CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150094

Project Title:
Investigating the regulation of miRNA and lncRNAs by p63 in mammary tumor progression and metastasis

Award Mechanism:
Individual Investigator

Principal Investigator:
Flores, Elsa R

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

Lay Summary:

Mortality in cancer is most often due to the development of distant metastases for which almost no effective systemic treatments exist. P63, a family member of the tumor suppressor p53, is often used as a prognostic marker for the treatment of breast cancer. The functions of p63 are beginning to be understood in contexts in which p53 function has been well established, including in response to chemotherapy and radiation (Flores et al., Nature, 2002), in tumor suppression and metastasis (Su et al., Nature, 2010), and stem cell maintenance (Su et al., Cell Stem Cell, 2009; Chakravarti et al., PNAS, 2014). The overarching goal of this application is to develop treatments for metastatic breast cancer. We will do this by using mice generated in my laboratory with isoform-specific null alleles of p63 that have distinct roles in tumor suppression. Both TAp63-/- and deltaNp63+/- mice develop metastatic tumors, and TAp63 suppresses metastasis by regulation of small RNAs that can in turn target the expression of many genes. We have also extended these findings to multiple human tumor types including breast, skin, and lung cancer, indicating this function of TAp63 is widely important. DeltaNp63 also regulates small RNAs in skin stem cells further indicating that the regulation of small RNAs by p63 is critically important in the development and treatment of cancer. What is unknown is how each p63 isoform regulates small RNAs in critical suppression pathways of metastasis in the mammary gland. What is also unknown is how these small RNAs, making up the majority of our genome, function in cancer. In collaboration with Dr. Gunaratne and Dr. Coarfa (co-investigators), we will use our p63 mutant mice with breast cancer as preclinal models to identify non-coding small RNA targets that suppress breast cancer metastasis. We are well positioned to pursue these studies because of our published research in small RNA biogenesis and our unique mouse models.