



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180259

Project Title:
PTEN Promotes Diabetic breast cancer metastasis

Award Mechanism:
Individual Investigator

Principal Investigator:
Lin, Chunru

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

Lay Summary:

Diabetic women have an increased risk of developing breast cancer compared to women with normal blood glucose levels; however, the responsible mechanism is not known. We have shown that PTEN, a famous tumor suppressor, is uniquely modified under high glucose conditions. This modification (PTENK27-polyUb) alters its activity, allowing it to dephosphorylate serine/threonine residues, including on proteins Twist1, Snai1 and YAP1, and promoting epithelial mesenchymal transition (EMT). This is significant because EMT has been shown to contribute to metastasis and drug resistance in breast cancer. In human breast cancer tissues, PTENK27-polyUb is elevated in hyperglycemic patients. Also, mice that lack PTENK27-polyUb had impairments in both mammary gland morphogenesis and lung metastasis.

To establish the molecular linkage between diabetes and breast cancer, we will accomplish the following specific aims: 1) characterize HOTAIR-regulated MEX3C-PTEN signaling induced by glucose; 2) demonstrate the serine/threonine phosphatase activity of PTEN K27-polyUb in dephosphorylating Twist1, Snai1 and YAP1 and promoting EMT; and 3) determine the role of PTEN K27-polyUb in promoting cancer metastasis under diabetic conditions using xenograft and genetically edited PTENK80R/K80R mice. The proposal elucidates a mechanism that contributes to hyperglycemia-induced tumorigenic effects and is significant to diabetic breast cancer patients. Successful completion of the objectives should reveal the mechanistic link between diabetes and breast cancer and should provide the rationale for developing anti-EMT therapies for diabetic breast cancer patients. This study will also clarify the importance of blood glucose management for breast cancer patients with diabetes, to curtail the increased risk of lung metastasis and chemoresistance. Future studies could evaluate the benefits of managing blood glucose levels in diabetic women as a preventive measure against breast cancer pathogenesis.