Targeting branched-chain amino acid metabolism for the treatment of chronic myeloid leukemia

Maxwell Swain DO/MSBS '27[1], Elitsa Ananieva PhD[1]

[1]Des Moines University, Department of Biochemistry and Nutrition. Des Moines, Iowa.

Chronic myeloid leukemia (CML) is caused by a chimeric fusion of human chromosomes 9 and 22. This produces a hybrid BCR-ABL tyrosine kinase that drives abnormal myeloid cell proliferation. BCR-ABL positive CML is treated with tyrosine kinase inhibitors (TKIs). Mutations in the BCR-ABL gene chimera reduce the efficacy of TKIs. Our study aimed to target genes influencing CML metabolism as a new approach to overcome CML resistance to TKIs. We focused on the branched-chain amino acid (BCAA) metabolism since it stimulates CML growth. By using the eukaryotic promoter database (EPD) we found that the transcription factor JUN-B has putative binding sites in the promoter regions of 4 genes in BCAA metabolism, *BCAT1*, *BCAT2*, *BCKDHA* and *DBT*. JUN-B induces apoptosis, but it is silenced in CML. CML specimens, collected before (baseline, n=135) or after treatment with 400mg (n=30) and 800mg (n=33) Imatinib (TKI), were obtained from the R2-genomic analysis platform. T-test analysis tested the difference between the gene expression of JUN-B and the BCAA metabolic genes. In baseline specimens, there was a significant negative correlation between the expression of JUN-B and *BCAT1/BCAT2* suggesting that JUN-B is their negative regulator in CML. Treatment with Imatinib reduced the expression of *BCAT1* but not that of *BCAT2, BCKDHA or DBT*. Results suggest that *BCAT1* and *BCAT2* are downstream targets of JUN-B and Imatinib may reduce the burden of CML by downregulating the expression of *BCAT1*. These findings provided the background to investigate the mechanism of targeting BCAA metabolism in CML in TKI resistant patients.