CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140143

Project Title:
Dependence of Small Cell Lung Cancer on the Basic Helix- Loop-Helix Transcription Factors Ascl1 and NeuroD1

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Small cell lung cancer (SCLC) is one of several highly aggressive neuroendocrine carcinomas that together account for 20-25% of lung cancers. Nicotine is a causative factor. Prognosis is poor; the five-year survival for SCLC remains close to 5%. Two transcription factors, Ascl1 and NeuroD1, are essential for brain development and are also required for development of the neuroendocrine cells in the lung. In addition to reporting on lung status through their connection to the nervous system, lung neuroendocrine cells make hormones and neurotransmitters that send information to other lung cell types to coordinate the clearing of airways, and may stimulate growth of cells to repair and maintain airways. These two developmental factors, Ascl1 and NeuroD1, are present in many SCLC and other neuroendocrine lung cancers and are required for survival of tumors in which they are expressed. In the previous funding period, we used genome-wide methods to identify genes regulated by each of these factors in lung tumor cells. Analysis of these gene networks indicates that Ascl1 and NeuroD1: act in different populations of lung cells, drive tumors by different mechanisms, and act primarily by inducing different gene expression profiles. Using a mouse model of SCLC, we found that knockout of Ascl1 blocked the appearance of lung tumors, demonstrating that it is critical in vivo for these lung cancers. In contrast, knockout of NeuroD1 enhanced tumor growth. These findings suggest that Ascl1 and NeuroD1 initiate tumors by affecting different cell types. In addition to cell-based experiments in the mouse model, we will use gene network information to investigate proteins required for cancers driven by Ascl1 and NeuroD1. We have honed in on ten high priority candidates from the gene networks with excellent characteristics for drug development that could become therapeutic targets.