

A Novel Role of BMI1 in Androgen Receptor Pathway

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Background: Each year, over 240,000 American men are diagnosed with prostate cancer (PCa). B lymphoma Mo-MLV insertion region 1 homolog (BMI1) have been shown associating with metastatic prostate cancer by cDNA microarray analyses and tissue microarray analysis. BMI1 is an epigenetic component of a Polycomb Repressive Complex 1 (PRC1), maintaining gene repression. We have demonstrated that BMI1 promotes prostate cancer progression by repressing multiple tumor suppressors. However, its precise role in castration-resistant prostate cancer (CRPC) remains unclear.

Objective: Our preliminary data strongly suggest that BMI1 is a master regulator of castration-resistant prostate cancer (CRPC) progression. Our objective is to determine how BMI1 interacts with epigenetic complexes and with AR to regulate tumor suppressor gene expression. We aim to identify novel binding partners and regulators of oncogene expression, which will lead to a better understanding of AR signaling and dysfunction. Specifically, we will identify how BMI1 and PRC1 proteins mediate their oncogenic functions by recruiting AR and distinct binding partners to promote castration-resistance of PCa. Furthermore, we will evaluate the therapeutic efficacy of targeting BMI1 and of combinational targeting of BMI1 and AR in castration-resistant prostate cancer.

Methods and Results: By Immunoprecipitation and Immunoblot analysis, we discovered that BMI1 protects AR from MDM2-mediated ubiquitination and degradation. And this BMI1 novel function is independent of PRC1 complex. By tissue microarray analysis (TMA), we observed that BMI1 is upregulated in CRPC and NEPC, compared to non-CRPC patient samples. Importantly, BMI1 is dysregulated in hormone depletion therapy treated PCa patients, and BMI1 levels are positive correlated with AR and PSA. The cell proliferation assays demonstrated that PTC209, a newly discovered BMI1 inhibitor, could inhibit PCa cell growth, and achieved the synergistic effect with enzalutamide in AR+ cells.

Conclusion and Impact: Our study demonstrated a novel BMI1 function in regulating AR protein stability and AR pathway and this function is independent of PRC1 complex. Elucidating the precise role of BMI1 and identifying novel protein interactions in prostate cancer progression and castration-resistant prostate cancer will have a significant impact, not only in the field of prostate cancer, but also in understanding epigenetic regulation in other cancer types. In addition, our study will further the understanding of AR dysfunction in prostate cancer. Furthermore, pre-clinical testing of BMI1-targeted therapeutics on prostate cancer will provide a platform for future treatments of advanced PCa patients.

Funding Acknowledgements:

Prostate Cancer Foundation Young Investigator Award (PCF-13YOUN007)

Department of Defense PCRP Idea Development Award (PC141092)

American Cancer Society Research Scholar Grant (128382-RSG-15-192-01-TBE)