CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150403

Project Title:
On the role of DEAR1 in the regulation of cell polarity and progression from DCIS to invasive breast cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Ductal carcinoma in situ (DCIS) is one of the earliest forms of preinvasive breast cancer, and one of the most common findings on mammography. There is an urgent need to identify predictive and prognostic markers to identify DCIS with a heightened risk of progression to IDC for which more aggressive surveillance and treatment might be warranted, as well as individuals with favorable prognosis, who might be spared rigorous therapeutic regimens and for whom breast conservation therapy might be the preferred surgical option. To address this clinical issue, it is critical to identify the “drivers” of DCIS to IDC based on the underlying genetic abnormalities and aberrant pathways implicit in the progression of DCIS to IDC.

We have discovered a novel tumor suppressor gene, DEAR1, that we have shown regulates tissue architecture and polarity, an important property of normal cells to orient them properly in a particular tissue. We have also shown that DEAR1 regulates epithelial-mesenchymal transition (EMT), a process whereby cells lose their orientation or polarity, change their shape, become motile, invade and metastasize. Thus, loss of tissue polarity allows increased aberrant signaling from the tumor microenvironment to drive tumor metastasis, but the critical genes that regulate this communication are not known in DCIS. Our hypothesis is that DEAR1 regulates polarity and that loss of DEAR1 drives progression from DCIS to IDC. We will examine how DEAR1 regulates polarity, and study whether loss of DEAR1 results in migration and invasion from DCIS formed in a mouse model. This model will be treated with inhibitors of EMT and polarity to determine if inhibitors block progression from DCIS lesions. Our clinical goals are to develop a predictive biomarker panel and mutation signature to identify DCIS with the highest risk of progression to IDC and also to stratify aggressive DCIS for targeted therapies aimed at the polarity pathways regulated by DEAR1.