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Clinical and Gene Expression Data Reveal Subtypes of Pediatric T-Cell Acute Lymphoblastic Leukemia

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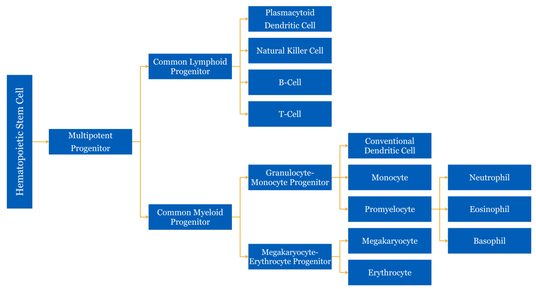
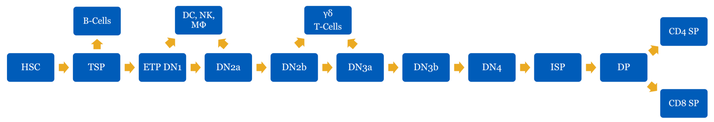
Introduction

Acute Lymphoblastic Leukemia (ALL) is a rapidly progressive cancer characterized by excessive immature leukocytes, which transform into leukemic cells and proliferate uncontrollably into lymphoblasts, blocking the production of normal cells.



T-ALL is a subtype of ALL where T-cell lymphoblasts are found in the bone marrow and blood, and it constitutes 10-15% of pediatric ALL cases. Unlike B-ALL, which has more clearly defined molecular subtypes that inform treatment selection, T-ALL lacks clinically defined molecular subtypes, hindering assessment and treatment determination.



We aimed to identify connections between clinical findings and gene expression in pediatric T-ALL to move towards defining more clinically meaningful subtypes of pediatric T-ALL.

Methods

We analyzed clinical and gene expression via bulk and single-cell RNAseq (scRNAseq) data from eight pediatric T-ALL patients from the Children's Mercy Research Institute Biorepository.

We performed a transcriptional analysis of specific genes to determine if the identified patient subtypes correlated with clinical matrices and if key genes exhibited the expected expression patterns based on clinical findings.

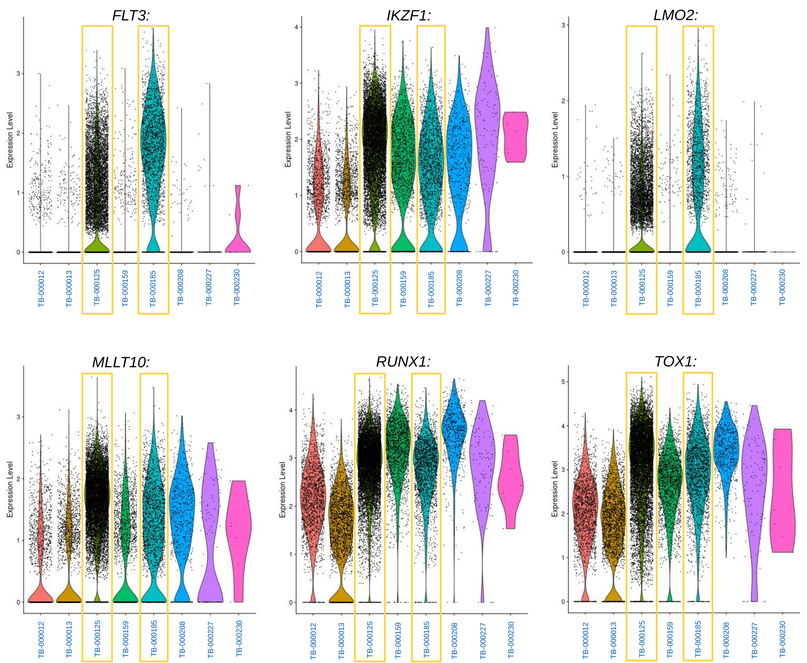
- We performed scRNAseq using the 10x Chromium system of blood and/or bone marrow samples (n = 8) collected at diagnosis.
- Sequencing data was generated for a total of 21,116 cells, and then carried out standard scRNAseq processing and normalization using Seurat 4.0.2 in R 4.0.3.

We compared the Children's Mercy cohort of T-ALL patients with external gene expression datasets from Alex's Lemonade Stand Foundation (ALSF) Single-cell Pediatric Cancer Atlas (ScPCA) Portal Project SCPCP000003.

Results

Children's Mercy Research Institute Biorepository

We observe similarities in gene expression between a known Early T-Cell Precursor (ETP) T-ALL patient (TB-000125) and a patient that was non-ETP T-ALL (TB-000185), suggesting subtype similarities that extend beyond ETP/non-ETP status.



ALSF ScPCA Portal Project SCPCP000003

We are currently comparing gene expression in the Children's Mercy cohort with that of patients from the ALSF ScPCA Project SCPCP000003.

Top Pathways Upregulated in ETP T-ALL

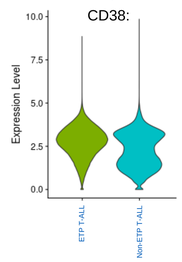
Biological Processes	P-Value
Response to Stimulus	2.106×10^{-36}
Immune System Process	1.866×10^{-35}
Immune Response	1.280×10^{-32}
Leukocyte Activation	9.190×10^{-32}
Cell Activation	3.734×10^{-31}

Top Pathways Upregulated in Non-ETP T-ALL

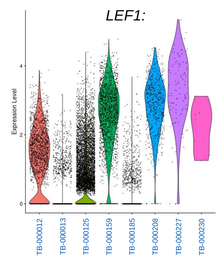
Biological Processes	P-Value
Anatomical Structure Development	4.944×10^{-4}
Multicellular Organismal Process	6.220×10^{-4}
Cell Differentiation	9.387×10^{-4}
Cellular Developmental Process	9.465×10^{-4}
Developmental Process	2.285×10^{-3}

ALSF ScPCA Portal Project SCPCP000003 (cont.)

We analyzed cell surface markers and gene expression patterns to validate findings within the Children's Mercy's T-ALL patients. Though the dataset displayed novel findings, we observed some similar expression levels as the Children's Mercy cohort.



ALSF SCPCP000003 cell surface marker expression shows similar as Children's Mercy Flow Cytometry in TB-000125 and TB-000185.



Gene expression seen in Children's Mercy patients is present in all of the top five pathways upregulated in Non-ETP T-ALL of ALSF SCPCP000003 patients.

Conclusion

Similarities in gene expression patterns among T-ALL patients emphasize the need for refined classifications of distinct subtypes to improve treatment selection and outcomes.

TB-000159 and TB-000208 show consistent gene and differential expression of immune-related markers, offering potential biomarkers for characterizing T-ALL subtypes and its prognosis.

- Gene Expression: *ETV6, LEF1, MLLT10, NOTCH1, RUNX1, TOX*
- Differential Expression (of T-cell receptor alpha with rearrangements): *TAL, LMO1, LMO2*

The diverse signaling pathway activities identified through bulk and single-cell RNA analyses present potential therapeutic targets for treatment strategies.

The ALSF ScPCA revealed unique gene expression patterns and cell surface markers distinct from those observed in the Children's Mercy Biorepository cohort.

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