CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100202

Project Title:
Analysis of histone code alterations and the role of histone demethylase JMJD3 using CHIP-seq in myelodysplastic syndrome

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Myelodysplastic syndromes (MDS) refer to a group of myeloid disorders characterized by infective hematopoiesis, increased risk of transformation to acute myelogenous leukemia, and death. There are no curative therapeutic modalities for most patients with MDS. Precise identification of genomic regions associated with specific histone modifications would allow the identification of genes aberrantly active. The advent of whole genome chromatin immunoprecipitation (CHIP) and sequencing (seq) technologies allows unbiased identification of such regions in human cancer cells. We have performed CHIP-seq of the active histone mark H3K4me3 in MDS. Particularly, analysis of CD34+ MDS cells identified multiple aberrantly up-regulated effectors of the NF-?B pathway and the histone demethylase JMJD3 to be over-expressed in MDS. These results were validated in a cohort of ~60 patients with MDS. Disruption of this pathway had an effect on NF-?B signaling in myeloid leukemia cell line. Based on this, we hypothesized that: 1) systematic analysis using CHIP-seq of genomic areas associated with specific histone marks (H3K4me3) or histone modification activities (JMJD3) will allow the identification of altered genetic networks in MDS; 2) that genes identified with #1 could potentially serve as therapeutic targets in MDS, and 3) that JMJD3 plays an important role in the pathogenesis of MDS. To study these hypotheses, we propose 1) to perform CHIP-seq analysis for H3K4me3 and JMJD3 in a well characterized group of patients with MDS; 2) To study the clinical-biological and potential therapeutic value of gene/s identified with aim#1 in a large cohort of patients with MDS; 3) To study the role of JMJD3 in MDS in normal and MDS derived cells and mouse engrafts systems. The results of these aims will allow us to better understand the molecular biology of MDS.