

Public Abstract

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Title:RNA-sequencing analysis in B-cell acute lymphoblastic leukemia reveals aberrant gene expression and splicing alterations

B-cell acute lymphoblastic leukemia (B-ALL) is a neoplasm of immature lymphoid progenitors and is the leading cause of cancer-related death in children. The majority of B-ALL cases are characterized by recurring structural chromosomal rearrangements that are crucial for triggering leukemogenesis, but do not explain all incidences of disease. Therefore, other molecular mechanisms, such as alternative splicing and epigenetic regulation may alter expression of transcripts that are associated with the development of B-ALL. It is important to investigate alternatively spliced RNA transcripts that may be affected by aberrant DNA methylation in B-ALL to gain a better understanding of the pathogenesis of this disease.

The goal of this thesis is to characterize the transcriptome landscape of patients with B-ALL using high throughput RNA-sequencing (RNA-seq) analysis. Specifically, the study aims to identify particular genes and their isoforms that might be controlled by aberrant DNA methylation in B-ALL and contribute to the development of this disease. By analyzing transcriptional patterns between B-ALL patients and healthy cord blood donors differentially expressed and alternatively spliced RNA transcripts have been identified. By examining differentially expressed genes with Ingenuity pathway analysis, the most significant signaling pathways and gene functions have been annotated. By analyzing causative gene networks, novel upstream regulators have been determined for B-ALL patients. Finally, a mechanistic study has been conducted using an in vitro B-ALL model to investigate if aberrant DNA methylation affects alternatively spliced genes associated with this disease.

Our pathway-centric approach may help to explore and characterize novel aberrant gene expression patterns for B-ALL patients, thereby complementing previous research findings aimed at deciphering the pathogenesis of B-ALL. Moreover, identified alternatively spliced transcripts may help better understand the molecular basis of post-transcriptional gene regulation in the context of B-ALL. By inferring a role for DNA methylation in the expression of alternatively spliced isoforms, new avenues might be explored for improved diagnosis, management and treatment of B-ALL patients in the future.