Award ID:
RP140323

Project Title:
Role of a Novel Histone Variant-Specific Epigenetic Reader ZMYND11 in Breast Cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Our genetic information is stored in DNA. In eukaryotes, DNA does not exist in a free state, but rather is packaged by proteins called histone into the higher-order structure, namely chromatin. This kind of architecture allows dynamic control of the underlying DNA to be expressed at an appropriate time. The histone proteins are heavily modified, i.e. adding chemical groups such as methyl or acetyl to the amino acids of histones, which renders another layer of regulation. The methyl groups on histones function as platforms to recruit protein factors called readers, which in turn bring additional proteins to modulate chromatin structure and the accessibility of the underlying DNA. This research proposal focuses on ZMYND11, which is a transcriptional corepressor and is downregulated in multiple cancers such as leukemias, breast, kidney, and lung cancers. We found that in triple-negative breast cancers, low ZMYND11 expression is associated with worse progonosis, and that ZMYND11 depletion conferred normal human mammary epithelial cells epithelial-to-mesenchymal transition, and overexpression of ZMYND11 suppressed the growth of triple-negative MDA-MB 231 cancer cells. At the molecular level, ZMYND11 can recognize methylation on specific histone residue histone H3 lysine 36 (H3K36), and this recognition is histone variant-specific. All these preliminary but exciting results led us to hypothesize that ZMYND11 is an H3.3-specific reader of H3K36me3 that links transcription elongation control to the suppression of tumor growth in triple-negative breast cancer. This proposal will use a variety of approaches including biochemical, structural, molecular and cellular, genetic and genomic approaches as well as xenograft mouse model to test this hypothesis. The proposed study will provide insights into the molecular basis of the H3.3-specific recognition of K36me3 by ZMYND11, and will likely identify ZMYND11 as a novel and important tumor suppressor in breast cancer.