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POSTER ABSTRACTS

618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Trajectory Inference Highlights Dynamic Expression of T-Cell Development Genes in Pediatric T-Cell Acute Lymphoblastic Leukemia

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Pediatric T-cell acute lymphoblastic leukemia (T-ALL) is a rare cancer with a diverse set of known drivers. Although genomic mutations driving T-ALL have been extensively characterized, these molecular subtypes do not inform patient treatment selection. In order to improve the utility of genomic data for pediatric T-ALL patients, further study is required to understand the molecular hallmarks and behaviors of T-ALL cells. One tool to investigate the behavior of subpopulations of cells is trajectory inference, which uses single-cell resolution data to infer putative relationships between cell populations, providing insight into cancer cell evolution. This method has the potential to identify subsets of cells that may respond particularly well or poorly to a given treatment based on their molecular profile, providing additional resolution in the effort to characterize T-ALL subtypes.

In this study, we used the 10x Chromium system to perform single-cell RNA sequencing (scRNAseq) of blood and/or bone marrow samples (n = 12) collected at diagnosis from eight pediatric T-ALL patients (Figure A). We generated sequencing data for a total of 21,116 cells and performed standard scRNAseq processing and normalization using Seurat 4.0.2 in R 4.0.3. Subsequently, we filtered down to cancer cell cluster(s) for each patient sample and used Slingshot 2.4.0 to identify cluster similarity and tradeSeq 1.10.0 to fit a generalized additive model for each putative trajectory and identify genes whose expression changed across each trajectory.

Each sample had 1-5 predicted trajectories for a total of 24 trajectories across the dataset. Each trajectory had 85-958 genes changing expression along it (total 3482 genes across the dataset). Nearly 40% of these genes only showed expression changes along a single trajectory, suggesting a high degree of heterogeneity not only across patients but also within individual patient samples. 6.5% of genes in this analysis show expression changes across at least 10/24 trajectories. These include genes known to be drivers of T-ALL, such as *BCL11B* and *ETV6*, demonstrating the ability of trajectory inference to capture known facets of T-ALL biology. Genes known to be involved in T-cell commitment (*RUNX1*, *TCF7*) and cellular self-renewal (*MEIS1*, *MEF2C*) showed changes in expression across a subset of trajectories as well. Other genes of interest including proto-oncogenes such as *JUNB* also show changes in expression across some trajectories but not others, even within a single patient (Figure B).

The data presented here demonstrate the value of trajectory inference methods to explore dynamic patterns of gene expression in scRNAseq data from pediatric T-ALL patients. By identifying putative trajectories within individual patients and comparing gene expression across these trajectories, we are able to more clearly resolve unique biological processes occurring in leukemic cells and potentially giving rise to treatment-resistant populations. Further interrogation of the genes identified in this analysis, correlation with known molecular subtypes, and extension to larger cohorts will improve our understanding of the molecular interactions driving disease progression, and ultimately improve treatment selection and prognosis for pediatric T-ALL patients.

Disclosures No relevant conflicts of interest to declare.

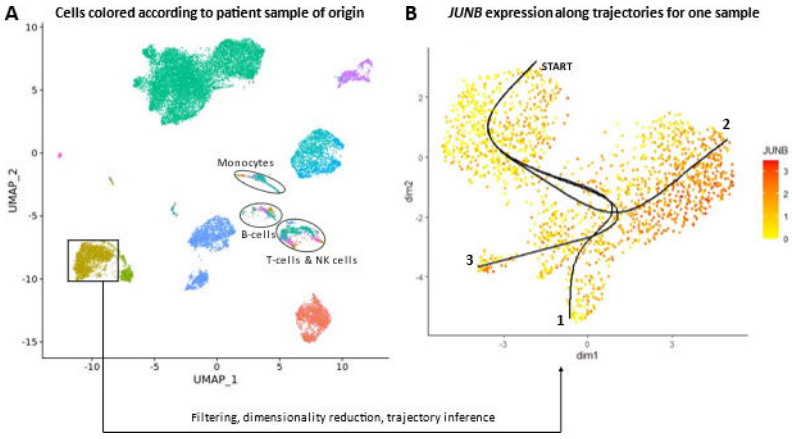

Figure 1

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