Abstract #1 | Poster

Targeting Wnt/β-Catenin–PI3K/AKT Crosstalk: Insight into lineage restricted B cell Oncogenic Co-operation

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The Wnt/β-catenin and PI3K/AKT signaling pathways are among the most evolutionarily conserved and ubiquitously active pathways which governs cellular growth, metabolism, survival, and fate determination. Traditionally studied as independent signaling cascades, several evidences suggest important crosstalk between these pathways, particularly in regulating metabolic reprogramming and maintaining cellular homeostasis. Dysregulation of these signaling networks has been strongly seen in hematological malignancies, including B-cell leukemia/lymphoma. In this study, we hypothesise that Wnt/β-catenin and PI3K/AKT signaling are strongly interconnected in B-cell leukemia/lymphoma to cooperate and to sustain leukemic cell physiology. Aberrant modulation of either pathway, or disruption of their coordinated signaling, results in profound cellular stress and altered immune responses, ultimately contributing to leukemogenesis. Our central hypothesis is that the Wnt/β-catenin and PI3K/AKT pathways work together, and their interaction may contribute to enhanced survival, proliferation and resistance to treatment, impacts on tumor suppressive function, and contributes to oncogenic transformation in Leukemia/Lymphoma. We will test the hypothesis in the following specific aims:

We are testing our hypothesis using four different objectives.

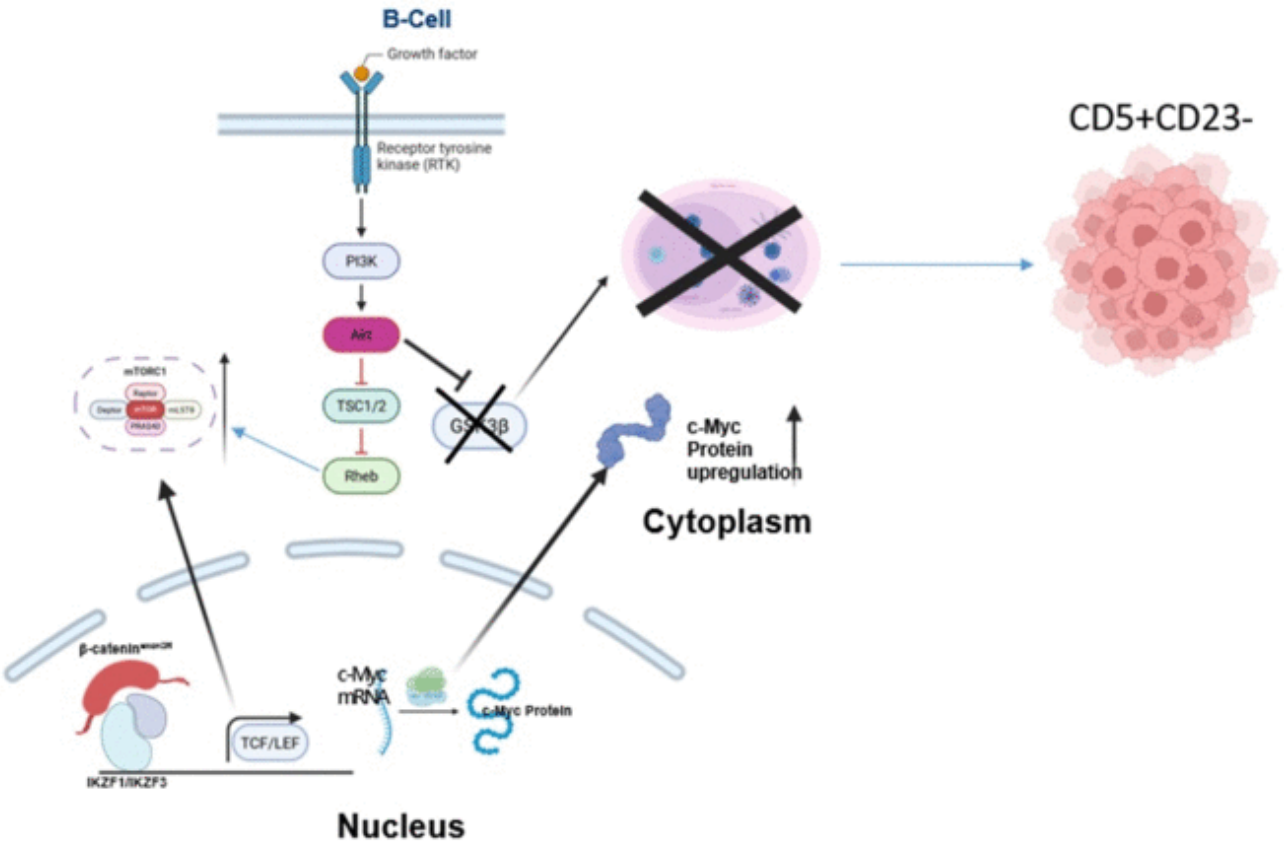
Objective 1: Determine possible modulations of β-catenin and AKT signaling in different Lymphoma cells *in vitro*.

Objective 2: Determine whether combined overactivation of of β-catenin and AKT *in vivo* alters specific type of Lymphomagenesis and resulting in a therapeutic advantage

Objective 3: Determine the role of T cell modulation driven by combined overactivation of β-catenin and AKT in B cells in Immune regulation and Tumor progression.

Objective 4: Investigate the oncometabolic profile of B cell lymphoblasts with altered PI3K/AKT and Wnt/β-catenin pathways.

Together, our approach may reveal how B-cell leukemia/lymphoma maintains stem-like properties and develops resistance to certain treatments. Understanding the interaction between the PI3K/AKT and Wnt/β-catenin pathways could help explain long-standing challenges in treatment resistance and disease persistence



Wnt canonical signalling and PI3K/AKT crosstalk underlies lineage-restricted oncogenic cooperation

AKT overactivation and β-Catenin Stabilization
→ Inhibits GSK3β
→ Stabilizes β-catenin
→ Enhances IKZF1 expression
→ Modulates mTOR signaling
→ Drives clonal expansion of $CD5^{+}$ MZ-like B cells