CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140408

Project Title:
Identification of a Novel Mechanism of mTORC1 and Autophagy Regulation for Cancer Therapy

Award Mechanism:
Individual Investigator

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

Lay Summary:

Breast cancer is a second most common cancer worldwide. Among several subtypes of breast cancer, triple negative breast cancer (TNBC) represents the most aggressive form of this disease, which accounts for 15-20% of breast cancer. There is no effective targeted therapy thus far for this disease. Chemotherapy is the major option for it. Although the patients with TNBC show initial response to the chemothrapy, they soon relape and the resistant mechanisms against this treatment subsequently occur. Therefore, it is very urgent to deveop a novel, effective thargeted therapy for TNBC. Our recent studies and preliminary results identified Skp2 is overexpressed in breast cancer and is required for TNBC progression and metastasis using mouse models, suggesting that targeting Skp2 is a promising strategy for TNBC. Morevoer, we identified Skp2 as a novel regulator for mTORC1, a critical player in cancer development, and autophagy. Autophagy is a self-digestion process and is a critical event that maintains cell homeostasis. Although autophagy is intially thought to be a tumor suppressive singal, recent studies suggest that autophagy is required for cancer development and progression in certain contexts. Thus, autophagy plays a dual role in cancer suppression and promossion depending on celluar contexts. Importantly, we show that simultaneously targeting Skp2 and mTORC1 using genetic and pharmacological apporches results in lethality in TNBC cell models. The goal of this study is to determine how Skp2 regulates mTORC1 activation and autophagy and to examine the efficacy of the combination of Skp2 and mTORC1 targeting in TNBC in vivo using animal models. Our study not only reveals a new mechanim by which mTORC1 and autophagy are regulated, but also unravels a novel concept that autophagy regulation can be applied as a new strategy for TNBC treatment. Our study is very novel and significant and may lead to a new effective treament for TNBC and other cancers.