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

Vishal Kothari[1], Jonathan F. Goodwin[14], Shuang G. Zhao[4], Justin M. Drake[10], Yi Yin[11], S. Laura Chang[4], Joseph R. Evans[9], Kari Wilder-Romans[4], Kristina Gabbara[4], Emanuela Dylgjeri[14], Jonathan Chou[3], Grace Sun[4], Scott A. Tomlins[5,7,8], Rohit Mehra[5,7,8], Kristen Hege[18], Ellen H. Filvaroff[18], Edward M. Schaeffer[12,13], R. Jeffrey Karnes[21], David A. Quigley[20], Dana E. Rathkopf[22], Housheng H. He[23,24], Corey Speers[4,8], Daniel E. Spratt[4], Luke A. Gilbert[2], Alan Ashworth[19,20],   Arul M. Chinnaiyan[5,6,7,8], Ganesh V. Raj[11], Karen E. Knudsen[14,15,16,17#], and Felix Y. Feng[1,2,3#]

Co-senior authors

Author affiliations:

Departments of Radiation Oncology[1], Urology[2] and Medicine[3], University of California at San Francisco, CA, USA. Departments of Radiation Oncology[4], Pathology[5], and Urology[6], Michigan Center for Translational Pathology[7], and Comprehensive Cancer Center[8], University of Michigan Medical School, Ann Arbor, MI, USA. Department of Radiation Oncology[9], OSF Healthcare, Peoria, Illinois, USA. Department of Pharmacology[10], University of Minnesota, MN, USA. Department of Urology[11], UT Southwestern Medical Center, Dallas, Texas, USA. Feinberg School of Medicine[12] and Department of Urology[13], Northwestern University, IL, USA. Departments of Cancer Biology[14], Urology[15], and Radiation Oncology[16], and Sidney Kimmel Cancer Center[17], Thomas Jefferson University, Philadelphia, PA, USA. Celgene Corporation[18], San Francisco, CA, USA. Department of Medicine[19] and Helen Diller Family Comprehensive Cancer Center[20], University of California at San Francisco, San Francisco, CA, USA. Department of Urology[21], Mayo Clinic, Rochester, MN, USA. Memorial Sloan Kettering Cancer Center, New York, NY, USA[22]. Department of Medical Biophysics[23], University of Toronto, Toronto, Ontario, Canada, Princess Margaret Cancer Center[24], University Health Network, Toronto, Ontario, Canada

Abstract

Background: Castration-resistant prostate cancer (CRPC) remains a leading cause of cancer related deaths in men worldwide despite paradigm shifts in the therapeutic advances. Thus, identification of biomarkers of aggressive disease early in the patient course to facilitate the desired treatment intensification; and identification of more effective therapeutic targets to reduce the mortality resulting from CRPC, are two critical needs in the management of this disease. 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 even when we stratified patients into basal (less AR-driven) and luminal (more AR-driven) subtypes. 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 inhibits Wnt-induced cancer phenotypes in CRPC as well as enzalutamide-resistant cells. We show that DNAPK regulates Wnt signaling by its interaction with and transcriptional regulation of LEF-1. Pharmacologic inhibition of DNAPK by a laboratory-grade inhibitor NU7441 or clinical grade DNAPK inhibitor CC-115 significantly reduced the VCaP (AR-dependent), LNCaP-AR (CRPC), and PC3 (AR-independent) xenograft growth *in vivo*, indicating the therapeutic potential of DNAPK inhibitors in all the three spectrums of otherwise lethal aggressive prostate cancer.

Conclusions: Investigating DNAPK as both a biomarker for treatment intensification and a therapeutic target may allow for personalization of therapy for CRPC patients. DNAPK may promote aggressive prostate cancer via upregulation of Wnt signaling. This provides rationale for investigating DNAPK as both a biomarker and a therapeutic target in aggressive prostate cancer.

Conflict of Interest: NA