

Title: Links between the T cell receptor repertoire and patient outcomes in racially diverse men with prostate cancer revealed by bulk and single cell analysis

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Background: Prostate cancer (PCa), the second leading cause of cancer-related death for US men, typically gains limited benefits from immune therapies. Interestingly, African American (AA) men respond far better to Sipuleucel-T and undergo different T cell responses than Caucasian American (CA) PCa patients. Growing evidence suggests that variations in TCR diversity and the spatial distribution of T cell clones may serve as biomarkers for cancer progression and response to immune therapy; however, the extent of the T cell receptor (TCR) repertoire's contribution to PCa progression and disparate racial responses to treatment remains unclear, highlighting the need for further study.

Methods: The rapid development of Next Generation Sequencing and single-cell transcriptomics provides a unique opportunity to examine the TCR repertoires of PCa patients in greater depth than previously possible. Bulk TCR-seq was performed on 25 AA and 30 CA treatment-naïve tumor biopsies to compare the percent of dominant and unique TCRs (D50) from each sample. Next, peripheral blood lymphocytes (PBLs) were isolated from 4 AA and 4 CA clinically-matched men undergoing radical prostatectomy for diagnosed PCa with no prior treatment. 10X Genomics GEX and V(D)J technologies were used to produce libraries of individual cell transcriptomes and TCRs, respectively.

Results: TCR-seq revealed significantly higher D50 scores in CA than AA tumors. Additionally, men that developed biochemical recurrence and metastasis had significantly higher tumor D50s than those that did not. Single cell V(D)J and RNA-seq identified key differences in the circulating T cell repertoires of AA and CA PCa patients. We also found variable prominence of mucosal-associated invariant T cell (MAIT) clones between patients.

Conclusions/future directions: By examining TCR sequences in a racially diverse cohort from an equal-access Military Health System, we have begun to identify differences in AA and CA repertoires that may contribute to variations in PCa initiation, progression, and response to therapy. These may eventually guide therapeutic options based on predicted responsiveness of an individual. The V(D)J and GEX data may be assessed for co-expression of activation, exhaustion, and anergy markers based on clonotype. The V(D)J data will also be used as a reference set to generate a panel for 10X Genomics Xenium. This will provide spatial data to examine the distribution of identified TCR clones in PCa tumor biopsies. Finally, we found differences in prominent MAIT clones between individual patients, which will be further evaluated.

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Source of Funding:

This work was primarily supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Congressionally Directed Medical Research Program's Prostate Cancer Research Program under a Health Disparity Fellowship award no. W81XWH-19-1-0302 to C.C. Schafer, and this work was partially funded by a Center for Prostate Disease Research, Uniformed Services University of the Health Sciences grant to G.T. Chesnut under award no HU0001-21-2-0021. This work was supported by the Prostate Cancer Foundation Young Investigator Award.