Loss of *CHD1* promotes chromatin dysregulation leading to heterogeneous mechanisms of resistance to hormone therapy in prostate cancer

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BACKGROUND:
Pharmacological targeting of driver alterations in cancer has resulted in many clinical successes but is limited by concurrent genomic alterations. One potential explanation for this heterogeneity is the presence of additional genomic alterations which modify the degree of dependence on the targeted driver mutation. Metastatic prostate cancer (mPCa) serves as a relevant example, where the target is the androgen receptor (AR) which functions as a lineage survival factor of luminal prostate epithelial cells. Next generation AR therapies such as abiraterone, enzalutamide and apalutamide have significantly improved survival of men with mPCa, but resistance remains an issue.

METHODS:

To gain functional insight into the genes impacted by the copy number alterations in mPCa, we screened 4234 short hairpin RNAs (shRNAs) targeting 730 genes often deleted in human prostate cancer (the prostate cancer deletome) for hairpins that confer *in vivo* resistance to enzalutamide.

RESULTS:
The chromodomain helicase DNA-binding protein 1 (*CHD1*) emerged as a top candidate, a finding supported by patient data showing that *CHD1* expression is inversely correlated with clinical benefit from next generation antiandrogen therapy. *CHD1* loss led to global changes in open and closed chromatin, indicative of an altered chromatin state, with associated changes in gene expression. Integrative analysis of ATAC- and RNA-seq changes identified 22 transcription factors as candidate drivers of enzalutamide resistance. CRISPR deletion of four of these (*NR3C1, BRN2, NR2F1, TBX2*) restored in vitro enzalutamide sensitivity in *CHD1* deleted cells. Independently derived, enzalutamide-resistant, *CHD1*-deleted subclones expressed elevated levels of 1 or more of these 4 transcription factors. This pattern suggests a state of chromatin plasticity and enhanced heterogeneity, initiated by *CHD1* loss, which enables upregulation of distinct sets of genes in response to selective pressure. This concept is further supported by RNA-seq data from a mCRPC patients cohort, in which we examined the co-association of *CHD1* levels with each of these four TFs across 212 tumors.

CONCLUSIONS:
We demonstrated that loss of the chromodomain gene *CHD1*, a commonly deleted prostate cancer gene, through global effects on chromatin, establishes a state of plasticity that accelerates the development of hormone therapy resistance through heterogeneous activation of downstream effectors.

CONFLICT OF INTEREST:
C.L.S. is co-inventor of enzalutamide and apalutamide and may be entitled to royalties. C.L.S. serves on the Board of Directors of Novartis and is a co-founder of ORIC Pharm, and was co-founder of Seragon. He is a science advisor to Agios, Beigene, Blueprint, Column Group, Foghorn, Housey Pharma, Nextech, KSQ, Petra and PMV.

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