs. tumor volume (N=12 rats). In contrast, lactate was not detected in DH tumors in the volume range 300-2858 mm^3 (Data not shown). To estimate lactate heterogeneity in the Dunning R3327 tumors, we measured the average standard error of the mean (SEM) of the lactate concentration/voxel for each tumor and then calculated the mean SEM (Fig. 3). Tumor lactate heterogeneity in the R3327-AT increased with tumor size (p=0.019 comparing cohorts of ~ 750 mm3 vs. 2000mm3) but a decrease in lactate heterogeneity was seen as the tumors grew to ~ 2600mm3. The average tumor perfusion parameters Ak_{ep} and slope decreased with tumor growth in R3327-AT (Ak_{ep}: 1.01 to 0.44 min^{-1}, Slope: 71 to 38) and in the DH (Ak_{ep}: 1.03 to 0.39 min^{-1}, Slope: 82 to 37) tumor models.

Conclusions

We have demonstrated differences in lactate between a fast and slow growing prostate tumor model, suggesting the possibility of using lactate as a biomarker for high grade prostate cancers. Non-invasive detection of lactate is feasible by magnetic resonance which could a very valuable tool for staging newly diagnosed prostate cancer patients and deciding whether more aggressive treatment is necessary. In addition, there is increased spatial heterogeneity of lactate as the tumor size increases which may reflect changes in tumor physiology that occur with tumor growth related to resistance, growth rate etc. Correlation of the above data with both histopathology (pimonidazole and hematoxylin and Eosin) and DCE-MRI data are ongoing .

Fig. 1

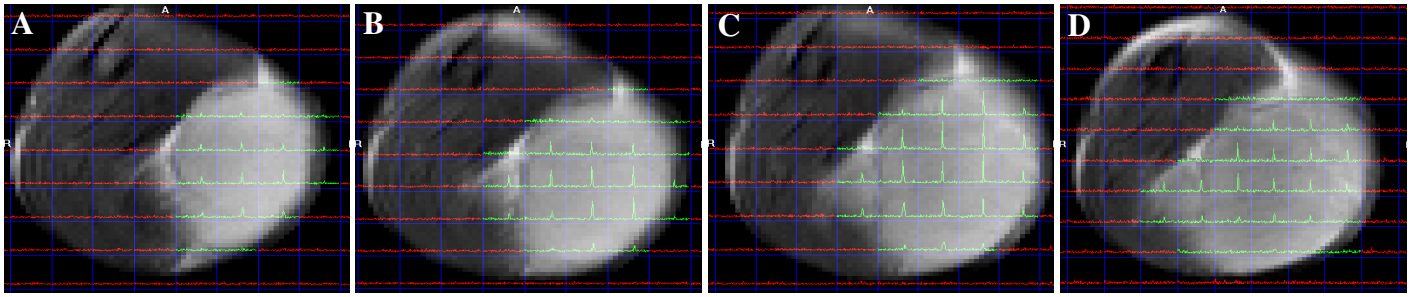

Fig. 2

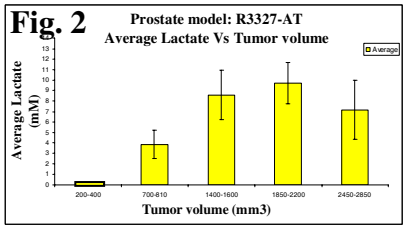

Fig. 3

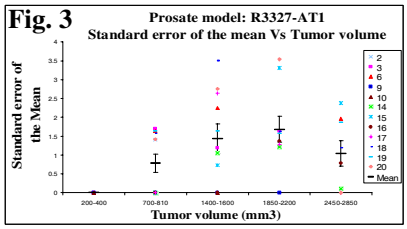

Figure legends:
Fig. 1 Representative lactate 2D-CSI spectra (sagittal slice) of R3327-AT prostate tumor model
Fig. 2 Bar graph of average tumor lactate (mM) vs tumor volume
Fig.3 Tumor heterogeneity graph of SEM vs Tumor volume

Acknowledgments

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Reference

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