CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1116

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
Miller, Kyle

Entity:
The University of Texas at Austin

Lay Summary:

After graduating from University, I received a Fulbright Fellowship to study nitrogen fixation in Senegal, West Africa. I spent a year collecting and molecularly characterizing new species of Rhizobium bacteria that are important in nitrogen fixation and agricultural plant production. I completed my Ph.D. with Julia Cooper at the University of Colorado Medical School and Cancer Research U.K. in London, England where I studied telomeres and how they function in genome maintenance. Telomeres define the ends of eukaryotic chromosomes and their preservation is one of the hallmarks of cancer. Using fission yeast as a model system, I studied the function of Taz1, the ortholog of the human telomere proteins TRF1/2. I found that Taz1 is critical in promoting genomic stability and telomere end-protection1-3. My work revealed an unanticipated role for Taz1 in promoting semi-conservative replication through telomeres. Using 2-D gel electrophoresis and genetic analysis, I found that replication forks often pause and break within telomere sequences and that Taz1 is required to promote replication fork progression through telomeres1. These findings defined a novel function for telomere binding proteins. Together, my work showed the importance of telomere proteins in protecting and replicating telomeres, a process critical for maintaining genomic stability and averting cancer. Importantly, this function of telomeres was later shown to be conserved in humans4. As a postdoctoral researcher with David Toczyski at UCSF, I analyzed the role of histone deacetylases (HDACs) in the DNA damage response (DDR) in budding yeast. My work revealed that the HDACs HST3 and HST4 are cell-cycle regulated and targets of the DNA-damage checkpoint. These enzymes regulate the histone modification H3K56Ac and deregulation of H3K56Ac renders cells extremely sensitive to DNA damage. Thus, the DDR functions to regulate chromatin through histone acetylations that participate in genome stability5. My work also led to the discovery of the novel HAT responsible for H3K56Ac, RTT109, which is required for genome maintenance in S. cerevisiae and S. pombe6,7.

To extend my work from model organisms into humans, I joined the lab of Stephen Jackson at the University of Cambridge, England. My training was supported by a Wellcome Trust project grant that I obtained to work on chromatin and the DDR. To determine the function of histone modifications in the DDR in human cells, we performed an extensive screen for DNA-damage-responsive histone marks. Although most histone marks are unchanged by DNA damage, H3K9Ac and H3K56Ac, represented two histone modifications that responded to DNA damageB. Collectively, this study revealed histone acetylations as being important targets in the cellular response to DNA damage in human

cells. As my work had implicated histone acetylations in the DDR, I performed a screen for HDACs that regulate these marks in human cells. I showed that HDAC1 and HDAC2 function in the DDR by localizing to DNA damage and deacetylating certain histone marks. Depletion of these enzymes rendered cells defective in DNA double-strand break (DSB) repair, particularly non-homologous end-joining (NHEJ), and sensitive to genotoxic stress9. These experiments for the first time linked chromatin with DSB repair by NHEJ. HDAC inhibitors represent a large class of anti-cancer drugs that have radio-sensitizing effects in patients. My work helped define the mechanism of action of HDAC inhibitors in cancer treatments. This work highlighted the need for HDAC1/2 specific inhibitors, which could be very effective in sensitizing cancer cells to the regular regime of existing cancer treatments, including radio- and chemo-therapies. I have recently extended my work on discovering the mode of action of potential anti-cancer drugs. Through a collaboration with chemists from the University of Cambridge that have designed a drug that binds specific DNA motifs in cells, we have discovered that the anti-proliferative effects observed for this compound occur through DNA damage induction10. Using ChIP-Seq of chromatin marks that define DNA damage sites, we have been able to map the affected genomic sites of this drug. Importantly, this analysis revealed that this drug leads to transcriptional inhibition of the oncogene SRC. Thus, I have used next-generation deep sequencing to define the in vivo targets of a drug10. This methodology should be widely applicable for determining in vivo targets of several classes of anti-cancer drugs, as well as proteins that function to maintain genome maintenance. My lab will continue this work in defining the role of chromatin in cancer and genome maintenance as well as determining the mechanism of action of anti¬cancer drugs, especially those compounds which function by inducing DNA damage, a pathway which is utilized by many chemo-theraupeutic agents in cancer treatments.