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ONECUT2: A Targetable Master Regulator of Progression to Neuroendocrine Differentiation from Prostate Adenocarcinoma

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BACKGROUND: Prostate adenocarcinoma can give rise to aggressive variants that are associated with rapid treatment resistance, metastasis, and death. Small cell neuroendocrine prostate cancer (NEPC) and adenocarcinomas with neuroendocrine (NE) features are examples of these variants, where the androgen receptor (AR) plays an insignificant role.

METHODS: OC2 was confirmed as a NEPC-relevant protein by computational modeling, enforced expression, silencing, RNA profiling, ChIP-Seq, luciferase reporter assays, flow cytometry, immunohistochemistry, in vivo experiments, functional assays, and surface plasmon resonance.

RESULTS: We have performed a master regulator analysis using 260 metastatic castration resistant prostate cancer (mCRPC) transcriptome profiles and developed a model transcription factor network. The transcription factor ONECUT2 (OC2) emerged as a prominent node. Microarray profiling identified a network of OC2-regulated genes that exhibit a highly positive correlation with NEPC signatures and a negative correlation with AR activation pathways. We observe elevated OC2 expression in NEPC clinical samples. We also find that loss of the master repressor REST during NEPC can result in up-regulation of OC2,

which thereby can impart NE features to mCRPC by direct up-regulation of the NEPC driver PEG10 and down-regulation of the NEPC inhibitor FOXA1.

Silencing OC2 potently suppressed growth and metastasis of CRPC cells in vivo. In-silico modeling revealed that OC2 can accommodate a small molecule in its DNA binding domain. We have identified a small molecule that phenocopies the effects of OC2 silencing. OC2 expression is associated with poor clinical outcome in NE cancer types other than prostate, suggesting that this pharmacological approach may benefit other NE cancer patients.

CONCLUSION: OC2 drives PC adenocarcinoma toward NEPC differentiation by blocking AR/FOXA1-activity and inducing PEG10. We have developed a novel drug-like inhibitor against OC2 that may be effective for patients with NEPC.