CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180553

Project Title:
Structural and Functional Characterization of the DNA Double Strand Break Processing Complex of Mre11-Rad50

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Texas Tech University

Lay Summary:

A hallmark of various forms of cancer is genomic instability caused by DNA damage, which can arise from hereditary or sporadic mutations. To combat the daily onslaught of unwanted DNA modifications, several parallel DNA repair systems have evolved to sense and repair the various lesions that affect our genome. When one of these repair systems goes awry, carcinogenic mutations and rearrangement of the DNA can occur. However, the recent success of new chemotherapies has shown that knocking out a second repair pathway presents a viable option for the fight against cancer (i.e., PARP inhibitors). Thus, it is critical to understand DNA damage repair pathways for both cancer prevention and treatment. DNA double strand breaks (DSBs) are a particularly detrimental form of damage, and at the heart of their repair process is the Mre11-Rad50-Nbs1 (MRN) protein complex. Central to understanding how this protein complex detects and repairs DNA DSBs is high-resolution structural studies that produce three-dimensional models describing in detail the shape of the complex. While several elegant studies have elucidated structural models for various components of MRN in different functionally important conformations, a picture of the full functional complex involving a DNA DSB remains elusive. The goal of this proposal is to determine structural models of the MRN complex bound to mimics of damaged DNA to allow for a better description of the motions that occur between various functional states. This work also seeks to characterize known MRN mutations that have likely lead to genomic instability and cancer in patients as well as a novel mutation that renders some cancer cells sensitive to existing chemotherapies. Success of this proposed work would present a better understanding of the working states of a critical DNA damage repair complex, increased knowledge for the initial steps in DNA DSB repair, and pave the way for future studies aimed at the discovery of novel MRN inhibitors.