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Genes Predictive of Aggressive Infant Acute Lymphoblastic Leukemia

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☐ Medical Student
☐ **Resident/Psychology Intern (≤ 1 month of dedicated research time)**
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IRB Number: STUDY00000085

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Given differentially expressed genes by Dr. Pushel, performed pathway analysis and then explored genes of interest for each cohort

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background:
Acute Lymphoblastic Leukemia (ALL) is a rapidly progressive cancer in which the bone marrow makes too many immature leukocytes that divide uncontrollably. *KMT2A*, or *MLL*, is a methyltransferase found in many types of leukemia, whose rearrangement (*KMT2A*-r) is present in approximately 2/3 of infants with ALL. *KMT2A-r* is associated with a very poor prognosis: roughly ⅔ of patients relapse within 1 year of diagnosis, and the relapsed *KMT2A-r* ALL is resistant to treatment (having nearly 100% morality). We explored gene expression in patient samples from three groups at diagnosis: *KMT2A-r* patients who relapsed, *KMT2A-r* patients who did not relapse, and *KMT2A-g* (germline) patients who did not relapse.

Objectives/Goal:
We were interested in determining the molecular characteristics that define the 3 groups of infant ALL patients and identify genes that can be markers or treatment targets for infants with ALL.

Methods/Design:
We generated single-cell RNAseq data for peripheral blood and/or bone marrow samples collected from infant ALL patients at diagnosis (*KMT2A-r* relapse: n = 18, *KMT2A-r* no relapse: n = 9, *KMT2A-g*: n = 9). Data were analyzed in Seurat, and differential expression analysis performed with a cutoff of $p < 0.05$. We used Ingenuity Pathway Analysis to identify overrepresented pathways for each group. After running through IPA

to determine pathways that these genes were enriched in, we chose the top 10 pathways with the lowest p-value for each group and performed literature reviews into each pathway and genes of interest to determine if they were known to play a role in ALL or other cancers.

Results:

The key pathways (and genes) of interest were Antigen Presenting (*B2M, CD74*), PI3K Signaling in B Lymphocytes (*BLNK, LYN*), IL-3 Signaling (*FOXO1*) for *KMT2A-g*. Interestingly, we also observed PI3K Signaling in B Lymphocytes (*CD81*) enriched in *KMT2A-r* No Relapse patients. In contrast for *KMT2A-r* patients who did relapse, Protein Kinase A Signaling (*NFATC3, PTK2B, PTPN1, SMAD3*), and Estrogen Receptor Signaling (*FOXO3, NR3C1, RUNX2*) pathways were enriched.

Conclusions:

We were able to identify genes and pathways that were enriched in each cohort. These may underlie distinct mechanisms driving ALL in each of the groups, making these great candidates for further research and treatment targets. For instance, there are studies showing that the repression of *FOX01* would be a feasible approach for B-cell precursor ALL treatment, and a similar approach could be explored in infant ALL. Though this study focused specifically on diagnosis data, future experiments are planned to examine the expression of genes in relapse samples and compare to paired diagnostic data. Ultimately, better understanding of the molecular mechanisms of infant ALL will allow for improved treatment selection and outcomes for those with this disease.