A New Intestinal Cell Culture Model To Discriminate the Relative Contribution of P-gp and BCRP on Transport of Substrates Such as Imatinib

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P-glycoprotein (P-gp/MDR1/ABCB1) and breast cancer resistance protein (BCRP/ABCG2) play an important role in transport of a wide variety of endogenous compounds, drugs and toxins. Transport of some drugs, for example the tyrosine kinase inhibitor imatinib, is influenced by both P-gp and BCRP. Establishing an intestinal Caco-2 cell culture model with specific knock-downs of P-gp and BCRP and double knock-down of both proteins, we aimed to elucidate the impact of each transporter on transport of imatinib. Stable single and double knock-downs of P-gp and BCRP were obtained by RNA interference (RNAi). Transporter expression was measured on RNA and protein level using real-time RT-PCR and Western blot, respectively. Functional activity was quantified by transport of specific substrates across Caco-2 cells. MDR1 and BCRP mRNA expression was reduced to 75% and 90% compared to wild-type control in single MDR1- and BCRP-knock-down clones, respectively. In double knock-down clones, MDR1 expression decreased to 95% and BCRP expression to 80%. Functional activity of P-gp and BCRP was diminished as transport of the P-gp-specific substrate (3)H-digoxin and the BCRP-specific substrate (14)C-PhIP was augmented in the opposite direction, when the respective transporter was knocked down. Similar effects were observed by chemical inhibition of the respective transporter. Bidirectional transport studies with (14)C-imatinib revealed an abrogation of asymmetric transport when P-gp was knocked down, either in single or double knock-down clones compared to wild-type cells. This was not observed in single BCRP-knock-down clones. In conclusion, this newly established cell system with single and concomitant knock-down of P-gp and BCRP can be used to quantify the specific partial impact of the transporters on transport of substrates that are transported by both proteins. For imatinib transport, the contribution of P-gp seems to be more important compared to BCRP in this Caco-2 cell system.

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