CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160242

Project Title:
Mechanisms and targeting strategies for SWI/SNF mutations in cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

The Cancer Genome Atlas (TCGA) projects have revealed many important mutations in human cancers. Among them, mutations in the subunits of SWI/SNF chromatin remodeling complex show strikingly high prevalence in a wide spectrum of human cancers, collectively occurring in 20% of all human cancers. For example, mutations in the core subunit of Snf2/Brg1 are found in almost 100% of small cell ovarian cancer. Given the high frequency of SWI/SNF mutations in human cancers, an important question of high research priority is: Can we understand these mutations and make use of our findings in cancer treatment? To answer this question, in this application, we propose to take a comprehensive approach by combining the strengths of yeast biology, human cancer cell lines and animal models to address the following three questions: (1) How does SWI/SNF complex regulate the integrity of the genome? (2) What is the functional significance of patient-derived SWI/SNF mutations? (3) Can we selectively target SWI/SNF-deficient cancer cells?Our study will have broad and significant positive impacts for cancer patients. (1) We will show that tumors with SWI/SNF mutations are sensitive to a class of drugs called PARP inhibitors, which are already used to treat patients with other kinds of cancer. As such, our finding will lead to the establishment of PARP inhibitors as an effective, life-prolonging treatment for cancer patients with mutations of SWI/SNF. (2) We will identify how patient-derived mutations of SWI/SNF works and such information will be instrumental to genomic counseling. (3) We focus on Snf2/Brg1 subunit of SWI/SNF in ovarian cancer because it is almost 100% mutated in small cell ovarian cancer. Given the high prevalence of SWI/SNF mutations in other human cancers including kidney, liver, gastric, colon, pancreatic and lung cancers, our study will benefit not only patients with ovarian cancer but also more broadly patients with SWI/SNF-deficient tumors.