Title: Hyperpolarized In vivo pH Imaging Reveals Grade-Dependent Acidification in Prostate Cancer

Authors: David E Korenchan, Robert Bok, Renuka Sriram, Kristina Liu, Romelyn Delos Santos, He cong Qin, Iryna Lobach, Natalie Korn, David M Wilson, John Kurhanewicz, and Robert R Flavell

Abstract Highlights: We performed hyperpolarized imaging of pyruvate-to-lactate conversion and interstitial pH in a murine prostate cancer model, the TRAMP mouse. Our results demonstrate a significantly lower pH in aggressive versus benign cancer and implicate MCT4-dependent lactate export as an acidification mechanism in this model.

Introduction: There is a strong clinical need to noninvasively distinguish benign versus aggressive prostate cancer (PCa). Hyperpolarized (HP) imaging has demonstrated higher lactate conversion from pyruvate and suggested a concomitant decrease in interstitial pH (pHe), although the latter has never been measured. In this study, we investigated whether aggressive and benign PCa in transgenic mice would demonstrate a significant difference in pHe.

Methods: Transgenic adenocarcinoma of the mouse prostate (TRAMP) mice were imaged at 14 T using sequences for 1H apparent diffusion coefficient (ADC) mapping, 1H T2-weighted anatomical imaging, HP [1-13C]pyruvate frequency-selective 3D gradient-spin echo imaging, and HP [13C]bicarbonate 2D chemical shift imaging. Within 48 hours of imaging, mice were euthanized for tissue collection. Tumor tissue was H&E-stained for histology and used to quantify monocarboxylate transporter 4 (Mct4) gene expression via RT-PCR. A trained pathologist classified each lesion as low- or high-grade based upon cell differentiation, glandular pattern, and necrosis. Imaging voxels containing 50% tumor or more were classified as low-grade or high-grade based upon histology. Voxels with a signal-to-noise ratio < 3 or 1H ADC value > 3x10^-3 mm^2/s were excluded. Non-parametric Mann-Whitney U-tests and Spearman regression were used.

Results: HP imaging was able to resolve metabolic differences between lesions demonstrating low- versus high-grade phenotypes by histology (figure A-D). High-grade lesions (n = 7) showed a higher Lac/Pyr ratio and a lower mean 1H ADC and mean/minimum pHe compared with low-grade lesions (n = 5, figure E-H). Only one low-grade lesion had a pHe overlapping with the high-grade lesions, demonstrating very good separation based on pHe. Mean lesion pHe and Mct4 expression showed a very strong negative correlation (figure I), suggesting that lactate-H+ co-export via MCT4 contributes to greater acidity (figure J).

Conclusions: In vivo hyperpolarized imaging of pyruvate-to-lactate conversion and pHe can be performed in a single imaging session. We observed a lower pHe along with higher lactate in high-grade lesions, suggesting that interstitial acidification may be a biomarker of PCa indolent-to-aggressive transition and is linked with lactate metabolism and export. Future studies will investigate the role of pHe and lactate in predicting immuno-therapeutic efficacy.