RNA-SEQUENCING ANALYSIS IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

REVEALS ABERRANT GENE EXPRESSION AND SPlicing ALTERATIONS

Olha Kholod and Kristen Taylor

ABSTRACT

B-cell acute lymphoblastic leukemia (B-ALL) is a neoplasm of immature lymphoid progenitors that is a leading cause of cancer-related death in children. The majority of B-ALL cases are characterized by recurring chromosomal rearrangements that are crucial for triggering leukemogenesis, but do not explain all incidences of disease. Therefore, the identification of aberrant gene expression patterns that may impact the development of B-ALL is important to gaining a better understanding of the pathogenesis of the disease.

To determine differentially expressed (DE) and spliced RNA transcripts in B-ALL patients RNA-seq analysis was performed. Using edgeR package, 3877 DE genes between B-ALL patients and healthy donors based on TMM (trimmed mean of M-values) normalization method and false discovery rate, FDR < 0.01 were identified. IPA revealed abnormal activation of ERBB2, TGFB1 and IL2 transcriptional factors that are crucial for maintaining proliferation and survival potential of leukemic cells. B-ALL specific isoforms were observed for genes with roles in important canonical signaling pathways, such as oxidative phosphorylation and mitochondrial dysfunction. A mechanistic study with the Nalm 6 cell line revealed that some of these gene isoforms significantly change their expression upon 5-Aza treatment, suggesting that they may be epigenetically regulated in B-ALL.

These results further our understanding of the transcriptional regulation associated with B-ALL development and will contribute to the development of novel strategies aimed towards improving diagnosis and managing patients with B-ALL.