

Abstract

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Title of doctoral thesis:

Interactions of cyclin-dependent kinase inhibitors with ABC efflux transporters *in vitro*: impact on multidrug resistance in cancer therapy

Cyclin-dependent kinases play an important role in cell cycle regulation and their enhanced activity can lead to the development of various malignancies. Therefore, these kinases have become a rational target for inhibition in cancer therapy and many compounds from the group of cyclin-dependent kinase inhibitors (CDKIs) are being evaluated in clinical trials.

ABC efflux transporters are expressed in physiological tissues, where they influence the absorption, distribution and elimination of their substrates including drugs and determine their pharmacokinetic properties. On the other hand, overexpression of ABC transporters in cancer cells can contribute to the development of multidrug resistance (MDR) against structurally and functionally diverse compounds. Three members of the ABC transporter family play the most prominent role in the development of MDR: ABCB1 (P-glycoprotein), ABCG2 (breast cancer resistance protein) and ABCC1 (multidrug resistance-associated protein 1). Inhibitors and substrates of ABC transporters may participate in drug-drug interactions when administered simultaneously in the treatment of various diseases, which can significantly affect the drug disposition in the organism and alter the therapeutic outcome or adverse effects.

The aim of my thesis was to elucidate the interactions of the selected CDKIs with ABC transporters using *in vitro* methods and to determine whether these interactions might affect the efficiency of conventionally administered anticancer drugs in human cancer cells.

Using the accumulation method in MDCKII cell lines overexpressing ABC efflux transporters we found that the tested CDKIs (purvalanol A, olomoucine II, roscovitine, flavopiridol, SNS-032, dinaciclib and palbociclib) are all inhibitors of at least one of the ABC transporters, whereas AT-7519 showed no inhibitory potency. In cancer treatment, drugs are often administered in combinations to increase efficacy and limit the risk of MDR. Employing the combination index method of Chou-Talalay in human cancer cell lines, we showed that simultaneous administration of a CDKI with inhibitory potency towards an ABC transporter and a cytotoxic substrate of this transporter can lead to increased intracellular accumulation of the substrate and pronounced synergistic anticancer effect. Applying the corresponding MDCKII cell model and monolayer transport assays, we also studied the substrate affinity of CDKIs toward ABC transporters and identified olomoucine II and dinaciclib as substrates of ABCB1 and ABCG2.

Employing *in vitro* methods we found that CDKIs interact with ABC transporters as inhibitors or substrates. In these cases, drug-drug interactions can occur when the CDKIs are administered simultaneously with other drugs. On the other hand, we also demonstrated that inhibitory activity of CDKIs toward ABC transporters can be exploited to battle the problem of MDR.