CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160035

Project Title:
The role of Prdm16 and histone H3 lysine 9 methyltransferase complex in MDS

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

We will address how a transcriptional regulator Prdm16 controls histone-modifying enzymes to aberrantly promote epigenetic silencing in myelodysplastic syndromes (MDS). MDS is a heterogeneous hematological disorder characterized by insufficient hematopoiesis, morphological dysplasia, and frequent progression into acute myeloid leukemia (AML). Since MDS is more prevalent in the elder patients, potentially curative therapies such as bone marrow transplant (BMT), which have high therapy-related mortality for elders, is not available. MDS occurs not only de novo but also as a consequence of chemo- or radiotherapies against other malignancies. Thus, understanding the pathogenesis of MDS has broad impact not only in hematological malignancies but also in other malignancies. We have generated a mouse MDS model by expressing a mutant form of Prdm16 expressed in human MDS and leukemias. We also found that the mutant Prdm16 induced the expression of multiple histone-modifying enzymes involved in gene silencing. We are testing the hypothesis that the mutant Prdm16 aberrantly recruits histone-modifying enzymes to its target genes, repressing their expression, promoting the expansion of malignant cells. The significance of our proposal is emphasized by the recent observation that MDS is primarily an epigenetic disease with DNA and histone modifiers recurrently mutated, yet the role of histone modification in MDS pathogenesis is largely unknown. The results from our study may provide a foundation to develop new therapies against MDS aimed to fully compromise the aberrant epigenetic program by blocking histone modification.