CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120168

Project Title:
Identification of Rheb and Notch-dependent Pathways in Tuberous Sclerosis Complex

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Texas Tech University Health Sciences Center

Lay Summary:

Tuberous sclerosis complex (TSC) is an inherited disease characterized by the presence of seizures, mental retardation, autism and tumors in multiple organs, including the brain, skin, lung, heart, and kidney. TSC is a result of mutations in either of two genes, TSC1 or TSC2, leading to the activation of the mammalian target of Rapamycin (mTOR). Abnormal differentiation is a hallmark of TSC lesions. For instance, brain lesions contain “giant cells” that inappropriately contain (express) proteins (markers) typical for neurons and glial cells The presence of both types of proteins suggests a lack of terminal differentiation, since only undifferentiated cells but not terminally differentiated cells (i.e. neuron or glia) can express both markers. Similarly, lung and kidney tumors lack terminal fate commitment since they express multiple differentiation markers. Notch family genes regulate cell fate decisions. For instance, Notch inhibits neuronal differentiation and promotes a glial differentiation. One would predict that TSC cells with their co-expression of neuronal and glial markers have dysregulation of Notch signaling. Indeed, we recently reported that Rheb activates Notch independently of mTOR. Thus, we hypothesize that combining Notch inhibition with other agents such as mTOR inhibitors will be effective form of therapy for TSC patients. Pre-clinical studies strongly suggest potential clinical applications for Notch inhibitors in cancer therapy and some of these inhibitors are already in clinical trials. It is expected that there will be substantial efforts in identifying more specific compounds to target the Notch pathway with lower toxicities for patients. It would be important to test these novel Notch inhibitors in relevant mouse models before testing in TSC patients.