

Spatial Mapping of Accessible Chromatin Landscapes in Prostate Cancer

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Abstract

Background: Androgen deprivation and androgen receptor (AR) pathway inhibitors have significantly improved survival outcomes in men with prostate cancer (PCa). Nevertheless, a substantial proportion of patients progress from biochemical recurrence to castration-resistant prostate cancer (CRPC), which is lethal and largely incurable. PCa progression thus represents a critical clinical challenge. Epidemiologically, African American (AA) men present with more advanced disease and show earlier onset compared to Caucasian American (CA) men; nevertheless, this disparity is not fully explained by socioeconomic factors alone, suggesting that biological variability may play a vital role in driving prognostic differences between AA and CA men. Genomic, transcriptomic, and proteomic differences between AA and CA PCa are emerging; however, the underlying epigenomic landscape, specifically differences in chromatin accessibility, remains insufficiently characterized. Defining how the chromatin-mediated regulatory programs differ between AA and CA men is pivotal to resolving the molecular mechanisms that may contribute to disparities in PCa progression and clinical outcomes.

Methods: In this proof-of-concept study, we used spatial ATAC-seq on a microfluidic DBiT-seq platform (AtlasXomics) to comprehensively characterize spatial intratumoral heterogeneity of chromatin accessibility in a clinically well-annotated cohort of 10 radical prostatectomy tissue specimens from 5 AA and 5 CA patients. These tissue specimens were obtained from the Center for Prostate Disease Research (CPDR) biorepository, which uniquely provides longitudinal clinical follow-up data within an equal-access healthcare framework at the Walter Reed National Military Medical Center (WRNMMC). This cohort and experimental framework enabled spatially resolved interrogation of epigenomic states while minimizing potential confounding attributable to disparities in health care access.

Results: High-resolution mapping of the genome-wide chromatin accessibility landscape of localized PCa across 10 tumor samples using spatial ATAC-seq revealed seven distinct spatial clusters characterized by heterogeneous contributions from epithelial, stromal, and immune cell populations. Despite spatial and cellular heterogeneity within tumors, the global distribution of accessible chromatin regions within epithelial cell populations was broadly similar between tumors from AA and CA patients, indicating conservation of large-scale chromatin accessibility landscapes across the two groups. Notably, transcription factor (TF) motif enrichment analysis within the epithelial subclusters unveiled a significant attenuation of chromatin accessibility at loci associated with CCCTC-binding factor (CTCF) motifs, accompanied by increased activity of epithelial-to-mesenchymal transition (EMT) programs in tumors from AA men compared to CA men.

Conclusion: These data underscore a critical, yet unexplored mechanistic vulnerability, prompting the hypothesis that suppressed CTCF expression or functional disruption directly drives the accelerated, aggressive tumor phenotypes characteristically observed in early-stage disease among AA men. Overall, our analysis of chromatin accessibility in localized PCa provides valuable insights into race-associated epigenomic changes in tumor progression and therapeutic resistance.

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