CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP110178

Project Title:
Identification of the MicroRNAs-TRAF6 pathway as a therapeutic target for prostate cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Growth-factor receptors undergo ubiquitination upon ligand engagement, which is known to be critical for receptor internalization to the early endosome. It is unclear whether ubiquitination of the signaling components downstream of growth-factor receptors is also critical for protein trafficking and signaling activation. Our study has shown for the first time that protein kinase Akt/PKB undergoes K63-linked ubiquitination by E3 ligase TRAF6 within the PH domain, which is critical for Akt/PKB membrane recruitment and subsequent phosphorylation and activation. Our study has several novel and important findings. First, we have identified that TRAF6 is a direct E3 ubiquitin ligase for Akt/PKB, which is required for endogenous Akt/PKB ubiquitination and phosphorylation upon IGF-1 stimulation. The finding that WT TRAF6, but not its E3 ligase dead mutant, rescues defects of Akt phosphorylation and cell survival in Traf6-/-MEFs upon stimulation with various growth factors suggests that activating E3 ligase activity of TRAF6 by various growth factor signals, such as IGF-1, is likely required to target Akt to the plasma membrane, in turn inducing Akt phosphorylation. Since TRAF6 is known to play an important role in TLR signaling and the innate immune response, our results expand its known role in not only the inflammatory response but also the survival and oncogenic signaling pathway. Finally, our study suggests that aberrant Akt ubiquitination observed in the cancer-associated mutant (Akt E17K) contributes to its constitutive Akt membrane localization and T308 phosphorylation. In summary, our findings that TRAF6 is critical for Akt ubiquitination, phosphorylation, and tumorigenesis. With the predicted outcome, our proposal will advance not only our current understandings of how the oncogenic Akt signal is regulated, but also suggests that microRNAs (miRNAs) /TRAF6 targeting may be an attractive approach for the treatment of human cancers.