Role of SLC7A11 in L-asparaginase therapy response in acute lymphoblastic leukemia

Matúš Kolárik[1,2,4], Maryna Vasylkivska[1,2], Markéta Žaliová[1,2,3] , Jan Trka[1,2,3], Kateřina Hložková[1,2] and Júlia Starková[1,2,3]

[1] Childhood Leukemia Investigation Prague

[2] Department of Paediatric Haematology and Oncology, Second Medical Faculty, Charles University Prague

[3] University Hospital Motol

[4] 1st Medical Faculty, Charles University Prague

Recent studies have shown an important role of amino acid metabolism and transport in cancer. A study by Ferguson et al. reported a correlation between the expression level of SLC7A11 (cystine/glutamate antiporter) and sensitivity to L-asparaginase in paediatric BCP-ALL (B-cell acute lymphoblastic leukaemia). L-asparaginase is a critical component of standard ALL treatment protocol. However, patients show high levels of interindividual differences in their responses. Our recent study showed an important role of glutamate, a by-product of L-asparaginase activity, both *in vitro* and *in vivo.* The transport of glutamate in cancer cells is not entirely understood. That is why we investigated the relationship between SLC7A11 and L-asparaginase treatment in more detail.

Firstly, we showed that some ALL patients and cell lines express SLC7A11.

Next, we tested the sensitivity of B- and T-ALL cell lines towards SLC7A11 inhibitors erastin and sulphasalazine. Considerable tolerance variability towards treatment was observed. However, no effect specific to the lineage origin of cell lines was detected. The effect may be caused by limiting cystine influx into the cell. On the other hand, we cannot rule out possible side effects of inhibitors themselves. The mechanisms of action of erastin and sulphasalazine need to be better understood.

For this reason, we also used cystine depletion. Complete or severe cystine depletion caused a drastic decrease in the viability/proliferation of cell lines, which deepened over time. However, cystine concentrations, which resembled the normal range in human plasma (25 - 50 µM) led to similar cell counts as full media (208 µM).

A combination of L-asparaginase with SLC7A11 inhibitor or cystine depletion was tested in subsequent experiments. Surprisingly, L-asparaginase improved cell survival under cystine-limiting conditions by either directly depleting cystine or erastin treatment.

In the future, we plan to investigate mechanisms leading to cell survival under cystine depletion in the presence of L-asparaginase. We are currently investigating potential factors, such as variations in glutathione metabolism or the trans-sulphuration pathway, that could contribute to differences in ALL cell lines. Combination of these mechanisms may lead to explanation of different degree of ability of cells to survive L-asparaginase treatment.