Oncogenes MYC, MAX, and MNT Upregulate Branched Chain Amino Acid Metabolism in Peripheral T Cell Lymphoma

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Abstract

Peripheral T cell lymphoma (PTCL) is an aggressive non-Hodgkin lymphoma arising in T lymphocytes. Overexpression of the oncogenes ***MYC*, *MAX*, and *MNT*** is implicated in non-Hodgkin lymphomas where these genes control growth and proliferation by regulating the expression of metabolic genes. The mitochondrial branched-chain aminotransferase (***BCAT2***) and ketoacid dehydrogenase (***BCKDHA*, and *DBT***) genes encode for enzymes that breakdown branched-chain amino acids (BCAAs). BCAAs are a source of energy and metabolites for lymphoma cells. We aimed to investigate whether the expression of *MYC*, *MAX* and *MNT* correlate with that of *BCAT2*, *BCKDHA*, and *DBT* and to understand whether overexpression of *BCAT2, BCKDHA* and *DBT* in PTCL patients correlates with lower cancer survival.

The genomics analysis and visualization platform (R2) was used to access information about the overall survival and gene expression of 193 specimens from newly diagnosed PTCL patients. Kaplan Meier survival curves were downloaded from the platform along with the 2log expression values of each gene of interest. Pearson's correlation coefficient (R) was used to measure the strength and direction of the relationship between the oncogenes and the metabolic genes.

Results indicated a positive and statistically significant correlation between *BCAT2* and *MYC*, *BCKDHA* and *MYC/MAX*, and *DBT* and *MAX/MNT*. Overexpression of *BCAT2, BCKDHA,* and *DBT* correlated with significantly lower PTCL survival. The findings suggested that the oncogenes upregulate the BCAA metabolic genes in PTCL. While the molecular mechanism of these correlations needs to be addressed experimentally, the findings may serve as a basis for future pharmacotherapy for PTCL patients.

Objective

Bioinformatic data was used to correlate the gene expression of *MYC/MAX/MNT* oncogenes and three BCAA metabolic genes while also monitoring the patient survival prognosis with the long-term goal of finding potential therapy targets.

Background

Peripheral T-Cell lymphoma[1] is a heterogenous non-Hodgkin lymphoma that encompasses many subtypes of cancers comprising of peripheral and cutaneous forms developed from T-cells and Nature killer (NK) cells.

MYC*[2] and *MAX*[3]** are proto-oncogenes coding for proteins that form a heterodimer regulating the transcription of specific target genes. ***MNT*[4]** encodes a protein member of the ***MYC*/*MAX complex.

***BCAT2*[5], *BCKDHA*[6],** and ***DBT*[7]** genes encode proteins involved in the catabolism of branched chain amino acids, leucine, isoleucine, and valine.

The genomics analysis and visualization platform (R2)[8] was used to access data about the overall survival and gene expression of 193 specimens from newly diagnosed PTCL patients[9] comprising of patients from various subsets of PTCL including Anaplastic Large Cell Lymphoma (ALK+ and ALK-), Angioimmunoblastic T-Cell Lymphoma, Adult T-cell leukemia/lymphoma, and extranodal NK/ T-cell lymphoma.

Kaplan Meier survival curves were downloaded from the platform along with the 2log expression values of each gene of interest.

Pearson's correlation coefficient (R) was used to measure the strength and direction of the relationship between the oncogenes and the metabolic genes.

