Investigating DNAPK as a therapeutic target and a prognostic biomarker in castration-resistant prostate cancer.

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Abstract

Background: Despite paradigm shifts in the therapeutic advances in the treatment of Castration-resistant prostate cancer (CRPC), it remains a leading cause of cancer related deaths in men worldwide. Thus, two critical unmet needs persist in prostate cancer management. First, to identify biomarkers of aggressive disease early in the patient course to facilitate the desired treatment intensification; and second, to identify more effective therapeutic targets to reduce the mortality resulting from CRPC. The objective of this study is to address both of these needs.

Methods: We analyzed the expression of all known kinases in 545 prostatectomy samples, obtained from high-risk patients with long term (>10 years) clinical follow up, as kinases represent the most actionable class of therapeutic molecules. We ranked the kinases by their fold change in expression between prostate cancers (PCas) that subsequently metastasized vs those that did not. High-throughput as well as standard molecular and biochemical assays were used to carry out mechanistic, phenotype and *in vivo* studies.

Results: By systematically exploring the prognostic relevance of all known kinases in a large cohort of high-risk prostate cancer samples with a long term (<10 years) clinical follow up, we identified DNA dependent protein kinase (DNAPK) as the top kinase associated with metastatic progression in patients treated with prostatectomy. High expression of DNAPK is associated with poor clinical outcomes. Intriguingly, a combined GSEA analysis using expression data from patient samples and cell line models revealed that DNAPK regulates the Wnt signaling pathway. Further validation

demonstrated that Wnt signaling is induced by castration (ADT) in cell line models and drives castration resistance, which is reversed after DNAPK inhibition. We show that DNAPK curbs Wnt-induced cancer phenotypes in CRPC as well as enzalutamide-resistant cells, and that DNAPK regulates Wnt signaling by its interaction with the Wnt transcription factor LEF-1. Pharmacologic inhibition of DNAPK by a laboratory-grade inhibitor NU7441 significantly reduced the CRPC xenograft growth *in vivo*. Further, a clinical-grade inhibitor CC115 (currently in phase-I clinical trials) showed profound reduction in VCaP (AR-dependent) and PC3 (AR-independent) xenograft growth.

Conclusions: Investigating DNAPK as both a biomarker for treatment intensification and a therapeutic target may allow for personalization of effective therapy for CRPC patients in the future. While further exploration of the biomarker potential of DNAPK may provide a clinical tool to guide early treatment intensification for patients with high-risk disease; a detailed evaluation of the therapeutic potential of DNAPK inhibition across the prostate cancer continuum may provide impetus for the rapid translation of DNAPK inhibition as a novel biomarker-guided therapeutic strategy in incurable CRPC, thereby resulting in a significant advance towards the goal of personalized medicine.

Conflict of Interest: NA

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