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YOU ARE INVITED TO ATTEND THE

DEFENSE OF THE DOCTORAL

DISSERTATION

"Novel RBP-Jk splice variant inhibits canonical Notch signaling and reduces proliferation of Non-small cell lung cancer cells"

by

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Molecular Biology, Genetics, & Cancer Track

B.S., 2010, Syracuse University

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Department of Microbiology, Biochemistry, and Molecular Genetics

Monday, January 25th, 2021
11AM

Meeting Link:
https://zoom.us/j/6392078077?pwd=cTVXZHRDalp4ZTFLSkY5ZlBwQXVHUT09
Meeting ID: 639 207 8077 Passcode: CLG12521

ABSTRACT

Recombination signal binding protein immunoglobulin region kappa (RBP-Jk) is a sequence specific DNA binding protein and the major effector of the canonical Notch Signaling Pathway. Notch signaling has been extensively studied due to its etiologic role in viral and non-viral cancers. However, most biochemical and genetic models for Notch target gene transcription have considered only a single RBP-Jk isoform, canonical RBP-Jk1 (Jk1). Our lab has discovered a novel isoform, RBP-JkP10 (JkP10) whose transcript lacks a Jk1 exon which encodes protein surfaces predicted to bind activated Notch1 (NICD1) and mastermind like transcriptional coactivator (MAML1). Those interactions are necessary to form the Notch1 transcriptional activation complex.

Fluorescence Activated Cell Sorting (FACS) of Notch driven, Non-Small Lung Cancer (NSCLC) cells showed that ectopic expression of JkP10 reduced expression of the cell proliferation marker Ki67 and increased cells in the S phase measured by Propidium Iodide. Ectopic JkP10 increased NSCLC cell's fractionalized DNA content and caspase 3/7 activity. Measured by RT-qPCR, ectopic JkP10 reduced the expression of c-MYC and Cyclin D1. We hypothesized that ectopic JkP10 reduced the growth of NSCLC cells by repressing transcription of Notch1 target genes.

In RBP-Jk null B-cells, ectopic JkP10 reduced the expression of c-MYC and Cyclin D1 and luciferase expression of Notch target promoter reporter vectors. By fusing Jk isoforms to the VP16 transactivation domain we demonstrate that JkP10 binds DNA and can compete with canonical Jk1 for promoter binding. Supporting the prediction that cognate JkP10 may be unable to form a transcriptional activation complex with NICD1, we found that ectopic Jk1 but not JkP10 rescued transactivation of Notch target promoters by ectopic NICD1 in the Jk null cells. However, co-immunoprecipitation experiments have been unable to confirm that JkP10 fails to interact with NICD1.

Molecular Beacon probes showed that the ratio of JkP10 to Jk1 transcript is greater in non-malignant lung epithelial cells compared to NSCLC cells, suggesting JkP10 could be tumor suppressive in lung epithelial cells. We hypothesize JkP10 inhibits Notch1 signaling by binding to Notch1 target promoters and remaining in a transcriptionally repressive state due to its inability to form a productive transactivation complex with NICD1.