Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Markéta Svobodová

Supervisor: doc. RNDr. Jakub Hofman, Ph.D.

Title od diploma thesis: Study on interactions of selected targeted drugs with ABC drug transporters

Cancer is one of the most common causes of death and its incidence is constantly increasing. Treatment mainly includes a combination of drug therapy, surgery and radiotherapy. A new approach, with huge potential, is the use of targeted anti-tumor therapy. This approach is based on specific interaction with tumor cells that reduces the negative effects occuring in conventional chemotherapy. Despite intensive research, we still face insufficient response to treatment. The main cause of therapy failure is the emergence of multidrug resistance (MDR) and the formation of metastases. The MDR phenomenon is most often associated with the overexpression of ATP binding cassette (ABC) transporters. These are responsible not only for the excessive efflux of anticancer drugs from cells, but also mainly affect their pharmacokinetics. Inhibition of these transporters increases the intracellular concentration of the cytostatic and provide the ability to modulate MDR. Therefore, one of the aims of this work was to investigate the inhibitory activity of three small molecule targeted drugs (capmatinib, pralsetinib, tazemetostat) against ABCB1 (P-gp), ABCG2 (BCRP) and ABCC1 (MRP1) transporters in MDCKII cell lines. The results were obtained using accumulation studies with model fluorescent substrates, hoechst 33342 and calcein AM. All targeted anticancer drugs demonstrated an inhibitory effect on all of the examined ABC transporters, except for tazemetostat, which did not inhibit ABCG2. Based on these results, we continued with combination studies to investigate the combination effects of these three targeted drugs with doxorubicin, a confirmed victim of MDR mediated by ABCB1 and ABCC1 transporters. For all combinations, we were able to demonstrate the ability of selected targeted drugs to modulate doxorubicin resistance. In conclusion, we can state that our results provide important insights and can serve as a valuable starting point for subsequent *in vivo* studies.