CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170126

Project Title:
A Novel Pathway to Reduce BRCA1-Associated Breast Cancer Risk

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Breast cancer risk is significantly elevated for women who carry germ-line mutations in the tumor suppressor gene BRCA1. While breast tissue is composed of multiple cell types and all of them inherit the same BRCA1 mutation in mutation-carrying women, BRCA1-associated breast cancer specifically originates from a cell type called luminal progenitor cells. BRCA1 plays a critical role in repair of damaged DNA, which is universally important for all proliferating cells in the body. Thus, it remains a puzzle as to why breast luminal cells in BRCA1 mutation carriers are most susceptible to tumor development.

We recently uncovered an antagonizing relationship between BRCA1 and a dedicated transcription factor called NELF in regulation of breast luminal progenitor cell activity and breast tumorigenesis. Of note, this antagonizing link between BRCA1 and NELF is DNA repair-independent and luminal cell-specific. We therefore hypothesize that this previously unappreciated functional link contributes to tissue-specific development of BRCA1-associated breast tumors. We further propose that attenuation of NELF activity can reduce breast cancer risk among BRCA1 mutation-carrying women. To test this novel hypothesis, we have assembled a multidisciplinary team of laboratory and clinician scientists, and will combine mouse genetics, functional genomics, and comparative analyses of clinical samples. A better understanding of the DNA repair-independent antagonism between BRCA1 and NELF in the physiologically relevant tissue context will fill a critical knowledge gap and thus advance breast cancer research to a new level.