CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150319

Project Title:
Leukemia inhibitory factor receptor signaling and function in cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Deregulation of signaling pathways that control organ size, such as the AKT-TOR and Hippo-YAP pathways, can lead to tumorigenesis and metastasis. A major barrier in eradicating the death and suffering from breast cancer is the shortage of clinically proven prognostic markers and therapeutic agents for metastasis. Although many breast cancer metastasis-promoting genes have been reported, they have not been translated into clinical benefits except HER2. On the other hand, few genes have been established as metastasis suppressors. Using a high-throughput sequencing approach, our laboratory identified leukemia inhibitory factory receptor (LIFR) as a novel breast cancer metastasis suppressor downstream of the miR-9 microRNA (miRNA) and upstream of Hippo signaling. We found that LIFR suppresses both invasion and colonization steps of metastasis by promoting cell membrane localization of Scribble, leading to activation of a Hippo kinase cascade and functional inactivation of the transcriptional co-activator YAP. We found that LIFR is commonly downregulated in all subtypes of human breast cancer, and that loss of LIFR in non-metastatic stage I-III breast tumors is highly associated with poor clinical outcomes in approximately 1,000 patients. In this project, we will determine the mechanism by which LIFR promotes Scribble membrane localization and activates Hippo signaling. To investigate the role of LIFR in regulating Hippo signaling, tumorigenesis and metastasis in vivo, we have generated a Lifr conditional knockout mouse model, and confirmed that Lifr is indeed required for activation of the Hippo pathway in mice. In addition, the functional YAP target CTGF is likely to be a therapeutic target, and thus we will test a human CTGF-neutralizing antibody (FG-3019, Fibrogen) as a therapeutic agent in preclinical models. These studies will reveal new molecular mechanisms underlying tumorigenesis and metastasis and novel targets for therapeutic intervention.