Results

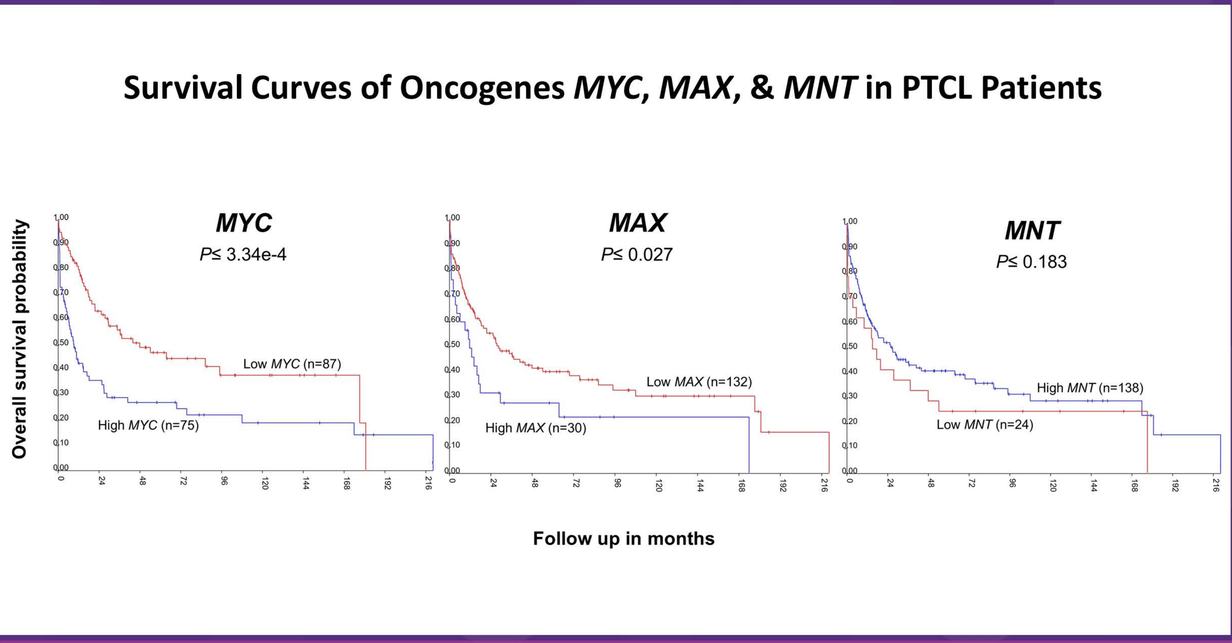

Figure 1: Kaplan Meier survival curves comparing the overall survival of patients with high and low expression of *MYC, MAX,* and *MNT as* pulled from R2[8] and measured in Log2. PTCL – Rosenwald[9] had n (sample size) of 193 patients.

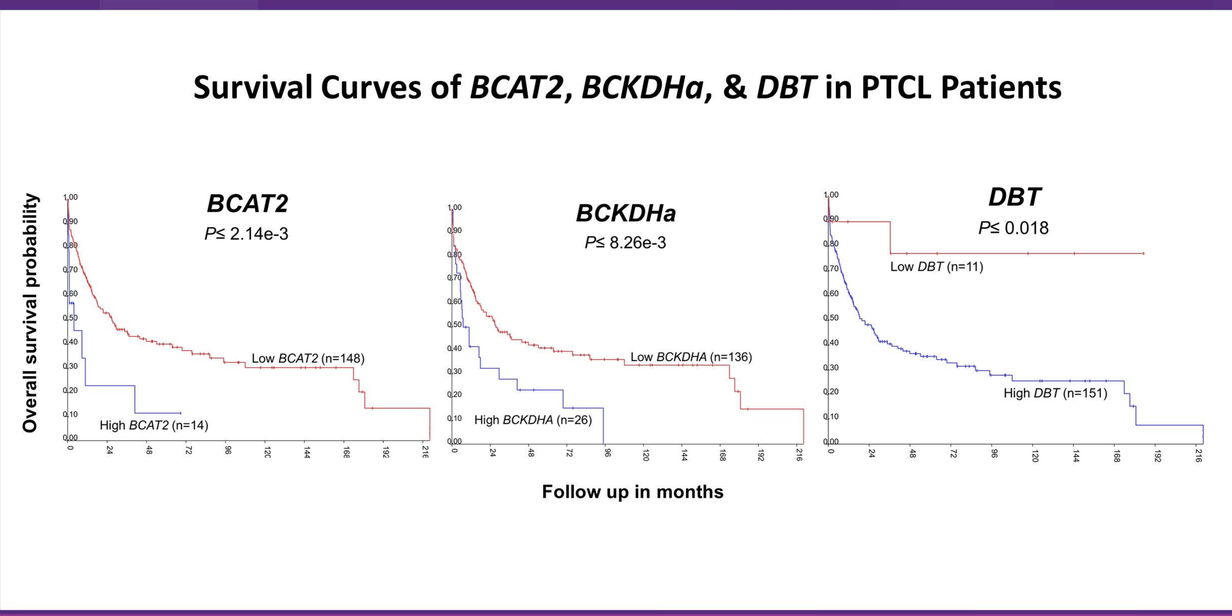

Figure 2: Kaplan Meier survival curves comparing the overall survival of patients with high and low expression od *BCAT2, BCKDHa,* and *DBT as* pulled from R2[8] and measured in Log2. PTCL – Rosenwald[9] had n (sample size) of 193 patients.

Table 1. Gene Correlation Analysis

	MYC	MAX	MNT
BCAT2	R=0.413 p= 2.32e-9	R=-0.202 p= 4.93e-3	R=-0.044 p= 0.541
BCKDHA	R=0.144 p= 0.046	R= 0.241 p= 7.19e-4	R=0.111 p= 0.123
DBT	R=-0.118 p= 0.102	R= 0.141 p= 0.050	R=0.461 p= 1.51e-11

Conclusion and Limitations

The survival curves obtained from the Rosenwald[9] study via the R2 genomics platform[8] yielded results indicating that:

1. The gene expression of oncogenes *MYC*[2] and *MAX*[3] and the BCAA genes *BCAT2*[5], *BCKDHa*[6], and *DBT*[7] positively correlated with poor patient survival. *MNT*[4] correlation was statistically insignificant.

2. There was a statistically significant positive correlation between:
2a. *MYC* and *BCAT2*
2b *MYC* and *BCKDHA*
2c *MAX* and *BCKDHA*
2d *MAX* and *DBT*
2e *MNT* and *DBT*

3. There was a statistically significant negative correlation between
3a *MAX* and *BCAT2*

The statistically significant correlations between the oncogenes and the BCAA metabolic genes warrant further studies to establish the molecular mechanisms in play. With the potential development and understanding of the aforementioned mechanisms, these correlations can serve as a basis for future targeted pharmacotherapy for PTCL patients.

Limitations:
The Rosenwald PTCL study had a higher number of males (92) than females (55) potentially indicating a gender bias. It also included various subtypes of PTCL patients including AICL, Adult T-cell Lymphoma, and ALK+/- ALCL patients, which may undermine potential variation between the subtypes.

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