Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Anna Giannitsi

Supervisor: RNDr. Jakub Hofman, Ph.D

Title of diploma thesis: **The role of biotransformation enzymes in the resistance of cancer cells against standard cytostatics**

Drug resistance is currently one of the major problems of chemotherapy. Tumor cells are able to defend themselves against the effect of cytostatic drugs due to various mechanisms which leads to a failure of anticancer therapy. The effort to describe new mechanisms of resistance and to develop new therapeutic methods, which would limit this therapeutic obstacle, is logically the subject of many studies. The activity of drug metabolizing enzymes and the subsequent decrease of intercellular concentration of anticancer drugs belongs to one of the possible mechanisms of pharmacokinetic resistance. Enzymes of I. and II. phase of biotransformation participate in this phenomenon. Cytochromes P450, main enzymes of the I. phase, play a major role in the metabolism of many cytostatic agents producing either pharmacologically active or inactive metabolites. Increased expression in tumors and the involvement of individual isoforms into the overall metabolism of cytostatic, which is deactivated by their activity, seems to be one of the reasons that contribute to the failure of standard anticancer therapy. The evaluation of the actual impact of this phenomenon is unfortunately very difficult due to many factors, mainly including complexity of metabolic pathways, interindividual differences in tumor-specific enzyme expression and also the fact that drug resistance is a complex phenomenon that is mediated by a number of other mechanisms which, all together, lead to the failure of therapy. Detailed description of relationships between intratumoral expression of biotransformation enzymes, the metabolism of anticancer drugs and its eventual modulation could help optimize pharmacotherapy in oncological patients.