CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170250

Project Title:
Regulation of 53BP1 by novel 53BP1-binding proteins in DNA repair

Award Mechanism:
Individual Investigator

Principal Investigator:
Chen, Junjie

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

Lay Summary:

Human cells have to constantly cope with DNA lesions that occur naturally or are induced by exogenous sources like sunlight exposure. Several distinct DNA repair pathways have evolved in humans that deal with different types of DNA damage. Interestingly, distinct DNA repair pathways sometimes compete with each other and lead to different outcomes such as cell death, senescence, and/or mutagenesis. Understanding the intricate relationships between these repair pathways is critical for cancer therapy, since radiation and many commonly used chemotherapeutic agents kill tumor cells by inducing DNA damage. The integrity of these repair pathways in cancers dictates the therapeutic response of patients to these treatments.

Indeed, the fundamental discovery of repair mechanisms that are dependent on BRCA1/2, two genes associated with breast cancer, has revealed the determinants of therapy responses in BRCA mutant cancers. BRCA mutant ovarian cancer displays appreciable response to poly (ADP-ribose) polymerase inhibitors (PARPis), which led to the recent approval of PARP inhibitor Lynparza (olaparib) for the treatment of advanced ovarian cancer patients with BRCA mutations. Unfortunately, treatment of BRCA mutant cancers with PARPi is not curative. Resistance to therapy is a major clinical problem, which necessitates approaches that will overcome this resistance and augment responses in BRCA mutant cancers. One major resistance mechanism is the loss of expression or mutations in other DNA repair proteins like 53BP1, which paradoxically restores DNA repair and renders BRCA1-deficient tumor cells resistant to PARPi. Our goal in this proposal is to define novel mechanisms of 53BP1 regulation and function in DNA repair. The proposed studies will be performed as a basic laboratory investigation, but the knowledge gained in these studies will reveal therapy resistance mechanisms and allow us develop more effective treatment strategies for cancer patients.