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Identification of Subtype-Specific Therapeutic Targets for Precision Medicine Applications in Small Cell Lung Cancer

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BACKGROUND: Small cell lung cancer (SCLC) is an incurable neuroendocrine cancer for which targeted therapies are lacking. Heterogeneity between tumors is evident and may underlie apparent failures in clinical trials. Therefore, personalized treatments based on tumor subtype are needed. Four SCLC subtypes have been described based on NE marker and transcription factor (TF) expression. SCLC-A is the preponderant subtype and is characterized by the TF Achaete-scute homolog 1 (ASCL1). The goal of the current study is to identify vulnerabilities specific to the SCLC-A subtype.

METHODS: We developed an innovative approach integrating epigenetics and proteomics. We identified super enhancers, which are cell type-specific genomic regions thought to regulate oncogene expression. They are enriched in the histone epigenetics mark H3K27ac. Therefore we performed H3K27ac ChIP-seq on 12 SCLC cell lines and 4 SCLC patient-derived xenografts (PDX) representing 3/4 known subtypes. This approach was complemented with proteomics to identify ASCL1 interactors in the SCLC-A subtype. Here, ASCL1 was immunoprecipitated from SCLC-A cells and immune pellets were analyzed by mass-spectrometry.

RESULTS: 1) All super enhancers identified for all cell lines and PDX models distribute across 3 groups, which is consistent with the current SCLC subtype classification. 2) Unique and shared super enhancer-associated genes were identified for SCLC-A and other subtypes. These represent potential subtype-

specific therapeutic targets. 3) 247 ASCL1-interacting proteins were detected in the SCLC-A subtype, including the TFs NKX2.1 and PROX1. 4) ASCL1, PROX1 and NKX2.1 co-immunoprecipitate in SCLC-A cells. 5) They bind ~2000 common regulatory regions on the SCLC-A genome. 6) ASCL1, PROX1 and NKX2.1 downstream targets include the ion channels SCN3A and KCNB2; 7) siRNA-mediated knock-down of ASCL1, PROX1 and NKX2.1 results in loss of SCN3A, KCNB2, and reduction in SCLC-A cell survival.

CONCLUSION: Overall, we demonstrate a strategy that stratifies tumors and identifies candidate tumor subtype-specific therapeutic targets.