

Prostate Cancers Harbor Mutually Exclusive Genomic Drivers That Are Enriched Within Non-T cell Inflamed Tumors

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BACKGROUND: While immunotherapy has seen dramatic successes in a variety of malignancies, the majority of patients fail to respond. In particular, less than 10% of patients with metastatic, castrate-resistant prostate cancer (mCRPC) respond to immunotherapy. Based on previous work demonstrating improved clinical activity of immunotherapies in patients with a T cell-inflamed tumor microenvironment, as well as the evidence that specific oncogene pathways may mediate T cell exclusion, we investigated whether non-T cell-inflamed CRPC samples showed evidence for distinct molecular aberrations that might explain immune escape.

METHODS: RNAseq gene expression data were analyzed from two prostate cancer cohorts, The Cancer Genome Atlas of primary tumors (n=437), and a Stand Up to Cancer mCRPC cohort (n=43). These datasets were interrogated for common molecular alterations and their association with non-T cell inflamed and T cell-inflamed cancers, focusing on copy number deletions of *PTEN*, *RB1/CDKN2A*, and activating mutations in *CTNMB1* (β -catenin). Similar approaches were used to analyze 30 solid tumor types from TCGA (n=9555).

RESULTS: Our analysis identified that 94% of primary prostate cancers harbor a non-T cell-inflamed (65%) or intermediate (29%) tumor microenvironment, with only 6% of patients having a T cell-inflamed gene signature. Similar results were found in mCRPC patients. Higher frequencies of *PTEN* loss and *CTNMB1* activation, as well as a significant enrichment of *RB1/CDKN2A* deletion, were found in non-T cell-inflamed primary and metastatic prostate tumors. Moreover, we observed a direct correlation between the expression of *PTEN/RB1* and *CD8A* expression within the tumor microenvironment. Analysis of 30 human cancers revealed that loss of *PTEN* and/or *RB1/CDKN2A* correlates with T-cell exclusion across multiple malignancies. When combined with β -catenin pathway activation, we found that these alterations are mutually-exclusive, with 1% of the non-T cell-inflamed tumors sharing all three mechanisms, 24% sharing two out of the three, and 75% of the samples harboring only one mechanism.

CONCLUSIONS: We show that deregulated PTEN/PI3K, Rb and Wnt- β -catenin signaling networks are enriched in a mutually exclusive manner within non-T cell-inflamed prostate cancers, suggesting that that such cancers may evolutionarily co-opt non-redundant signaling pathways to achieve a common goal of immune evasion. Targeting these pathways pharmacologically may provide an opportunity to enhance responsiveness to immunotherapy.

CONFLICTS OF INTEREST: None.

FUNDING ACKNOWLEDGEMENTS: PCF Challenge Award, NCI Prostate SPORE (University of Chicago/Northwestern), BMS International Immuno-Oncology Network, American Cancer Society, Cancer Research Foundation