ONECUT2 reprograms the AR network and activates non-canonical EZH2 in aggressive prostate cancer

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Background: Treatment of aggressive prostate cancer remains a serious challenge because of the frequent emergence of a range of resistance pathways. We previously established that the master transcription factor (TF), ONECUT2 (OC2), drives therapeutic resistance via multiple mechanisms and acts as a survival factor. Moreover, OC2 is active in hormone-naïve tumors, leading us to investigate potential OC2-induced changes in cistrome architecture in the context of androgen receptor (AR) expression and activity. We included the transcription factor Kaiso in this analysis because Kaiso is an AR cofactor that has been implicated in African American prostate cancer.

Methods: We conducted CUT&RUN analyses of the TFs OC2, AR, and Kaiso in OC2-Control and OC2-enforced (OC2-OE) castration-sensitive model LNCaP to interrogate potential chromatin perturbations arising from OC2 activity. These profiles were compared to the OC2 and AR CRPC cistromes. Additionally, we characterized chromatin states associated with altered TF binding using LNCaP-specific chromatin state annotations. We integrated ATAC-seq and RNA-seq from OC2-OE LNCaP to validate TF activity and conduct gene set enrichment analysis. To assess PRC2 and EZH2 activity, we integrated H3K27me3 CUT&RUN and EZH2 ChIP-seq data from LNCaP cells. Finally, we analyzed TF activities in OC2-OE and enzalutamide-resistant models.

Results: We found that OC2 drives reprogramming of AR and Kaiso at polycomb-associated regions and bivalent promoters of genes associated with neuronal development, EMT genes, and steroid hormone receptors. In cell lines and patient samples, OC2 appears to suppress PRC2 activity or be associated with reduced PRC2 activity. Notably, OC2-induced reprogramming of these factors is associated with the activation of the non-canonical EZH2 function. Integrated transcriptomics of human CRPC and patient-derived xenograft cohorts indicate that OC2 and non-canonical EZH2 activity are strongly associated.

Conclusions: These findings support a role for OC2 in AR reprogramming in hormone-dependent prostate cancer cells, which persists in the CRPC cistrome. Our findings suggest that OC2 activation results in displacement of the PRC2 complex and activation of the non-canonical EZH2 function. Kaiso also appears to collaborate with OC2 to promote lineage plasticity. These findings provide a rationale to co-target EZH2 and OC2 to suppress therapeutic resistance in aggressive prostate cancer.

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