Hyperpolarized C^{13} MR imaging of modulations in prostate cancer metabolism as a response to therapy

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Highlight: Hyperpolarized ^{13}C MRI is a valuable technique for non-invasive evaluation of metabolism in-vivo. In this study we evaluate the utility of HP lactate as a metabolic biomarker of neuroendocrine differentiation of castrate resistant prostate cancer and develop a clinically translatable non-invasive imaging tool for early detection and appropriate therapeutic intervention.

Purpose: The goal of this study is to monitor real-time changes in metabolic pathways in prostate cancer as it undergoes therapy and advances from castrate resistance to more treatment resistant aggressive phenotype by using novel hyperpolarized ^{13}C metabolic imaging techniques.

Materials and Methods: TRAMP (Transgenic Adenocarcinoma of the Mouse Prostate) mice were divided into four treatment groups: castrate resistant (castrated and had >20% tumor growth signifying castrate resistance, Group I), apalutamide (ARN-509) treated (one and two weeks of treatment, group II and group III respectively for neuroendocrine enrichment) and carboplatin treated (after one cycle of carboplatin following ARN509, group IV). All the treatment groups underwent serial imaging at week 0 (post-castration), week 1 and 2 (post-ARN509) and week 4 (post-carboplatin). Hyperpolarization was performed using a 3.35T dynamic nuclear polarizer. The copolarized 80mmol/L [1-^{13}C]pyruvate and ^{13}C urea were rapidly dissolved with dissolution buffer and injected into each mouse over 12s. Imaging was performed on a Bruker 3T scanner and a dual tuned $^{1}H/^{13}C$ volume coil. Dynamic ^{13}C spectra was acquired using a 2D CSI sequence, beginning 10s after the start of the HP injection with a temporal resolution of 4.25s with 15 time-points and a flip-angle of 10°. Images were acquired with a FOV of 32 x 32 mm, matrix size of 8 x 8 and slice thickness 8 mm. Metabolite maps were obtained via SIVIC and analyzed using MATLAB program. Serum was collected at each week to perform Neuron-Specific Enolase (NSE) activity assay (marker for presence of neuroendocrine phenotype).

Results: The ARN-509 treated TRAMPs showed increase in the rate of tumor growth at week 1 and 2 (figure-2a). The lactate-to-pyruvate area-under-curve (L/P) ratio analysis showed an increase for groups II and group III (figure-2b). The pyruvate-to-lactate conversion rate, $k_{PL}$of CRPC tumors was 0.06 ± 0.03. The changes in Kpl for the treatment groups were similar to the L/P ratio (figure-2c). Carboplatin treated TRAMPs had a reduction in tumor growth rate, L/P ratio and k_{pl}. The urea AUC analysis showed that post ARN-509 the AUC decreased and increased after carboplatin treatment (figure-2d). The enolase activity (pmol/min/μL) increased from 235.6 ± 112 (group I) to 323.8 ± 185 (groups II) and 364.6 ± 127 (group III).

Discussion: The increase in tumor growth rate, L/P ratio and k_{pl} indicate resistance to ARN-509. While the decrease in all the three metrics after carboplatin treatment indicate a response. The decrease in urea AUC indicate increase in clearance likely due to increase in cellularity. The increase in enolase activity might be due to the presence of neuroendocrine phenotype in tumors as clinically it has been shown that resistance to ARN-509 drives the tumor to neuroendocrine phenotype. Future work will focus on evaluating the changes in metabolism of castrate resistant prostate cancer without ARN-509 and carboplatin intervention to evaluate the metabolic differences from treated tumors. Immunohistochemical staining for neuroendocrine markers and ki67 will be performed to confirm enrichment and proliferation.

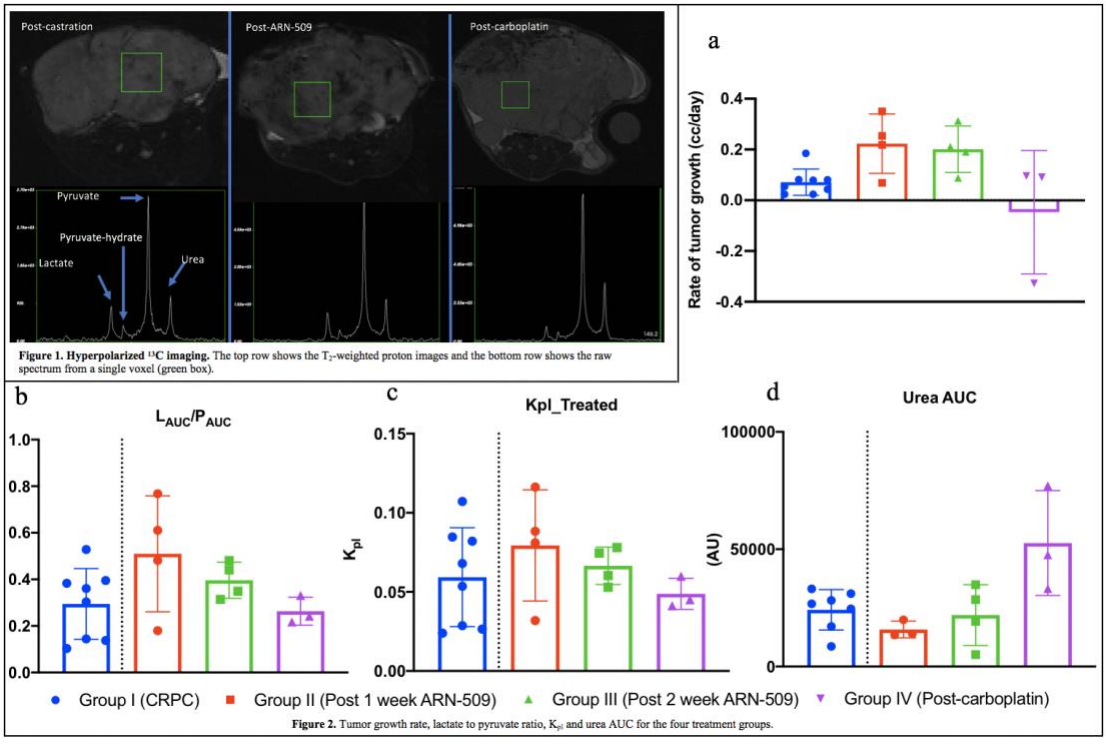

Figure 1. Hyperpolarized ^{13}C imaging. The top row shows the T_2-weighted proton images and the bottom row shows the raw spectrum from a single voxel (green box).

Figure 2. Tumor growth rate, lactate to pyruvate ratio, K_{pl} and urea AUC for the four treatment groups.