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Integration of Transcriptome and Proteome Datasets for Finding Novel Biomarkers in Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is characterized by abnormal proliferation, differentiation, and accumulation of lymphoid precursor cells in bone marrow. Understanding the biological mechanism behind the disease and finding disease-related biomarkers is a critical issue since the cure rate among patients needs to improve. In this regard, we firstly collected deregulated proteomics and transcriptomics data in ALL from public databases. Then, the listed gene-related miRNAs and transcription factors were identified as two main gene regulators. Moreover, the regulatory sub-network of the miRNA-TF-gene was constructed and the most important genes and TFs were identified including CCND2, TP53, ALDOA, GATA6, NFIC, YY1, and TPM3. Besides, the GO-ontology of the collected gene list was determined using the DAVID bioinformatics tool. Among the enrichments, cell cycle, cell division, gluconeogenesis, and apoptosis were identified as the most significant processes. This work will provide some significant genes and TFs and pathways associated with the ALL pathology.

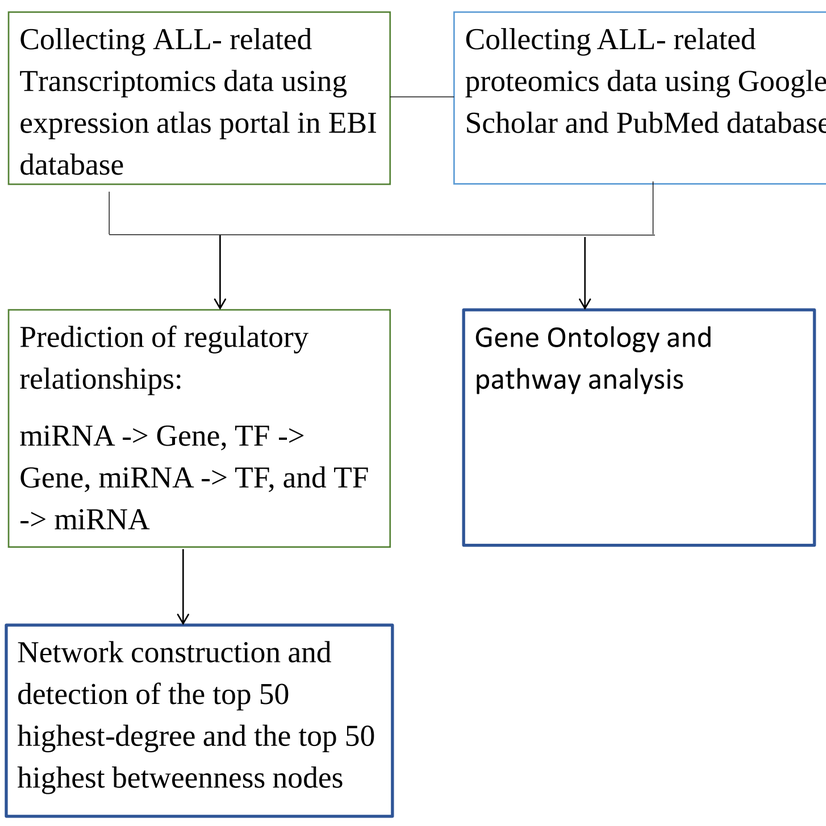
Keywords: Regulatory network, Transcription Factor, Proteomics, Transcriptomics

Introduction

Acute lymphoblastic leukemia is characterized by abnormal proliferation, differentiation, and accumulation of lymphoid precursor cells. The etiology of ALL is largely unknown in most cases and it makes our understanding of the disease so complicated. The strongest association to date exists with genetic factors. Despite being characteristic hallmarks of ALL, these chromosomal abnormalities are not enough to generate leukemia. No specific genetic changes have been identified to be used for treatment or prognosis of ALL so far. Studies show that current advances of the existing therapeutic agents have enhanced the survival rate in affected children by higher than 90% . Whereas, the cure rate among adults ALL is estimated to be 20%-40%. Systems biology is a field of study that describes the structure and behavior of the biological systems. The systems biology view relies on multiple technologies named “omics” that consists of genomics, transcriptomics , and metabolomics.

Among the different gene regulators, micro-RNAs and transcription factors are the best-characterized regulators. Recent studies showed that there is a regulatory network between miRNAs and TFs. Evaluating the regulatory network between miRNAs, TFs and target genes might provide significant information about the biology of a specific disease. The aim of this study is to use integrated proteomics and transcriptomics data to identify potential biomarkers of ALL disease.

