ORT_12 - Identification of new targets for T-Cell Acute Lymphoblastic Leukemia therapy through Systems Biology

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Introduction: T-cell acute lymphoblastic leukemia (T-ALL) accounts for 12% to 15% of all cases of ALL diagnosed in children and 25% in adults. It is a genetically heterogeneous disease caused by the malignant transformation of T-cell precursors. Twenty percent of all T-ALL patients relapse within two years after diagnosis. Recurrent disease is challenging to cure, and relatively few new drugs have been developed for children with resistant disease. Intensive care is essential to improve the chances of survival in patients. However, the treatment is very long and not rarely, with life-threatening side effects. Identifying new molecular targets in T-ALL is essential to minimize and overcome the harmful impacts of current therapeutic regimens.

Objectives: Our goal is to identify these targets by evaluating differentially expressed genes in T-ALL along with the application of systems biology in order to identify highly connected proteins.

Methodology: We used RNA-seq data (freely available in databases) of peripheral T cells and thymocytes at different stages of maturation from healthy individuals for comparison with the RNA-seq of Jurkat and MOLT-4 T-ALL cell lines. Normalized controls' RNA-seq data were subtracted from cell lines' RNA-seq data to calculate the differential expression. Proteins classified as overexpressed were extracted from the reference list of interactome genes (IntAct, 2017 version, EBI) to calculate the number of connections of each gene.

Results: Five of the ten main targets for each cell lineage were common to both, including oncogenes, chaperones, regulatory proteins, and histone modifiers. However, unique genes were also identified for each cell lineage. More importantly, the identified targets showed few differences depending on the control used for comparison, suggesting that our method is consistent.

Conclusion: Therefore, we successfully identified new therapeutic targets not previously described in the literature and initiated knockdown experiments to express specific shRNA molecules for the target genes to reduce the amount of corresponding proteins in the cell lines and evaluate the cell phenotypes in the future.

Keywords: Leukemia, T-ALL, Systems Biology