CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140429

Project Title:
The Role of DIRAS3 (ARHI) in Initiating Autophagy and Tumor Dormancy

Award Mechanism:
Individual Investigator

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

Lay Summary:

Each year in our country, more than 22,000 women develop ovarian cancer. Despite progress in surgery and chemotherapy, the disease still proves lethal in 70% of cases. One reason for poor outcomes is the ability of metastatic ovarian cancer cells to remain dormant for years after treatment, only to grow progressively and kill patients. Little is understood of this process. Our group has developed the first mouse model for tumor dormancy in ovarian cancer and has shown that “autophagy” is required to maintain cancer cells in a nutrient poor environment with a poor blood supply. Through “autophagy” or “self-eating”, cancer cells consume their own parts to generate much needed energy. In earlier studies, we have found a “tumor suppressor” protein called DIRAS3 that puts the brakes on cancer cell growth, initiates autophagy and induces dormancy. The DIRAS3 protein is found in normal cells, but is lost in 60% of ovarian cancers, as well as in a majority of cancers from different organs. DIRAS3 protein can be lost in cancers by several different mechanisms. Replacement of DIRAS3 protein can inhibit cancer cell growth, slow motility, regulate autophagy and sustain tumor dormancy. As DIRAS3 is important for inducing tumor dormancy, we will first determine why levels of DIRAS3 protein increase when starving ovarian cancer cells are deprived of the building blocks of protein. Then we will determine how DIRAS3 turns on autophagy in combination with the BECN1 protein. Under normal conditions, BECN1 is prevented from inducing autophagy by winding around a second BECN1 molecule and sticking to a third protein called Bcl-2. We will test whether DIRAS3 acts by physically displacing Bcl-2 from the two BECN1 molecules and unwinding the pair of BECN1 proteins. Finally, we will develop novel “targeted” protein that acts like a drug to block the ability of DIRAS3 to initiate autophagy and to induce dormancy, making cancer cells more susceptible to elimination.