Ketone Bodies as a biomarker of the metabolic shift in castration resistance progression: therapeutics implications

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Background: Prostate cancer (PCa) that progresses after androgen deprivation therapy (ADT) (i.e., castration-resistant prostate cancer [CRPC]) remains incurable. Recent reports indicate that metabolic changes (e.g., increase in fatty acids [FA]) occur during PCa progression and may underlie CRPC growth. Interestingly, expression of mitochondrial acetyl-CoA acetyl transferase (ACAT1), a key enzyme in the ketogenic/ketolytic process, has been associated with aggressive PCa (1) and PCa biochemical recurrence following ADT (2). Thus, we hypothesize that tumor-produced ketone bodies (KB) are an energy source implicated in the CRPC progression of a subpopulation of PCas.

Methods: To investigate the metabolic alterations associated with CRPC, we used a PCa patient derived xenograft (PDX), MDAPCa183, which express AR, has TMPRSS2|ERG rearrangement, and ERG outlier expressions. A genomic characterization of MDAPCa183 tumors using whole genome, exome and transcriptome sequencing to identify point mutations, copy number alterations, chromosome rearrangement and gene expression was previously performed and published. Now, we performed a metabolomics profiling of MDAPCa183 tumors growing in intact mice (Controls), MDAPCa183 tumors harvested 10 days after castration of tumor bearing mice (when blood testosterone reach castration levels; early response to castration-ERC) and at relapse.

Results: We subjected mice bearing MDAPCa183 tumors to castration and performed metabolomics analyses of PDXs growing in intact mice (Control), ERC and relapsed tumors. We found that the MDAPCa183 tumors growing in intact mice had high ERG and high and nuclear AR. Relapsed tumors, did not expressed ERG and AR expression was lower with cytoplasmic and nuclear cellular localization. These results suggest that the MDAPCa183 tumors progressed to castration without canonical AR signaling activation reflecting progression with partial or complete loss of AR dependence. Metabolomics analyses of MDA PCa 183 tumors after castration of tumor bearing mice indicated that relapsed tumors had a significant increase in FA and KB content compared to MDA PCa 183 tumors at ERC. KB (beta-hydroxybutyrate, acetoacetate and acetone) are high-energy mitochondrial fuels that can be converted back into acetyl-CoA, and re-utilized as an energy source. To further ascertain the implications of ACAT1(critical enzyme involved in the conversion of ketone bodies into acetyl-CoA) in CRPC progression, in an in-silico approach, we evaluated the relapse free survival time following radical prostatectomy in patients expressing high or low ACAT1. The Ross-Adams et al. (3) PCa dataset (GSE70769, 2015) demonstrated significant association of high ACAT1 expression with patient relapse free survival.

Conclusion: Our studies indicate *that tumor-produced ketone bodies are an energy source implicated in the CRPC progression of a subpopulation of PCas*. These metabolic changes may potentially serve as early biomarkers of CRPC progression and may identify a therapeutic window for early intervention.

Conflict of Interest: none

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