CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150102

Project Title:
Genome stability and immune diversity controlled by the POLQ pathway

Award Mechanism:
Individual Investigator

Principal Investigator:
McBride, Kevin

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

Lay Summary:

Genetic alterations are fundamental in cancer development. These arise frequently after the DNA in our chromosomes is damaged and broken. Such damage can occur when cells are exposed to background or medical radiation. Breaks are also introduced into DNA during normal processes that generate our immune systems. Such breaks can be dangerous, leading to deletions within genes, or to rearrangements between chromosomes. To defend against harmful consequences of DNA breaks, cells have mechanisms to repair them. This proposal deals with a new mechanism for DNA break repair that we have discovered, controlled by an enzyme called POLQ.

The POLQ-dependent repair process has profound consequences. First, we have discovered recently that it is a powerful defense pathway against chromosome translocations. Chromosome translocations abnormally join two DNA segments together, causing events which greatly contribute to the growth of cancer cells. Known translocations are estimated to drive about 20% of cancer cases. Lymphomas and leukemias have well-known perilous chromosome translocations, but they are also important in prostate cancer, lung cancer, and many other solid tumor types. Understanding the origin of translocations and finding ways to minimize their formation is an important problem in cancer research.

Second, we find that POLQ participates in a fundamental but little-studied mechanism that generates immune diversity. The immune system is an important tool in cancer defense and current therapy. Understanding the POLQ-controlled process in detail will open the possibility of manipulation to improve development of therapeutic antibodies against difficult targets. Moreover, higher expression of POLQ is correlated with poor outcome for several human cancers. We find that higher amounts of POLQ in cells confers protection against DNA breaks. Our proposed studies may therefore provide a basis for predictive studies regarding response of cancers to radiation treatment.