Role of Hypoxia in Aggressive Prostate Cancer – A Hyperpolarized 13C MR Study
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Target audience: Investigators of tumor metabolism, hypoxia, and progression.

Purpose: Like many solid tumors, hypoxia develops in human prostate cancer and is believed to play a key role in promoting tumor progression and poor response to therapy1. There is also evidence that the hallmark up-regulation of tumor glycolysis and lactate production is in part a response to the increasingly hypoxic tumor microenvironment with disease progression2. Increased tumor lactate production and its excretion leads to a acidic tumor microenvironment during tumor progression can be uniquely imaged using a multi-probe hyperpolarized (HP) 13C MRI approach3. The purpose of this study was to use a combination of 14T 1H multiparametric MRI and multi-probe 13C MR to determine the impact of tumor hypoxia on prostate cancer progression using the TRAMP model of prostate cancer. The TRAMP model was selected since it nicely mimics changes in pathology and metabolism of human disease.

Methods: Based on histopathology, mice were categorized into 3 groups - normal prostate (n=6) early stage tumors (n=9, ± 50% poorly differentiated) and late stage tumors (n=9, ± 50%) (Fig. 2A). Imaging studies were performed on a wide-bore 14T microimaging system (Varian Instruments) equipped with 100 G/cm gradients and multinuclear capabilities. Multiparametric 1H MR imaging was comprised of T2-weighted anatomic images and diffusion weighted scans to obtain apparent diffusion constant maps (ADC). For the hyperpolarized experiments, [1-13C]pyruvate was co-polarized and injected with 13C Urea3. 13C bicarbonate was polarized and injected separately in the same exam. HP 13C MRI was acquired using a frequency specific 3-D GRASE imaging sequence. Normal prostate and TRAMP tumors underwent H&E staining (pathology), KI-67 (proliferation), and pimonidazole (PIM, hypoxia). Additionally, mRNA expression analyses of genes key to the observed metabolic and micro-environmental changes were performed.

Results and Discussion: T2-weighted images (Fig.1) demonstrate both the contrast and size difference when progressing from the normal prostate (0.04 ± 0.01cc) to early (0.27 ± 0.07cc) and late stage tumors (3.39 ± 0.80cc). Like the human situation, early stage tumors demonstrated both areas of normal glandular structure and regions where the ducts were replaced by cancer cells, whereas, late stage disease exhibited sheets of poorly differentiated cells. These changes in cellularity were reflected in progressive decreases in ADC with disease progression (Figs. 1 & 2B). The magnitude of the ADC changes with cancer grade were very similar to those reported in prostate cancer patients4. Metabolically, the lactate to pyruvate (Lac/Pyr) ratio was significantly increased with progression from normal (0.39 ± 0.04) to early (0.83 ± 0.07) and late stage (2.13 ± 0.18) disease (Figs. 1 & 2C). While the normal prostate was non-proliferative and normoxic, there was an increase in both proliferation and hypoxia in early stage disease, and a more dramatic increase in late stage disease (Fig. 2A). Cells in late stage tumors were > 90% proliferative and nearly 20% of the tissue was hypoxic. This relatively large increase in hypoxia in late stage disease resulted in a 2-fold increase in HIF-1α and VEGF and a 4 fold increase in LDHc levels relative to normal and early stage tumor (Figure 2C). MCT4, the transporter primarily responsible for lactate efflux from the cell and extracellular acidification was also increased by 7 fold in late versus early stage cancer, resulting in an acidic interstitial pH measured using hyperpolarized bicarbonate5 in advanced disease (6.92 ± 0.21) relative to both normal prostate (7.35 ± 0.08) and early stage disease (7.30 ± 0.10). These findings and the strong correlations between increased HIF-1α expression and the expression of LDHc (0.97), MCT4 (0.74) and VEGF (0.8) in late stage disease suggest that hypoxia plays a significant role in driving metabolic and micro-environmental changes associated with prostate cancer progression.

Conclusions: This study demonstrates that hypoxia is significantly increased in TRAMP tumors, and is responsible for driving metabolic and micro-environmental changes that favor disease progression. Moreover these metabolic and micro-environmental changes can be imaged using a multi-probe hyperpolarized 13C MRI approach. These pre-clinical findings recapitulate the human situation where increasing levels of hypoxia have been measured with increasing clinical stage, and correlated with poor clinical outcomes5. A non invasive measurement of hypoxic aggressive disease would also be clinically invaluable as it’s a major impediment to radiation therapy, where patients with high grade hypoxic tumors are three times more resistant to radiation therapy6.


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