

## GLUTAMINE AS A SENSITIZING FACTOR FOR THE THERAPY OF SOLID TUMORS

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Metabolic transformation of cancer cells includes an increase in the consumption of glutamine, which can even lead to a „glutamine addiction“. This study focuses on depletion of glutamine via treatment with asparaginase, which can create an option for sensitization of cancer cells to chemo/radiotherapy. Glutamine is the most abundant amino acid in the circulation and its role in the cell metabolism involves the synthesis and import of other amino acids, proteosynthesis, and synthesis of purine and pyrimidine bases. After deamination and subsequent conversion to 2-oxoglutarate, its carbon skeleton serves as an anaplerotic substrate for the Krebs cycle. In addition to its role in energetic metabolism, 2-oxoglutarate can serve as a resource for the antioxidant system through its role in the regeneration of NADPH.

In this study, *in vitro* effect of asparaginase, a drug commonly employed for the long-term therapy of the acute lymphoblastic leukemia, which decreases the blood levels of asparagine and glutamine, was simulated. The effect of acute and chronic depletion of glutamine and asparagine on the cell resistance was studied using human cell lines, namely pancreatic adenocarcinoma (PaTu), cervix carcinoma (HeLa), and non-cancer fibroblasts MRC-5. The effect was tested in relation with oxidative stress induced by hydrogen peroxide, chemotherapeutic effect of doxorubicin and oxaliplatinum, and radiotherapy.

Our results show, that the simulation of asparaginase significantly increases the sensitivity of cancer cells to oxidative stress and oxaliplatinum. For this effect, a simultaneous depletion of glutamine and asparagine is required. Acute depletion of both amino acids is accompanied by decrease of an antioxidant capacity, lower activity of mTORc1 and changes in levels of intracellular amino acids and intermediate metabolites. On the other hand, all the described phenomena were less pronounced in the non-cancer fibroblasts.

In conclusion, while asparaginase is clinically used for the long-term chemotherapy of leukemia, this study suggests a potential role of its acute exposure as a chemosensitizing factor in the therapy of solid tumors.