ATM Loss Confers Greater Sensitivity to ATR Inhibition than PARP Inhibition in Preclinical Prostate Cancer Models

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Background: Alterations in DNA damage and repair (DDR) genes are common in advanced prostate tumors and are associated with unique genomic and clinical features. ATM is a DDR kinase that has central role in coordinating DNA repair and cell cycle response following DNA damage, and ATM alterations are present in approximately 5% of advanced prostate tumors. Recently, inhibitors of poly (ADP-ribose) polymerase (PARP) have demonstrated activity in advanced prostate tumors harboring DDR gene alterations, particularly in tumors with *BRCA2* alterations. However, the role of alterations in DDR genes beyond *BRCA2* in mediating PARP inhibitor sensitivity is poorly understood.

Methods: We are developing preclinical tools to dissect the cellular impacts of DNA repair deficiency in prostate cancer. We have assembled a large panel of immortalized DNA repair deficient cell lines, representing multiple DNA repair genes and pathways. These cell lines provide a tractable system to test the functional impact of mutations in a wide variety of DNA repair genes. In addition, we are using CRISPR/Cas9 technology to delete or mutate DNA repair genes in prostate epithelial and tumor cell lines. To date, we have created numerous ATM knockout models across a series of prostate tumor cell lines. We are characterizing the DDR properties of these cell lines using multiple approaches and are also developing cell- and tissue-based tools to meausure DDR function from clinical prostate tumor samples.

Results: Our preliminary data using complementation assays in DNA repair deficient cell lines suggest that prostate tumor-specific missense mutations in DNA repair genes such as *ATM* and *FANCD2* can confer DNA repair deficiency. We find that ATM loss alters DDR signaling and modestly sensitizes to DNA damaging agents. However, ATM loss does not impact HR function in these models and only minimally sensitizes to PARP inhibition. Conversely, ATM loss robustly sensitizes prostate cancer cells to inhibition of the related DDR kinase ATR.

Conclusions: DNA repair pathway alterations in prostate tumors can drive a DDR deficient phenotype and impact sensitivity to DDR-directed agents. ATR inhibition may be a more attractive therapeutic strategy than PARP inhibition for prostate tumors with ATM loss.

Conflict of Interest Statement: N/A.

Funding Acknowledgements: The authors acknowledge funding from the Prostate Cancer Foundation and the Dana-Farber/Harvard Cancer Center (DF/HCC) Prostate SPORE.