CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110076

Project Title:
Deconstructing oncogenic activity of p53 mutations

Award Mechanism:
Individual Investigator

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

Lay Summary:

The p53 gene is mutated in most human cancers. This molecular alteration represents perhaps the most common genetic change shared across the spectrum of tumors seen in the clinic. The product encoded by p53 belongs to a class of 'tumor suppressor' genes, which restrict tissue growth through a variety of mechanisms. Typically, both allelic copies of tumor suppressor genes are found to be lost or inactive in cancers. However, this is not seen for p53. Instead, one copy is typically lost while the remaining copy is retained, expressing a mutant form of the protein. So, why are these 'missense' p53 mutants regularly found in tumors? Thirty years after its initial discovery a definitive answer to this simple question still eludes us. Historically, intensive efforts were designed to understand the consequence of eliminating normal p53 gene action. However, recent evidence affirms long-held suspicions that p53 mutants actually acquire unknown activities pivotal for cancer formation. Studies described here adapt a rigorous genetic platform to understand how mutational variants of this tumor suppressor become endowed with new properties that convert it to an oncogene. We also investigate how this regulatory network intersects with the physiology of stem cells that are stressed by unscheduled growth or genotoxic agents. Work in this proposal is generally applicable to cancers, since p53 mutants appear in all cancer types and studies outlined here could illuminate novel therapies to attack their activity. In addition, we enable an alternative format for stratifying mutant variants in ways that may have clinical value, perhaps as tools to aid in prognosis or treatment.