CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180504

Project Title:
Elucidating the Epigenetic and Metabolic Vulnerabilities of Myeloproliferative Neoplasms

Award Mechanism:
Individual Investigator

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

Lay Summary:

Myeloproliferative neoplasms (MPNs) are progressive blood cancers that can strike anyone at any age, and for which there is no cure. MPNs are characterized by alterations of multiple signaling and epigenetic pathways, yet the molecular processes controlling MPN progression from chronic to leukemic transformation remain unknown. This is a major impediment for developing target-based therapies to selectively eliminate cancer stem cells to prevent disease progression and/or relapse. The challenge is twofold: 1) to identify the genetic complexity of MPN pathophysiology, and 2) to control the progression of MPNs from indolent to life-threatening stages. Inactivation of EZH2, the epigenetic enzyme critical for gene silencing, is one of the most frequent mutations in MPNs. We have developed a new genetic model of MPNs containing blood-specific activation of oncogenic RAS and inactivation of EZH2. While loss of EZH2 alone markedly accelerates disease progression to myelofibrosis and acute leukemia, concurrent inactivation of EZH2 and EZH1, a homolog of EZH2, completely abolishes MPN development. These results establish distinct roles of EZH1 and EZH2 in cancer pathogenesis, and highlight a specific epigenetic vulnerability for blood cancers caused by EZH2 mutations. In this project, we aim to elucidate the relationship between epigenetics and metabolism by focusing on the role of EZH1 and EZH2 in myeloid neoplasms. The central hypothesis is that EZH1 is indispensable for EZH2-deficient leukemia-initiating cells by differential regulation of gene expression and intracellular metabolism. We will determine the requirement of EZH1 for EZH2-deficient leukemia cells, the molecular targets regulated by EZH1 and EZH2, and the role of branched-chain amino acid metabolism in leukemia development. Our studies will identify epigenetic and metabolic vulnerabilities for blood cancers and provide new insights into generalizable principles to selectively eradicate cancer-initiating cells.