Abstract

Acute lymphoblastic leukaemia (ALL) is the most frequent malignancy in childhood. Despite the very successful ALL therapy, relapses occur to 15-20 % of children. One of the possible relaps causes is the resistance to therapeutics. ALL is treated with combined chemotherapy in which cytostatic agent L-asparaginase plays the essential role. L-asparaginase depletes extracellular asparagine and glutamine. Antagonist of the L-asparaginase is asparagine synthetase enzyme, which synthesizes the cellular asparagine. The specific antileukaemic effect of L-asparaginase is believed to be thanks to lower activity of the asparagine synthetase in leukaemic cells comparing to the healthy cells. The asparagine and glutamine deficiency harms the cellular proteosynthesis and induces apoptosis. Mechanism of the L-asparaginase cytotoxic effect and mechanism of corresponding resistance is still not fully explained.

This bachelor thesis is a part of a project studying mechanisms of leukaemic cells resistance to L-aparaginase. In the model leukaemic REH cell line a deletion del(5)(q34) was discovered, which cannot be found in the resistant clone of these cells. This thesis focuses on proving different sensitivity of leukaemic cells, with or without the deletion, to L-asparaginase. The limiting dilution was used to obtain REH clone cell lines positive or negative for the deletion. In order to determine the impact of the deletion del(5)(q34) on the viability of these cells lines, the apoptotic and cytotoxic tests were used. The L-asparaginase enzyme and ultraviolet radiation were used as the apoptotic inducers. The L-aparaginase was chosen for its specific effects on leukaemic cells whereas the UV radiation represented a non-specific lethal signal.

Results of this bachelor thesis confirm the participation of deletion del(5)(q34) in processes responsible for the sensitivity of leukaemic cells to L-aparaginase. Cells with this deletion are more sensitive to the cytotoxic effecs of L-asparaginase, whereas absence of this deletion leads to higher resistance of the cells. This likely relates with the response of ALL pacients to their therapy. (In Czech)

Keywords

L-asparaginase, leukaemia, resistance, deletion, apoptosis