CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140367

Project Title:
Targeting BRD4 in Breast Cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Treatment of breast cancer based on histological diagnosis and detection of molecular markers present in cancer cells has been valuable in designing appropriate regimens for targeted therapy. Nevertheless, the clinical outcome remains uncertain due to the heterogeneity of tumor microenvironments and the genetic traits of individuals. Even though high-throughput sequencing technology has made it possible to profile an individual's genome for personalized medicine, many cancer-driver genes and their expression patterns often exhibit an undetectable or minor difference between cancer and normal cells. This highlights the need for developing new diagnosis and prognosis strategies. Recently, two small compounds against the epigenetic regulator BRD4 have shown promising anticancer effects in cultured cells and animal models associated with a subset of blood and solid (including breast) cancers. To understand the molecular basis of this drug sensitivity and target selectivity, we analyzed BRD4 protein status in seven breast cancer cell lines representing different progression stages and found that the long (L) form of BRD4 is found mainly in normal and immortalized but less aggressive breast cancer cells. In contrast, the short (S) form of BRD4 is predominantly expressed in highly aggressive breast cancer cells. This finding suggests that BRD4-L is tumor-suppressive and BRD4-S is oncogenic, and the transition between these two protein isoforms is indicative of the progression of breast cancer cells and their sensitivity to epigenetic drug treatment. We propose to test this intriguing hypothesis by defining the functional role of BRD4-L and BRD4-S in regulating breast cancer cell growth and gene expression using biochemical, molecular biological, synthetic chemistry, genomics, and proteomics approaches. These studies will unravel the mechanisms by which BRD4 regulates normal and cancer cell growth and will provide a rationale for BRD4-targeted cancer therapeutics.