Award ID:
RP150197

Project Title:
Understanding How NCOA6 Suppresses Endometrial Cancer by Inhibiting the Wnt/beta-Catenin Pathway

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Endometrial cancer (EMC) is a disease with high mortality. Enhanced uterine (U) sensitivity to estrogen (E), activation of the Wnt/beta-catenin (W/bC) pathway and inactivation of the Pten tumor suppressor are main driving forces of EMC. However, it is unknown what controls the U E sensitivity and holds the W/bC activity to prevent EMC. Our preliminary study suggests that NCOA6, a gene expression coregulator, may be a potent suppressor of EMC by inhibiting the U E sensitivity and W/bC activation. We found NCOA6 is frequently mutated in human EMC. Deletion of NCOA6 from mouse uterus increased E sensitivity, activated the W/bC pathway, caused EMC development and accelerated the growth of EMC with Pten deletion. Thus, we hypothesize that NCOA6 is a novel tumor suppressor in the endometrial epithelial cells (EECs), and it suppresses EMC by repressing U E sensitivity and W/bC activation. In specific aim 1 (SM1), we will implant Pten null EECs with and without NCOA6 into normal uteri to test if NCOA6 null EECs will develop EMC faster than EECs with NCOA6. We will also delete NCOA6 in either EECs or stromal cells in mouse uteri to examine the cell type-specific tumor suppressor function of NCOA6. We predict NCOA6 in EECs is responsible for its tumor suppressor function. In SA2, we will elucidate the mechanism by which NCOA6 upregulates sFRP2, sFRP4, Dkk3 and Axin2 genes to inhibit W/bC. These 4 genes are in vivo inhibitors of W/bC and their expression is downregulated in NCOA6 null EMC cells. We will identify specific transcription factors that work with NCOA6 to drive the expression of these 4 genes. We will also test if restoration of the expression of these 4 genes or the usage of chemical W/bC inhibitors will inhibit EMC growth induced by NCOA6 deficiency. These studies will prove NCOA6 as a new EMC suppressor and offer a pre-clinical proof of concept for restoring NCOA6 function or inhibiting the NCOA6 mutation-activated W/bC as therapeutic strategies for EMC.