

B7-H3 IS A CHECKPOINT IMMUNOTHERAPY TARGET IN ADVANCED PROSTATE CANCER HARBORING PTEN AND TP53 DEFECTSDi Zhao*, Wei Shi, Yin Wang. *UT MD Anderson Cancer Center, Houston, TX, United States*

Background Prostate cancer is the most diagnosed cancer in men worldwide and the leading cause of cancer death in men worldwide. Genetic inactivation of *PTEN* and *TP53* are common in advanced prostate cancers. Checkpoint immunotherapy has yielded meaningful responses across many cancers but shown minimal activity in advanced prostate cancer. Prior studies showed that overexpression of immune checkpoint B7-H3 (CD276) correlates with the increased risks of clinical recurrence, disease spread, and poor outcomes in various cancer types, including prostate cancer. However, the roles of B7-H3 in prostate cancer development and its tumor microenvironment remain unclear, partially due to the lack of tissue-specific deletion mouse models. This gap in knowledge hinders the application of immunotherapy targeting B7-H3 in prostate cancers.

Methods To identify *PTEN*- and *p53*-associated immune checkpoints, we performed multi-omics analyses of expression patterns of 51 checkpoint molecules in human prostate cancer samples. Then, we generated a novel genetically engineered mouse model to elucidate the role of B7-H3 in tumor development and progression of *PTEN/p53*-deficient prostate cancer. We also performed unbiased immunoprofiling using Mass Cytometry (CyTOF) and Immunofluorescence to visualize B7-H3's impact on immune components in prostate tumors.

Results Our multi-omics analyses in human samples revealed that B7-H3 is one of the most significantly overexpressed immune checkpoints in prostate tumors containing *PTEN* and *TP53* genetic inactivation. Mechanistically, we found that the *PTEN*-AKT pathway co-operates with the *p53* pathway in modulating B7-H3 expression in cancer cells. In *Pten/Trp53* genetically engineered mouse (GEM) models, prostate-specific deletion of *Cd276* resulted in markedly delayed tumor progression. *Cd276* deletion also reversed the immunosuppression characterized by increased tumor-infiltrating lymphocytes.

Conclusions Our studies provide the genetic evidence for the tumor-promoting and immunosuppressive role of B7-H3 in prostate cancer and offer insights into combinatorial strategies for immunotherapy targeting B7-H3 in CRPC harboring *PTEN* and *TP53* defects.

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