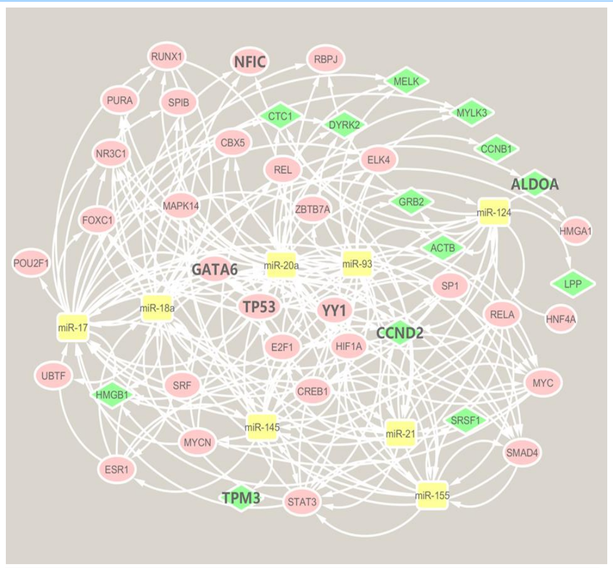
Materials and Methods



Results

Biological processes	%	p-value
Cell division	9.6	3.04E-15
Mitotic nuclear division	7.0	9.76E-12
Sister chromatid cohesion	3.8	6.41E-08
Mitotic cytokinesis	2.3	1.57E-07
Microtubule-based movement	3.3	2.15E-07
Response to reactive oxygen species	2.3	1.85E-06
Retina homeostasis	2.3	2.27E-06
Cell-cell adhesion	5.3	2.93E-06
Removal of superoxide radicals	1.5	3.67E-06
Negative regulation of apoptotic process	7.0	3.80E-06

Molecular functions	%	p-value
Protein binding	67.8	2.60E-16
Microtubule binding	5.5	6.10E-09
Cadherin binding involved in cell-cell adhesion	6.0	1.10E-07
Exogenous lipid antigen binding	1.3	1.10E-06
Endogenous lipid antigen binding	1.3	1.10E-06
Protein kinase binding	6.3	3.00E-06
Antioxidant activity	1.8	3.10E-06
Microtubule motor activity	2.8	9.30E-06
Lipopeptide binding	1.3	1.50E-05
ATP binding	14.6	2.40E-05



KEGG PATHWAY	%	p-value
Hematopoietic cell lineage	3.0	2.10E-05
Pathogenic Escherichia coli infection	2.0	4.10E-04
Complement and coagulation cascades	2.3	5.20E-04
Biosynthesis of amino acids	2.3	6.90E-04
Cell cycle	2.8	1.90E-03
Primary immunodeficiency	1.5	2.10E-03
Glycolysis/gluconeogenesis	1.8	9.40E-03
Carbon metabolism	2.3	1.20E-02
Estrogen signaling pathway	2.0	1.80E-02
Platelet activation	2.3	2.50E-02

Discussion, Conclusion and Suggestions

- In the proposed regulatory network, the genes with the highest degree and betweenness were determined as **CCND2**, **ALDOA**, and **TPM3** that play roles in cell division, glycolysis/gluconeogenesis, and cytoskeletal organization, respectively. Moreover, **GATA6**, **NFIC**, **TP53**, and YY1 are the TFs with the highest degree and betweenness that are mainly involved in DNA binding, cell apoptosis, and cell proliferation.
- CCND2, has a key regulatory function in G1- to-S-phase progression in the cell cycle.
- NFIC, regulates cell proliferation and differentiation by binding to a DNA sequence.
- GATA-6, a member of GATA family is another DNA-binding transcription factor with cell division regulatory function.
- Expression and function of the Yin Yang 1 (YY1) TF is known to be associated with cell cycle progression and differentiation.
- Tropomyosin3 (TPM3), mediates a myosin-actin response to calcium ions and takes part in the stabilization of cytoskeletal microfilaments. Several studies showed involvement of TPM3 in progression of cancer.
- There are some critical cell pathways which are reported to be deregulated in ALL, that our findings confirm some of them such as **Glycolysis** , **oxidative damage**, **apoptosis**.

Nowadays, scientists are doing research on leukemia via proteomics and transcriptomics approaches. Nevertheless, the total real biomarkers of leukemia including ALL is not available.

In this study, by creating regulatory subnetwork of integrated proteomics and transcriptomics datasets, we tried to find data that are repeatedly identified in several studies. There is potential in the integration and use of (multi)omics data for a better understanding of the molecular mechanisms, processes, and pathways of different ALL. Only by use of detailed phenotyping, specific and consistent sample collections, integrated systems biology approaches will be able to provide new insights into the complex pathophysiology of ALL.

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