CHD1-loss Promotes Tumor Heterogeneity, Lineage Plasticity and Therapy Resistance

Background: Targeted therapies for driver oncogenes have transformed the management of many cancers but the magnitude and duration of response remains variable. One potential explanation is the presence of additional genomic alterations which modify the degree of dependence on the targeted driver mutation. Metastatic castration resistant prostate cancer (mCRPC) serves as an example, where the target is the androgen receptor (AR). Compared to primary disease, mCRPC is characterized by extensive heterogeneity at both genomic and transcriptional levels, including genomic copy number alterations (CNAs), which are presumed to contribute to the resistance to AR targeted therapies.

Method: To gain functional insight into the genes impacted by the CNAs in mCRPC, we screened 730 genes often deleted in mCRPC for CNAs that confer *in vivo* resistance and identified the chromodomain helicase DNA-binding protein 1 (*CHD1*) as a top candidate modifying resistance, a finding supported by patient data showing that *CHD1* expression is inversely correlated with clinical benefit from therapy.

Results: Depletion of *CHD1* confers significant resistance to enzalutamide both *in vitro* and *in vivo*. Furthermore, we observed global changes in open and closed chromatin after the depletion of *CHD1*, indicative of an altered chromatin state, with associated changes in gene expression. Integrative analysis of ATAC-seq and RNA-seq, combining with CRISPR-based screen, identified four heterogenous resistance drivers (*GR, BRN2, NR2F1, TBX2*), which are elevated in different independently derived, resistant, *CHD1*-deleted subclones. Significantly increased transcriptional heterogeneity, as well as lineage plasticity was observed in these resistant tumors and in the tumor samples from a large mCRPC patients' cohort. Finally, GR inhibition with both genetic and pharmacological approaches restored the enzalutamide sensitiivty in resistant tumors with elevated GR signaling.

Conclusion: These results suggest *CHD1*-loss establishes a state of chromatin plasticity that accelerates the development of AR targeted therapy resistance through activation of heterogeneous downstream effectors, which mediated the transition away from luminal lineage identity and AR dependency. This model not only provides an innovative explanation for the increased transcriptional heterogeneity in mCRPC, but also suggests that proper clinical interventions targeting these heterogenous resistance drivers may be a novel avenue to overcome resistance towards AR targeted therapies.