CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150084

Project Title:
Role of PTEN feedback mechanism in cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Over four decades ago, Alfred G. Knudson proposed a ground-breaking model for tumorigenesis, suggesting that cancer is a consequence of genetic mutations that inactivate specific genes which suppress the growth of cancer cells. This visionary working model has greatly advanced our understanding of cancer, and has directly led to the discovery of numerous tumor suppressor genes, including PTEN (phosphatase and tensin homolog). PTEN was found to be frequently disrupted in multiple sporadic tumor types, and mutated in the germlines of patients with cancer predisposition syndromes such as Cowden disease. PTEN protein is known to govern a plethora of cellular processes, including cell survival, proliferation, and metabolism, by suppressing the highly oncogenic PI3K-AKT-mTOR signaling pathway through its lipid phosphatase activity. Of interest, tumorigenesis is exquisitely sensitive to even subtle variations in PTEN dosage, and consequently, mechanisms regulating PTEN protein expression play a critical role in cancer susceptibility and tumorigenesis. Thus restoring PTEN functions in cancer directly or indirectly holds great therapeutic promise. In this proposal, inspired by our recent discovery of a novel PTEN feedback mechanism in metastatic prostate cancer and triple-negative breast cancer, we aim to verify our initial findings by a direct genetic approach in the mouse, explore their therapeutic potential, and maximize the response of tumor cells to targeted therapy while reducing harmful side effects to healthy cells. In addition, we expect that the innovative mouse models we develop for these studies will become invaluable tools in future cancer research, given their pleiotropic tumor phenotypes. We anticipate the outcomes of this project will open new avenues for genetic analysis, pathway studies and clinical applications, and should have a profound impact on our approach to cancer both in the clinic and the lab.