Abstract

Acute lymphoblastic leukemia (ALL) is the most common malignant disease in children. Despite great advancements in treatment of this disease, around 15-20 % of patients suffer a relapse. One of the possible reasons for relapse is developed resistance to cytostatic drugs. L-asparaginase is an important chemotherapy component for childhood ALL and resistance to this drug often complicates treatment. To date, causes of developing resistance have not been sufficiently described. This thesis is a part of a greater research project focusing on mechanisms of L-asparaginase's activity and reasons for developing resistance to this chemotherapeutic agent. Differential metabolic requirements of cancerous cells have been described as early as 1924 by O. H. Warburg and they have been subject to scientific inquiry since.

This study aimed to describe the relationship between basal metabolic determinants of leukemia cells and their sensitivity to L-asparaginase. For this reason, two metabolic pathways, glycolysis and oxidative phosphorylation, were studied in detail using a Seahorse Bioanalyzer. Further, expression of specific genes involved in glycolysis was detected. Content of mitochondrial reticulum in cells, expression of the asparagine synthetase gene, and cell size were also studied. Experiments were conducted on 19 leukemia cell line models, which represented both genotypes and phenotypes of various types of leukemia. 11 cell lines represented acute lymphoblastic leukemia, 9 of which were B-precursor lines (B-ALL) and 2 were T-precursor lines (T-ALL). The remaining 8 cell lines represented myeloid leukemia in the acute (AML) or chronic (CML) phase. Findings of this study confirm the relationship between glycolytic activity in cells and their sensitivity to L-asparaginase. Several genes have been discovered, whose increased expression is correlated to increased glycolytic activity in cells. As a result, these could become potential markers of metabolic determinants in patient samples.

(In Czech)

Keywords

L-asparaginase, leukemia, resistance, metabolism, glycolysis, oxidative fosforylation