CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100188

Project Title:
Loss of Rho GDI alpha enhances metastasis and resistance to tamoxifen

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Estrogen receptor (ERa) is an effective treatment target in breast cancer, but sooner or later resistance develops and patients recur with metastatic lesions that do not respond to continued treatment. We discovered that a protein called Rho guanine disassociation inhibitor (Rho GDIa) was expressed at lower levels in metastatic ERa-positive tumors. Knockdown of Rho GDIa expression generated a tumor that was resistant to the antiestrogen tamoxifen which is used clinically to treat patients with breast cancer, and these cells with lower Rho GDIa metastasized at a high frequency. Rho GDIa knockdown also activated the Rho signaling pathway known to be involved in tumor metastasis, and increased downstream p21-activating kinase (PAK1) activity, increasing ERa phosphorylation at serine 305. This leads to inappropriate activation of ERa. Levels of the metastasis-associated protein MTA2 protein were also enhanced with Rho GDIa knockdown, so that Rho GDIa/MTA2 levels combined may predict breast cancer recurrence in tamoxifen-treated breast cancer patients. In Aim 1 of the grant, we will examine Rho GDIa's effects on ERa, and in Aim 2 we will determine how Rho GDIa affects MTA2 function. Aim 3 will determine if Rho GDIa and MTA2 together predict clinical breast cancer hormone response and patient outcomes. Breast cancer metastasis remains the most significant clinical problem we face in breast cancer, and the ultimate cause of mortality in patients. We hope that we have identified a "chink in the armor" of breast cancer which has the potential to greatly facilitate successful treatment.