Title: Chromatin accessibility analysis uncovers regulatory element activation landscape in prostate cancer progression

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Abstract

Prostate cancer (PCa) is the second most frequent cancer diagnosis made in men and 18% of cases progress to lethal castration-resistant prostate cancer (CRPC) making it fifth leading cause of death worldwide. Aberrant oncogene functions and structural variation alter the chromatin structure in cancer cells. While gene regulation by transcription factors (TFs) and chromatin states has been studied before, chromatin accessibility and its relevance in aberrant gene expression during PCa progression is not fully understood. Here, we report a genome-wide chromatin accessibility analysis of clinical tissue samples of benign prostatic hyperplasia (BPH), untreated primary prostate cancer (PC) and CRPC. We integrated the results with transcriptome, methylome, and proteome data of the same samples to uncover disease-relevant regulatory elements and their association to altered gene expression during PCa progression. Our results show that while promoter accessibility remains generally consistent during disease initiation and progression, chromatin accessibility at distal sites is vastly variable and reprogrammed. We identify consistent progression-related chromatin alterations during the progression to CRPC. By studying the TF binding patterns, we demonstrate the activation and suppression of androgen receptor-driven regulatory programs during PCa progression and identify complementary TF regulatory modules characterized by e.g., MYC and glucocorticoid receptor binding. By correlation analysis we assign at least one putative regulatory region for 61% of genes and 83% of proteins differentially expressed during PCa progression. Taken together, our analysis of the chromatin landscape in PCa identifies putative regulatory elements for the majority of cancer-associated genes and characterizes their impact on the cancer phenotype.