Androgen receptor deregulation drives bromodomain-mediated chromatin alterations in prostate cancer

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Abstract

Background:
Global changes in chromatin accessibility may drive cancer progression by reprogramming transcription factor (TF) binding as previously hypothesized. In addition, epigenetic readers such as bromodomain containing protein 4 (BRD4) have been shown to associate with these TFs and contribute to aggressive cancers including prostate cancer (PC).

Methods:
We applied formaldehyde-assisted isolation of regulatory elements and sequencing (FAIRE-seq) to human prostate tumors tissue and androgen receptor (AR) –overexpressing cell lines models to retrieve accessible chromatin. We used JQ1 and RNAi toward bromodomain-containing proteins (BRDs) to assess their effect on viability, chromatin opening, and the transcriptome. Finally, we undertook an integrative analysis of BRDs transcripts levels, immunostainings, transcriptomics and chromatin status using thousands of patient samples in 7 independent cohorts, to establish the predictive value of a bromodomain-dependent gene signature.

Results:
Chromatin accessibility defines castrate-resistant prostate cancer (CRPC). We show that the AR deregulation alone is a driver for chromatin relaxation and that AR/androgen-regulated BRDs mediates this effect. We also report that BRDs are overexpressed in CRPCs and that ATAD2 and BRD2 have prognostic value. We have developed the first ten-gene(BROMO-10) candidate stratification signature for both the prognostication of prostate cancer and response to bromodomain inhibitors. This requires further validation ideally in trials cohorts.

Conclusions:
Targeting bromodomains in selected patients provides a compelling rational for combination therapy in which BRD-mediated TF binding is enhanced or modified as cancer progresses.

Key words: androgen receptor; prostate cancer; epigenetics; bromodomain; signature; chromatin

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