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POSTER ABSTRACTS

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

Prior Knowledge Integration Improves Relapse Prediction and Identifies Relapse Associated Mechanisms in Childhood B Cell Acute Lymphoblastic Leukemia

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Introduction

Despite decades of research and advancement in frontline treatments of B cell acute lymphoblastic leukemia (B-ALL), relapse remains the major barrier to survive this diagnosis in children and young adults. Although the majority of children will respond to initial treatment, 50% of children who relapse will die. Hence, there is a critical unmet need to prevent relapse in these patients. Previously, using proteomic features and predictive modeling we reported that patients who will eventually suffer relapse have cells predictive of their future relapse detectable at the time of diagnosis. These cells sit at the pro-B to pre-B transition in B-cell development and have elevated expression of signaling proteins: SYK, rpS6, CREB and 4EBP1. Although, our model outperformed standard risk models such as NCI criteria and MRD relapse risk, our model lacks higher accuracy and precision. Here, we utilize novel immunological Elastic-Net (iEN) model for relapse prediction which incorporates per-feature prior knowledge into the predictive model and improves the predictive power of the model.

Methods and Results

We analyzed 160 diagnosis bone marrow samples of children with newly diagnosed B-ALL treated on the cooperative group protocols. These samples comprised multiple cytogenetic subtypes and were annotated for clinical outcome (MRD status, relapse status, time to relapse) and patient attributes. Cells in these samples were analyzed using single-cell mass cytometry and expression of markers defining B cell developmental stages(CD34, CD38, CD127, CD24, TdT, CD179a, CD179b, IgHi, IgHs, CD19, CD20), signaling molecules (p4EBP1, pSTAT5, pPLC-γ2, pAKT, pSYK, pRPS6, pERK1-ERK2, pCREB) and transcription factors(TFs) (IKAROS, PAX5) were detected in the basal condition as well as after short-term ex vivo stimulation. Following data acquisition and preprocessing, cells were developmentally classified to the closest healthy B-cell population using a single-cell developmental classifier. Following cell-type classification, 1) frequency of cells with each of signaling molecules and TFs in the unstimulated state and in response to each of 3 stimulations, 2) age and WBC counts for each patient were extracted. These data were split in 90% training and 10% validation cohort. Prior knowledge for signaling molecules and TFs in response to each ex vivo stimulation condition is included after evaluation by a panel of expert cancer biologists such that molecules more consistent with known relapse biology have score of 1 and less consistent molecules have <1. This prior knowledge and training phase data were utilized to construct the iEN. The performance of model was determined using ten-fold cross-validation. Once constructed the model was applied to a validation cohort.

The iEN predicts relapse status with AUROC 0.85 ± 0.06 and outperforms our published model as well as standard risk models. Piecewise regression analysis of iEN revealed that pro-BI and pro-BII cells highly expressing pSYK, pCREB, pRPS6, p4EBP1 and pAKT have the highest coefficient magnitudes and are associated with relapse, consistent with our prior results. These molecules act within the network downstream of the pre-B cell receptor, suggesting relapse associated cells to have activated preBCR signaling. The transcriptomic profile of these cells revealed enrichment of PI3K-mTOR pathway genes, consistent with activated signaling profiles predicted by iEN. However, these cells were also enriched for expression of genes associated with metabolic pathways: oxidative phosphorylation, glycolysis, and fatty acid metabolism. Using a CyTOF panel focused on metabolic proteins, we confirmed co-expression of preBCR associated molecules and metabolic proteins (GLUT1, Enolase 1 and lactate dehydrogenase A) in pro-BI (TdT+/CD24-/CD179a+/CD179b+) and pro-BII (TdT+/CD24+/IgMi-/IgMs-) cells from relapse patients. Together this data suggests a relationship between active preBCR signaling with cellular metabolism and relapse.

Conclusions

Supervised predictive models integrating specific domain knowledge may improve prediction of relapse and identification of relapse associated mechanisms in B-ALL. Further analysis and integration of clinical data are underway and will be presented.

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