CHRD 2024: Abstract Submission Form

Presenter Name
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Presenter Status
PhD Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
THE LMO2 ONCOGENE ESTABLISHES AUTOCRINE FLT3 SIGNALLING IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Background
Everyday, a Canadian family receives heartbreaking news: it's T-cell Acute Lymphoblastic Leukemia (T-ALL). This aggressive blood cancer is a subtype of acute leukemia, the most common childhood cancer. T-ALL is molecularly defined by oncogenes like LMO2, which is associated with poor outcomes and mutations in signaling pathways including FLT3. Although aberrant activation of FLT3 has been shown to promote drug resistance and relapse, how FLT3 is dysregulated in T-ALL remains poorly understood.

Objective
We hypothesize that FLT3 cooperates with LMO2 to drive leukemia progression and relapse. To address this, we will 1) assess the functional relationship between LMO2 and FLT3, and 2) define how FLT3 signaling is dysregulated in T-ALL.

Methods
We have utilized ChIP-seq, RNA-seq and ATAC-seq, combined with flow cytometry to understand how LMO2 regulates FTL3 in our Lmo2-driven (Lmo2Tg) mouse model of T-ALL. To assess LMO2-mediated regulation of FLT3 signaling, we performed co-culture assays and utilized ELISA to measure FLT3-Ligand (FLT3-L). To decipher FLT3 signaling regulation, we performed flow cytometry of cells treated with the FLT3 inhibitor Gilteritinib. Statistical method: 2-way Student's t-test (Mean ± SEM).

Results
ChIP-seq data revealed that both FLT3 and FLT3-L are transcriptional targets of LMO2, thereby leading to aberrant co-expression in T-cell progenitor populations responsible for progression in Lmo2Tg T-ALL. ELISA confirmed that preleukemic Lmo2Tg T-cell progenitors secrete 13.1 ± 5.1 more FLT3-L than their normal counterparts. Incubation of conditioned media from preleukemic Lmo2Tg T-cell progenitors led to activation of FLT3 signaling, which can be inhibited using Gilteritinib. Importantly, our data suggests Lmo2 induces an autocrine FLT3 signaling loop in relapse-inducing cells, which are known to drive T-ALL progression and relapse.

Conclusion
Both FLT3 and FLT3-L are transcriptionally regulated by the initiating oncogene LMO2, thereby establishing an aberrant LMO2-induced autocrine FLT3 signaling loop in T-ALL.

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No

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