Targeting the Mitochondrial Pyruvate Carrier in Castration-Resistant Prostate Cancer

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Background: While the majority of patients with metastatic prostate cancer will initially respond favorably to androgen deprivation therapy, most will experience relapse and progression of castrate resistant prostate cancer (CRPC) within 1-2 years. Newer second generation agents targeting the androgen signaling axis in CRPC, including abiraterone and enzalutamide, have demonstrated an improvement in overall survival, however this benefit is on the order of months. These agents have demonstrated however that the androgen receptor remains active and is necessary for progression in advanced disease. We sought to identify processes downstream of the androgen receptor that represent viable targets for therapeutic intervention in lethal castrate resistant prostate cancer.

Methods: We performed an integrative analysis of genes overexpressed in CRPC under the control of AR with an emphasis on genes involved in metabolism. We identified MPC2, a recently characterized subunit of the mitochondrial pyruvate carrier (MPC), as a direct AR target gene. Examining patient-derived gene expression data sets, we found that MPC2 expression increases during tumor progression and increased MPC2 expression relative to its heteromeric binding partner MPC1 correlates with significantly decreased disease-free survival. Using a combination of qRT-PCR and Western blotting we confirmed androgen induction of MPC2 in AR positive prostate cancer cell lines. ChIP-qPCR demonstrated androgen induced AR binding to two intronic enhancers in the MPC2 locus. Using a combination of pharmacologic and genetic approaches to target the MPC, we show that disruption of MPC function increases glycolytic flux and dramatically suppresses oxygen consumption rate of prostate cancer cells. Furthermore, we show that inhibition of the MPC with the pharmacologic inhibitor UK5099 inhibits proliferation of AR positive models of prostate cancer including the CRPC models LNCaP abl and LNCaP C4-2, both in vitro and in vivo. Finally, we demonstrate that metabolic imaging using ^{13}C-hyperpolarized pyruvate MRI holds promise as an imaging based predictive biomarker of response to MPC inhibition.

Results: We identified the MPC2 gene as a downstream AR target gene that is significantly upregulated in prostate cancer and correlates with patient outcome. Furthermore we found that genetic or pharmacologic inhibition of MPC function significantly impairs prostate cancer cell proliferation in AR positive models of both androgen dependent and androgen independent prostate cancer.

Conclusion: These studies reveal that the MPC may represent a viable target for therapeutic intervention and future drug development to disrupt key aspects of prostate cancer metabolism in castration resistant prostate cancer.

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