Reprogramming normal human epithelial tissues to a common, lethal neuroendocrine cancer lineage

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Background: Current therapies inhibiting critical oncogenic pathways in epithelial cancers has led to multiple resistance mechanisms including the development of highly aggressive, small cell neuroendocrine carcinoma (SCNC). SCNC is increasingly appreciated in advanced cancer patients. Unfortunately, SCNC patients have a dismal prognosis due in part to a limited understanding of the molecular mechanisms driving this malignancy and the lack of effective treatments.

Methods: We utilized a human epithelial cell transformation assay in an organoid culture system to generate and investigate a genetically engineered SCNC tumor that recapitulates the histological and molecular features of clinical SCNC. Isolated primary human epithelial cells of prostate and lung were transduced with lentiviruses expressing a combination of oncogenic drivers, cultured as organoids, and transplanted into immunodeficient mice. The resultant tumors were analyzed by high-throughput sequencing techniques, RNA-seq and ATAC-seq, to investigate transcriptional and epigenetic profiles of the genetically engineered tumors.

Results: We demonstrate that a common set of defined oncogenic drivers, dominant negative *T**P**53,* activated **A**KT1, shRNA targeting ***R**B1,* **c**-MYC and **B**CL2 (**PARCB**) reproducibly initiate human prostate and lung SCNC from normal prostate and lung epithelial cells of multiple independent donors. These genetically engineered SCNC models fully recapitulate transcriptomes of human SCNC samples. We show that dual inactivation of p53 and Rb is required for driving histological and molecular features of prostate SCNC. Importantly, high-throughput sequencing techniques and computational analyses reveal that prostate and lung SCNCs have convergent cancer phenotypes in both the transcriptional and chromatin-accessibility landscapes despite normal human epithelial cells derived from prostate and lung possessing unique molecular landscapes. We identify shared active transcription factor binding regions in the reprogrammed prostate and lung SCNCs by integrative analyses of epigenetic and transcriptional landscapes.

Conclusions: Our study provides a novel platform to study the biology that drives and promotes SCNC phenotypes. Our findings suggest that SCNCs arising from distinct epithelial tissues share common vulnerabilities that could be exploited to develop novel therapeutic approaches for treatment and prevention of the emergence of SCNCs.

Conflict of Interest: No conflict of interest.

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