Profiling the Prostate Cancer Epigenome Using Circulating Nucleosomes in Plasma

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Background: The prostate cancer epigenome undergoes dramatic reprogramming during tumorigenesis and treatment resistance. Despite the androgen receptor (AR) being expressed in both normal prostate and prostate cancer, the genomic occupancy of AR is altered in cancer to induce oncogenic transcriptional programs. Similarly, the enhancer landscape is reshaped in response to treatment to activate dormant fetal prostate transcriptional programs that drive resistance. These mechanistic insights could not have been elucidated through genomic or transcriptomic approaches alone and relied on profiling primary patient samples. However, performing comprehensive epigenetic profiling in patients with advanced disease has been limited by access to adequate biopsy specimens. Although circulating tumor DNA (ctDNA) provides a noninvasive method to identify genetic alterations, we investigated whether ctDNA could detect epigenetic reprogramming using cell free chromatin immunoprecipitation followed by sequencing (cfChIP-seq).

Methods: We performed cfChIP-seq for histone marks on 71 plasma samples from 46 patients including 34 patients with metastatic prostate cancer. A subset of patients provided serial samples to allow evaluation of temporal changes during progression. Samples also underwent whole genome sequencing for mutation and structural variant annotation. Radiographic and clinical findings were assessed at the time of collection.

Results: cfChIP-seq captures prostate cancer-specific regulatory elements, identifies epigenetic subtypes of mCRPC, and stratifies patients based on genomic and clinical correlates. Inferred transcription factor activity based on binding motif enrichment within regulatory elements confirm expected drivers such as AR and FOXA1 in adenocarcinoma and ASCL1 and EZH2 in neuroendocrine prostate cancer (NEPC). Using samples collected from serial time points, we observe reprogramming of the epigenome associated with treatment emergent NEPC. We also provide a framework to analyze cfChIP-seq results accounting for the highly variable tumor fraction that contributes to background signal.

Conclusions: Our results demonstrate that cfChIP-seq captures clinically relevant epigenetic alterations in advanced prostate cancers and is a powerful complement to current cell free DNA methods to identify dynamic changes in the epigenome during prostate cancer progression.

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