Developing Preclinical Models to Study DNA Repair Deficiency in Prostate Cancer

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DNA repair pathways alterations – particularly in the homologous recombination (HR) pathway – are common in prostate tumors and have important implications for prognosis and therapy selection. However, the clinical impact of specific DNA repair mutant alleles are often uncertain, and the mechanisms by which HR deficiency drives prostate cancer tumorigenesis and therapy response are poorly understood.

To better understand the role of HR pathway alterations in prostate cancer, we are working to establish functional approaches to dissect the cellular roles 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. By expressing WT or mutant versions of the DNA repair gene of interest in the corresponding repair-deficient parental cell line, we are able to quantify the ability of individual DNA repair alleles to support cellular DNA repair. Our preliminary data suggest that common missense mutations in DNA repair genes such as *ATM* and *FANCD2* confer functional DNA repair deficiency.

In addition, we are using CRISPR/Cas9 technology to knock out DNA repair genes in a variety of prostate epithelial and tumor cell lines. To date, we have created several *ATM*[/-] cell lines that exhibit features consistent with loss of DNA double-strand break checkpoint signaling. In addition, we find that ATM loss confers marked increase in sensitivity to ATR inhibitors but minimal increase in sensitivity to PARP inhibitors. We are performing comprehensive genomic and functional characterization of these isogenic DNA repair proficient/deficient cell lines in order to understand the impact of DNA repair deficiency on tumor behavior and therapy response.

Finally, we are working to establish an immunohistochemical (IHC) assay to provide a readout of HR pathway function from FFPE prostate tumor specimens. The assay utilizes a Rad51 antibody that forms nuclear foci in cells with intact HR function. We have previously validated this assay as a reliable marker of HR function in other tumor settings, and are now working to adapt the assay for use on fresh and FFPE prostate biopsies and prostatectomy specimens.

Loss of DNA repair pathway function has important implications for prostate cancer prognosis and treatment. However, the functional landscape of DNA repair alterations across prostate cancer is poorly defined and the role of DNA repair mutations in driving prostate cancer biology and therapy response is incompletely understood. Our preliminary data suggests that DNA repair pathway alterations in prostate tumors can lead to functional DNA repair deficiency that are sufficient to drive changes in the prostate tumor phenotype.

Conflict of Interest Statement: No conflicts to report.