Detection of aggressive prostate cancer through pH imaging using hyperpolarized ^{13}C magnetic resonance spectroscopy

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BACKGROUND

There is an unmet clinical need for imaging biomarkers distinguishing indolent from aggressive localized prostate cancer (PCa). The goal of this study is to measure interstitial acidification, lactate production, and perfusion in the TRAMP model of PCa using hyperpolarized ^{13}C MRI and to compare between indolent and aggressive disease. This multi-probe HP approach has strong potential for clinical translation in men with new diagnosis of intermediate grade prostate cancer or on active surveillance.

METHODS

Mouse imaging protocol: TRAMP mice were anesthetized, placed within a 14 T Varian imaging system, and subjected to ^{1}H apparent diffusion coefficient (ADC) mapping followed by two hyperpolarized (HP) injections with ^{13}C imaging. The first injection was comprised of co-polarized [1-^{13}C]pyruvate and [^{13}C]urea, followed by HP [^{13}C]bicarbonate (BiC) formed from [^{13}C]1,2-glycerol carbonate.

Pathology: The mouse was euthanized and the tumor tissue extracted within 24 hours of imaging. Tumor regions were classified by a trained pathologist as low- or high-grade based upon cell differentiation, glandular pattern and necrosis.

RESULTS

We have performed MP HP MRI including pH imaging with BiC, perfusion imaging with urea, and metabolic imaging with pyruvate in a cohort of TRAMP mice (Figure 1A-C). High grade tumors demonstrated acidic extracellular pH compared against low grade tumors, with a statistically significant difference seen between the two groups (Figure 3D). A threshold of minimum pH of 7.2 indicated a transition from low to high grade. Voxelwise linear regression was used to compare pHe, lactate, and perfusion (Figure 3E). A moderate inverse correlation between lactate production and pH, and a correlation between perfusion and pH was observed. However, considerable variation was seen in spatial distribution lactate and pHe (Figure 3B, C), suggesting that while lactate export may play a role, other mechanisms of acidification probably play an important role in establishing extracellular acidosis. Taken together, these data demonstrate that acidic pH is associated with high grade disease and aggressive behavior in the TRAMP model.

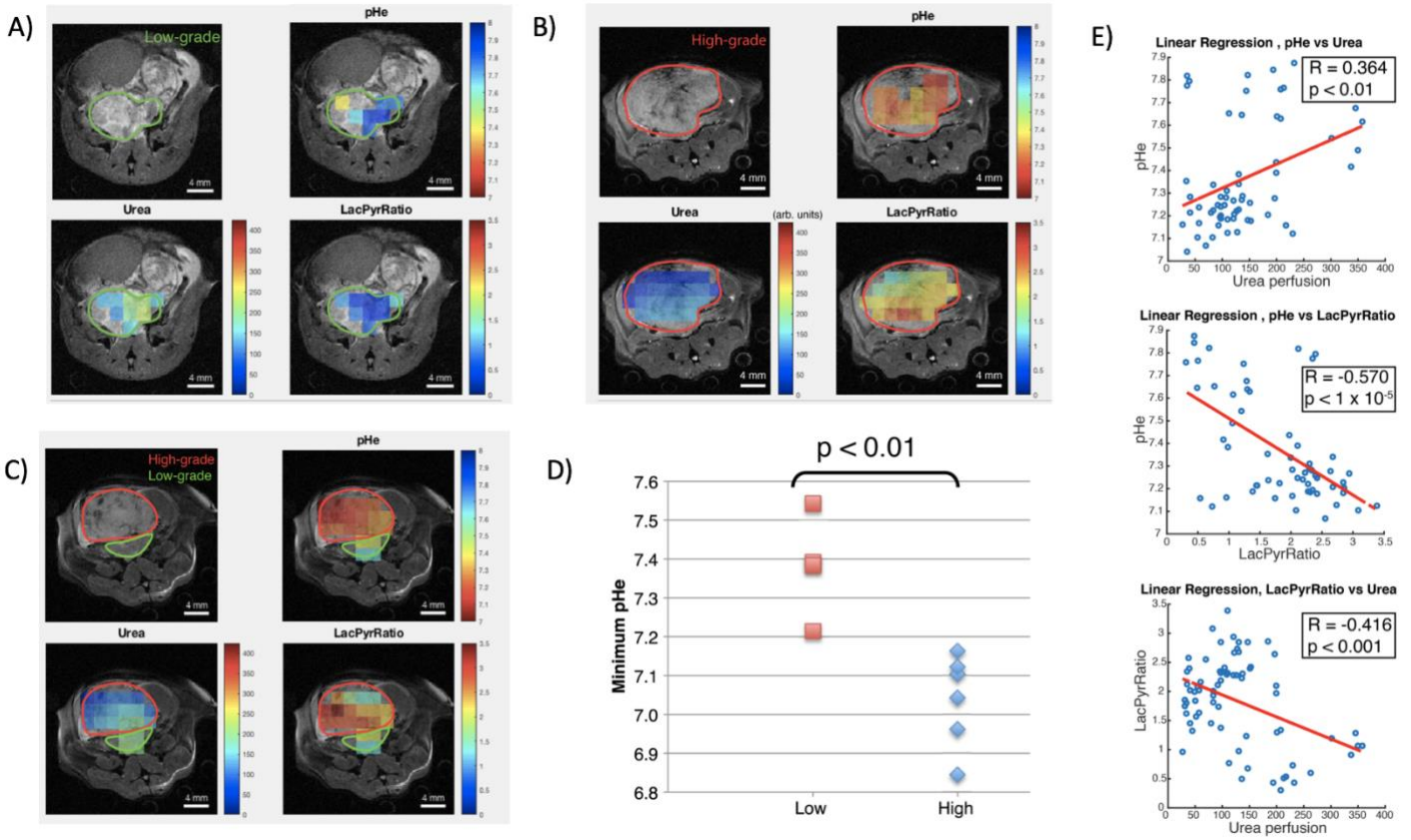

Figure 1. Multi-probe HP pH imaging (MP HP MRI) in the spontaneous transgenic adenocarcinoma of the prostate (TRAMP) mouse. A-C) Imaging in a mouse with a pathology proven low, high, or mixed grade tumor, respectively. D) Comparison of the minimum pHe between low and high grade tumors. High grade tumors had a significant reduction in pH. E) Voxel-wise linear regression comparing perfusion, metabolism, and pHe demonstrated a trend associating lower pH, increased lactate production, and reduced perfusion.

CONCLUSIONS

Using HP MRI, we observed a decrease in pH_e and perfusion and increased lactate production in high grade tumors. A threshold pH of 7.2 could be used to discriminate between low and high grade tumors in this model. These results establish interstitial acidification as a biomarker of PCa indolent-to-aggressive transition.

Conflicts of interest: None

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