Longitudinal Lactate 2D-MR Spectroscopic Imaging and DCE-MRI Studies in Prostate Tumors to Assess Tumor Hypoxia and Vasculature

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Introduction

Lactate is an important metabolite which reflects elevated tumor glycolysis, probable poor tissue perfusion and hypoxia, all of which are related to the malignant transformation of tumor. Lactate may be a marker for tumor diagnosis, increased risk of metastasis, and poor patient survival. A decrease in steady-state tumor lactate levels may relate to tumor response to radiation and chemotherapy (1), and may be a potential prognostic marker. This information may serve to assist in deciding appropriate treatment and also in monitoring normalizing the tumor vasculature using therapies targeting the tumor vascular system and vascular endothelial growth factor (VEGF). The aim of this study is to examine the lactate distribution within the tumor, at various stages of tumor growth, which reflects the tumor heterogeneity using the SelMQC (2) technique and to correlate with tumor perfusion parameters using DCE-MRI studies.

Methods

Animal studies were conducted in compliance with protocols approved by the animal care protocols in Memorial Sloan-Kettering Cancer Center (MSKCC). Rat model prostate tumors (R-3327-AT) were implanted subcutaneously in the thigh region in 4 Copenhagen rats. MR lactate determination and perfusion studies were conducted at four tumor sizes (I: 300-600mm^3, II: 700-1000 mm^3, III: 1200-1600 mm^3 and IV: 1700-2000 mm^3). The experiments in this longitudinal study were performed on a Bruker 4.7 T, 40-cm-bore animal scanner. The maximum gradient strength is 40 G/cm. A home-made 2 turn volume coil with 25 mm diameter was used as transmit-receive RF coil. Frequency selective 15 ms single-lobe Sinc pulses were employed for Sel-MQC editing. The ZQ →DQ coherence transfer pathway was selected in Sel-MQC experiments using a phase cycling gradient combination of g_1:g_2:g_3 = 0:-1:2 with duration δ_1 = δ_2 = 2 ms, δ_3 = 4 ms, and 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. Prior to 2D CSI, T2-weighted MR image was obtained as a scout image for choosing CSI slice. Following 2D CSI experiment, Gd-DPTA (0.2 mM/Kg) was injected intravenously to obtain dynamic contrast enhanced (DCE) MRI images (3 T1-weighted sagittal MR slices with 2 mm thickness; 0.2 mm spacing; 288 points and 12 sec temporal resolution) using T1-weighted spin-echo sequence (TR/TE=50ms/10ms; NEX=2). The rats were anesthetized with Isoflurane with air during the whole study (~ 2 hrs). MRS data processing was carried out using 3D CSI software (Provided by Columbia University) and DCE-MRI data was analyzed using IDL program to evaluate the rate constant 'k_{ep}' based on the a two-compartment model proposed by Hoffman based on that of Brix et al (3). k_{ep} is the rate constant for back flux of contrast agent from the extracellular extravasculature space to the plasm compartment.

Results

Fig. 1 A-D shows a representative lactate 2D-CSI spectra of sagittal slice with 5mm thickness, obtained as the tumor grew from 618 mm^3 to 2008 mm^3 using the Sel-MQC sequence. Lactate CSI spectra from different voxels were co-registered with the corresponding T2-weighted MR image. It is clear from CSI spectra that at early growth, the lactate is distributed with different levels within the core of the tumor (618 mm^3, Fig. 1A). At increased tumor size (1008 mm^3), heterogeneous distribution of lactate is noted (1B). With further growth (1608 mm^3, Fig. 1C,) part of the peripheral region of the tumor no longer contributes lactate signal, probably due to necrosis. When the tumor grew further (2008 mm^3, Fig. 1D), only few voxels have contributed for lactate signal with reduced signal-to-noise (S/N) ratio. This area appeared necrotic on the T2 weighted images (high signal intensity) – in areas not appearing necrotic on the images, lactate could still be detected (pathology pending). Corresponding DCE-MRI results were shown in Fig. 2 A-D and their respective k_{ep} values are 1.68, 0.65, 0.88 and 0.75 min^{-1}. The higher k_{ep} value 1.68 (Fig. 2A) is probably due to adequate capillary permeability across the tumor vasculature. The abrupt decrease of k_{ep} (Fig. 2B) is due to poorer vasculature which could induce inadequate tumor oxygenation, leading to increased lactate levels (Fig. 1B). Reduced k_{ep} values (Fig. 2C & 2D) can be well related with the lactate distribution with increased tumor volumes present with necrosis (Fig. 1C & 1D).

Conclusions

Reduced *in vivo* lactate signal intensities from 2D lactate CSI map obtained from MR spectroscopy and low tumor perfusion by DCE-MRI, supports the theory to reflect lack of tumor oxygenation due to poor capillary permeability. Hence these techniques may help for patients with aggressive tumors in the prognosis, monitoring and treatment planning at appropriate tumor stage. Correlation of quantitative lactate and pO2 measurements with tumor histopathology are in progress in our laboratory.

References: 1. B.G. Wouters and J. M. Brown Radiat. Res. **147**, 541 (1997). 2. He Q, et.al. J. Magn. Reson B. **106,** 203 (1995). 3. U. Hoffman, et al. Magn Reson Med. **33,** 506 (1995).

Fig. 1

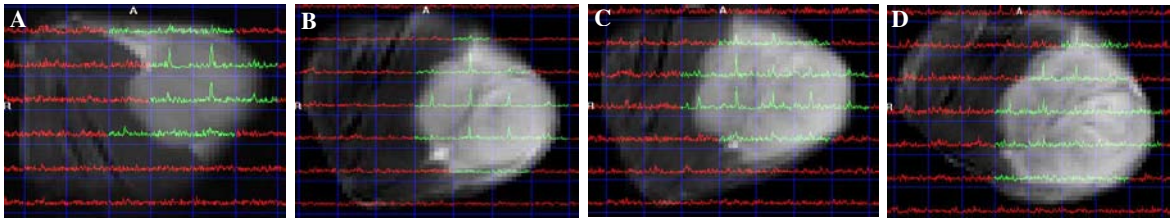

Fig.2