

ONECUT2 IS A MASTER REGULATOR TRANSCRIPTION FACTOR AND NOVEL DRUG TARGET IN AGGRESSIVE PROSTATE CANCER VARIANTS

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Background: In response to hormonal therapy, prostate cancers (PCs) exhibit patterns of phenotypic plasticity that are not well characterized. Mechanisms underlying this adaptive transition to treatment resistance are not understood. Despite evidence of AR activity in progressing cancer, signatures of AR activity can appear suppressed. There are no effective therapeutic strategies within this poorly understood spectrum of aggressive PC variants.

Results: We performed master regulator analysis using 260 metastatic castrate resistant (mCRPC) transcriptome profiles and developed a model transcription factor network for mCRPC. The non-canonical homeobox protein ONECUT2 (OC2) emerged as an unanticipated and prominent node in this unbiased model. Microarray profiling of the consequences of enforced expression and silencing of OC2 in human PC cell lines, combined with OC2 ChIP-seq, identified a broad network of OC2-regulated genes. OC2 forms a complex with AR, however the protein appears to regulate many genes independently of AR. OC2 activates neuroendocrine (NE) hallmark genes and directly regulates *PEG10*, a gene recently identified as a mediator of NE transdifferentiation in CRPC. OC2 antagonizes AR by suppressing expression of AR and of the AR licensing factor FOXA1. Silencing of OC2 potently suppressed growth of C4-2 and 22Rv1 CRPC cells as well as metastasis of 22Rv1 cells in mice. Multiple independent lines of evidence indicate that OC2 is targetable therapeutically. In silico modeling revealed that the OC2 tertiary structure can accommodate a small molecule in a pocket near the C-terminal DNA binding domain. Using this information, we identified a novel drug-like inhibitor that phenocopies the biological and molecular effects of OC2 silencing and inhibits 22Rv1 tumor growth in mice. Inferred OC2 activity in human CRPC correlates positively with aggressive variant/NE signatures and negatively with AR activation signatures. OC2 expression is highest in the recently identified PCS1 PC subtype, which exhibits poor prognosis¹.

Methods: OC2 was confirmed as a PC-relevant protein using enforced expression, silencing, RNA profiling, ChIP-Seq, ChIP-qPCR, luciferase reporter assays, flow cytometry, immunohistochemistry, quantitative imaging, in vivo experiments and functional assays.

Conclusions: OC2 is master regulator transcription factor and novel therapeutic target that operates in a subset of CRPCs where AR activity may be partially suppressed.

Conflicts of interest: None.

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