

ONECUT2 as a Central Regulator of Neuroendocrine Fate and Immune Silencing in Small Cell Lung Cancer

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Background: ONECUT2 (OC2) is a transcription factor (TF) recently identified as a regulator of lineage plasticity and tumor progression in prostate and small-cell lung cancers (SCLC). In this study we hypothesized that OC2 functions as a central regulator in SCLC and represents a novel therapeutic target.

Methods: We conducted a multi-omics analysis to investigate OC2 in SCLC, integrating bulk and single-cell RNA-seq, epigenomic profiling, and spatial proteomics. OC2 activity and its immune associations were assessed through transcriptomics and Phenocycler imaging. Epigenomic characterization, including chromatin accessibility and histone modification analysis, was performed to explore OC2 activation and regulatory targets. A TF activity-based classification framework stratified SCLC subtypes, and pathway analysis identified OC2-driven transcriptional programs. Preclinical models were used to assess sensitivity to OC2 small molecule inhibitors.

Results: OC2 expression and activity were linked to RB1 loss and low immune infiltration in SCLC. OC2 expression was predominant in epithelial cells that were spatially separated from immune cells, suggesting OC2 is involved in an immune-evasive process. TF-based classification suggests a broad regulatory role for OC2 across defined SCLC subtypes. Small molecule inhibitors of OC2 significantly impaired tumor cell viability in ASCL1- and NEUROD1-driven SCLC subtypes.

Conclusions: This study identified OC2 as a key regulator of lineage plasticity in SCLC, linking its activation to RB1 loss and immune exclusion. Multi-omics integration support significant influence from OC2 expression and activity on the immune microenvironment. These findings position OC2 as both a lineage driver and a therapeutic target in SCLC.

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