Dynamic Hyperpolarized ^{13}C MRS in a Spontaneous Mouse Model of Thymic Lymphoma

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Target Audience

Scientists and engineers interested in applying hyperpolarized MR methods to spontaneous transgenic models of cancer.

Introduction

Hyperpolarized (HP) MR can overcome the sensitivity limitations of conventional ^{13}C MRS, whereby a physiologic solution containing polarized ^{13}C-labeled metabolites is administered to patients and the chemical fate of the ^{13}C label is monitored in real time[1,2]. Pyruvate has a long T_1 relaxation time, the ability to rapidly enter cells, and it has a central role in cancer metabolism. The conversion of HP [1-^{13}C] pyruvate into lactate has been widely investigated as a biomarker for aerobic glycolysis in cancer[3]. To date, there have been extensive studies of HP ^{13}C MR using a subcutaneous mouse model of lymphoma[4-6], but to our knowledge no such measurement has been performed in a spontaneous transgenic model. The goal of this work was to evaluate the feasibility of detecting elevated aerobic glycolysis in a spontaneous murine model of thymic lymphoma, which is challenging due to the close proximity of the thymus to the heart, where high levels of pyruvate and its metabolites could confound data analysis. Successful demonstration has translational implications for disease staging with HP ^{13}C MR and to serve as a platform for evaluating response to experimental therapies.

Methods

p53-deleted mice develop thymic lymphoma at a 90% incidence rate[7]. Seven 14-week old p53-/- mice with varying stages of disease progression were subjected to MRI followed by slice-localized dynamic HP ^{13}C MRS. All scanning was performed on a 30-cm 7-T Bruker BioSpec MRI scanner. A 72-mm diameter dual-tuned ^{1}H/^{13}C volume resonator was used for ^{1}H imaging and ^{13}C transmission. To improve measurement sensitivity, an actively decoupled 15-mm diameter ^{13}C receive-only surface coil was placed directly over the thymus of each animal. Scout and three-plane localizers were acquired to confirm animal location and surface coil positioning in relation to the thymus. Multi-slice images of the chest provided a reference for subsequent ^{13}C slice positioning. Slices were obliquely positioned to avoid detection of signal in the heart. Prior to HP data acquisition, heavily T_1-weighted images with identical geometric coverage were acquired to confirm that no major vessels traversed the slice. Spatial localization was achieved through the combination of coil sensitivity and slice prescription as shown in Figure 1.

Polarization of a 26-mg sample of pyruvic acid, containing 15-mM OX063 and 0.6 μL of 1.5-mM Prohance, was performed using a HyperSense polarizer. Dynamic spectra were acquired with a pulse-acquire sequence (1500-ms repetition time, 120 repetitions, 15° flip angle, 8-mm slice, 5-kHz bandwidth, 3-min scan time) that was initiated prior to the injection of 200 μL of the HP solution. A separate anatomic imaging session was performed with a 35-mm ^{1}H volume coil to enhance SNR. Vital signs of the anesthetized mice were closely monitored throughout the imaging sessions.

Results

Tumor volumes were manually segmented (Figure 2) and spectroscopic data were processed using custom semi-automated Matlab scripts. Normalized lactate, calculated as the cumulative HP lactate signal over the total HP carbon signal, was determined for each metabolite time course. Tumor volume and normalized lactate were highly correlated (R^2 = 0.92 as shown in Figure 3).

Conclusion and Discussion

The excellent correlation between normalized lactate and tumor volume confirms that HP measurements are indeed modulated by the thymic lymphoma tumors. Based on evidence of a low but non-negligible normalized lactate signal measured in an animal not presenting tumor as determined through anatomical images, normal tissue in the upper chest contributes a small fraction of lactate signal. Therefore, future work should involve imaging methods with sufficient spatial resolution to differentiate metabolic signal produced in tumor from nearby tissues or areas containing large concentration of HP pyruvate such as the heart or other major vasculature. In conclusion, we have demonstrated the initial feasibility for using HP ^{13}C MRS to study thymic lymphoma in vivo in a transgenic mouse model.

References

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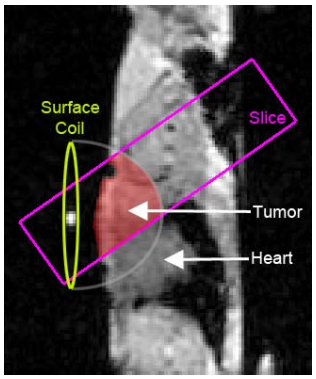

Figure 1: Spatial encoding strategy to avoid contamination of HP pyruvate flowing through the heart. A small reference phantom helps confirm placement of the surface coil.

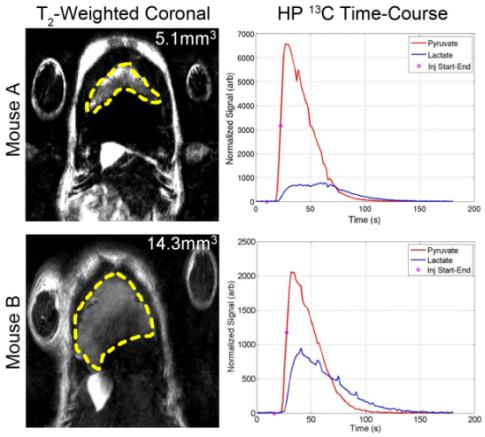

Figure 2: Representative tumor volume measurements (left) and corresponding HP timecourses (right).

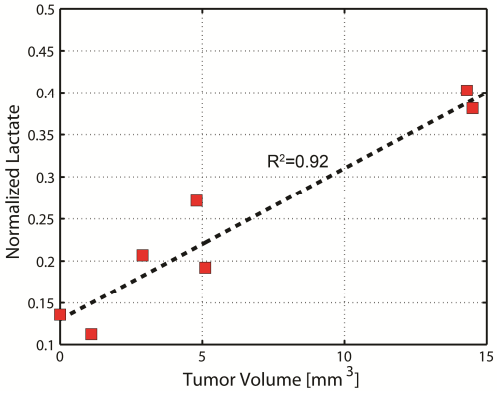

Figure 3: There is a high correlation between measured tumor volumes and the calculated normalized lactate values.