Abstract

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Membrane transporters are found throughout the body, where they are responsible for many vital functions. Important representatives of membrane transporters are P-glycoprotein (ABCB1), Breast cancer resistance protein (ABCG2) and multidrug resistance-associated protein 2 (ABCC2) belonging to the ATP-biding Cassette (ABC) family. Nucleoside transporters belonging to Solute Carriers family (SLC) transporters represent another important group. It has been well evidenced that these transporters also affect drug disposition and contribute to tumor resistance to anticancer therapy. Over working on this dissertation thesis, we investigated the mentioned transporters (with special focus on nucleoside transporters) in complex fashion. We described the expression profile of nucleoside transporters in the placenta at different stages of gestation. We also examined whether the expression of nucleoside transporters changes depending on the degree of differentiation or can be affected epigenetically, and we demonstrated the importance of the cAMP / protein kinase A signaling pathway in their regulation. Regarding drug disposition, we found that placental equilibrative nucleoside transporter 1 significantly facilitates mather-to-fetus transfer of nucleoside-derive drugs, anti-HIV abacavir and anti-HCV ribavirin, but do not affect placental kinetics of anti-HIV drugs, emtricitabine and zidovudine. Similarly, ABC transporters providing fetal protection did not reduce maternal-fetal transfer of ribavirin. We also addressed the role of equilibrative nucleoside transporter 1 in the chemoresistance of pancreatic ductal adenocarcinoma to adjuvant gemcitabine therapy. Within our cohort of patients, we were unable to confirm the

correlation between equilibrative nucleoside transporter 1 expression and patients' survival. We achieved a similar result in the analysis of other potential prognostic markers neurogenic locus notch homolog protein 3 (NOTCH3) and microRNA 21 (miR-21). Our data and published studies have broadened knowledge on the regulation of nucleoside transporters and their involvement in drug pharmacokinetics, as well as they evidenced lacking involvement of ABC transporters in the placental kinetics of nucleoside analogs.