CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170572

Project Title:
Probing Novel Concepts of the NF-kappaB Transcriptional Program in Human Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Normal cells produce master transcriptional regulators that control key biological processes. The genetic inactivation of these factors and the processes that control their activity promote cancer development. One of these transcriptional regulators is NF-kB, which modulates the synthesis of a vast array of genes that control inflammation and cell survival. Deregulated NF-kB activation (oncogenic addiction) leads to chronic inflammation and uncontrolled cell growth (both cancer drivers). Thus, selective inhibition of the NF-kB pathway to induce cell death has emerged as a rational therapeutic approach to combat cancer. To date, however, no clear unique mechanism exists to target cancer cells to oncogenic NF-kB activation. One common mechanism by which NF-kB controls cell survival (leading to tumor growth) is by inducing the synthesis of a set of pro-inflammatory and pro-survival genes, leading to inflammation-associated cancer. Thus, by understanding the mechanisms by which NF-kB synthesi es these genes we might be better poised to design alternative approaches to selectively target cancer cells over normal cells. NF-kB has no en ymatic activity, and thus it is not an appropriate target. However, NF-kB associates with factors that contain en ymatic activities required for turning-on its regulatory program. e have recently identified one novel and critical regulator of NF-kB transcription, whose activity promotes oncogenic addiction to NF-kB, and thus emerges as a key therapeutic target. The goal of this research proposal is to elucidate the function of this regulator of NF-kB in both normal and oncogenic states. Finally, the knowledge generated from this study will be exploited to examine the therapeutic potential of targeting this en yme in a variety of human cancers addicted to oncogenic NF-kB including breast, colon, lung, and lymphomas.