CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170086

Project Title:
Tumor suppression, p53 and retrotransposons

Award Mechanism:
Individual Investigator

Principal Investigator:
Abrams, John M

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

The p53 gene is mutated in a majority of human cancers. Collectively, these alterations represent the most common genetic change shared across the spectrum of tumors seen in patients. p53 belongs to a class of tumor suppressor genes that restrict tissue growth, but a definitive molecular explanation for how this gene prevents tumors still eludes us. To better understand actions of p53 that, when disabled, permit cancer formation we built a sophisticated genetic platform that enables functional interrogation of p53 variants seen in the clinic. From this we discovered that core functions of p53 are coupled to ancient factors that restrain mobile elements called retrotransposons (unlike most genetic material these can move to new genomic positions). Furthermore, all cancer associate variants were remarkably defective for this activity. Therefore, p53 mutations seen in patients probably disrupt links between this tumor suppressor and networks that silence mobile elements, triggering destabili ed genomes that are a well known hallmark of cancers. ur initiative tests predictions emerging from this hypothesis and defines the molecular mechanism by which p53 curbs mobile elements. Since p53 lesions frequently arise in all cancer types, our outcomes could enable new biomarkers and therapies that target retroelements and may have a broad impact. ther deliverables may enable formats that stratify mutant variants in ways that have clinical value, perhaps as tools to aid in the diagnosis of p53-driven cancers.