



NORTHERN

Analyzing genes for T-ALL CNS infiltration

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Abstract

T-cell Acute Lymphoblastic Leukemia (T-ALL) is the most prevailing cancer affecting children. It affects adults as well but not to the same extent as children. While there is currently an 80% cure rate for children, there is still a high probability for relapse and infiltration of the central nervous system (CNS). This infiltration of the CNS makes this disease difficult to treat. Existing treatment plans consist of cranial irradiation or intrathecal chemotherapy which can leave children with cognitive complications. The hypothesis we are testing is that key genes (including pathways involved in regulating autophagy and metabolism) underlie T-ALL CNS disease. Genes were tested for differential expression for CNS and non-CNS groups. In addition, co-expression of genes was determined by computing the Pearson R coefficient between pairs of genes.

Introduction

T-Cell Acute Lymphoblastic Leukemia (T-ALL) is a rare disease that mostly affects children at the rate of .13 cases to 100,000 individuals (Murthy, Pondai, Abedin, Aballah, 2018) The five-year survival rate is over 70% (Hoelzer & Gokbuget, 2009) and treatments primarily involve chemotherapy and radiation (American Cancer Society, 2018). However relapsed T-ALL has a poor prognosis and relapse often occurs when the Central Nervous System (CNS) is involved. This presents a current challenge, and motivates our research, to see and identify differences in gene expression of T-ALL between CNS and non-CNS patients. Tailored therapies represent one possible approach to treating individuals when the CNS is infiltrated (National Cancer Institute, 2020) aside from standard treatments involving chemotherapy and radiation. These treatments rely on the identification of expressed and co-expressed genes. Gene expression is essential to observe how different proteins assist and infiltrate the CNS.

Data set

Our analysis is based on a human microarray database with 27 T-ALL patients with no CNS involvement and 22 T-ALL patients with CNS involvement (Oruganti et al., 2017) Microarrays can test gene expression levels of thousands of genes.

Genes identification

Genes that have been identified to be involved with CNS infiltration include CARMA1 or CARD11, BCL10, MALT1, MAPK1, NOTCH1, ZAP70, and chemokine receptors and ligands CCR7, CCL21, CCL19, CXCR3, and CXCR4 (Cannon et al., 2017). In addition, genes associated with metabolism and autophagy, LAMTOR1-5, PI3K and ATK1 may be associated with CNS infiltration.

Significant genes (P-values)

Gene	CNS vs non-CNS p-value
CARD11	3.1e-3, 5.7e-3
AKT1	5.3e-3
CCL19	2.0e-2
CXCR3	2.3e-2, .40
NOTCH1	5.4e-2, .45
LAMTOR5 (HBXIP)	7.5e-2, .19
ZAP70	9.0e-2

Table 1. P values of CNS compared to non-CNS patients. P-values were computed with the Mann-Whitney test. The P-values are not adjusted for multiple comparisons. Some genes had more than microarray probe and hence more than one p-value.

The Pearson R coefficient can be used to test the level of correlation between two genes. Its value ranges between -1 for negatively correlated genes and 1 for positively correlated genes. The closer the absolute value the R value is to 1, the stronger the correlation.

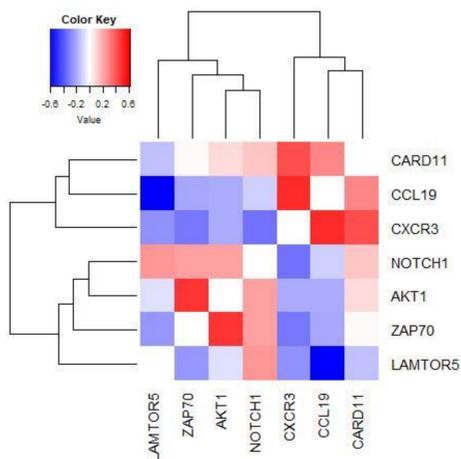


Figure 1. CNS proteins correlations in T-ALL

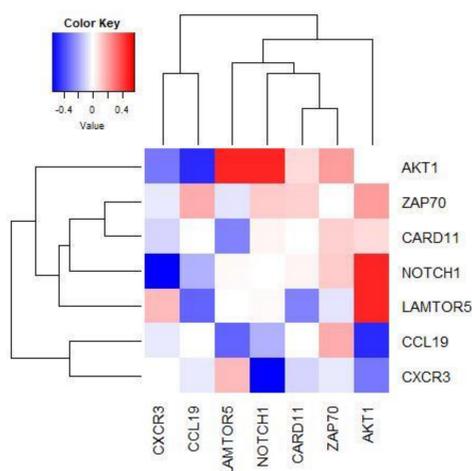


Figure 2. Non-CNS correlations in T-ALL:

Biological significance of Genes

Gene expression levels have been essential in identifying pathways for CNS infiltration.

After a foreign substance is recognized, the CARD11 protein is activated and binds to two other proteins, BCL10 and MALT1, to form what is known as the CBM complex which is involved in NF- κ B and mTOR activation (Cannon et al., 2017). NOTCH1 is a transcription factor that has been implicated in over 50% of T-ALL cases

ZAP70 is a kinase which regulates the motility, adhesion, and cytokine expression of mature T-cells (Jensen et al., 2009). MAPK1 is a kinase which regulates many processes including cell growth, adhesion, and survival (Jensen et al., 2009).

CCR7 is a chemokine receptor of which CCL21 and CCL19 are ligands. CXCR3 is another chemokine receptor which binds to CCL21. CXCR4 is a chemokine receptor which increases MAPK1/MAPK3 activation (Jensen et al., 2009).

Gene sets

We tested gene sets for differential expression. Gene sets are sets of genes that have been grouped together based on chromosomal location, function, or pathway. We tested 7,252 gene sets from the MSigDB data base. P-values were computed using the Mann-Whitney test and the modified Fisher's test consolidated the p-values into one p-value for the entire set (Torres et al. 2016). We identified 27 gene sets with p-values less than .01. The most differentially expressed gene set had a p-value of 9.7e-4. However, due to the multiple comparison correction, none of the gene sets can be considered significant.

Discussion

CARD11, AKT1, CCL19, CXCR3, NOTCH1, LAMPTOR5, and ZAP70 were found to have small P-values for CNS patients compared to non-CNS patients.

From our Pearson R analysis of CNS infiltrated genes, we found CCL19/LAMTOR5 to be negatively correlated and AKT1/ZAP70 and CXCR3/CCL19 to be positively correlated. From our Pearson R analysis of non-CNS patients, we found CXCR3/NOTCH1 and CCL19/AKT1 to be negatively correlated and ATK1/LAMTOR5 and AKT1/NOTCH1 to be positively correlated.

Our results could lead to the development of additional studies with more patients and more statistical power. Even though the p-values of the genes are not very low, they may be reduced in a study with higher number of patients.

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