molecular pharmaceutics

editorial

Transport−Metabolism Interplay

The hypothesis that cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp) played complementary roles in drug absorption and disposition was first proposed 15 years ago.[1] Around the same period, these two proteins were also found to be concomitantly induced following drug treatments in the LS180 colon cancer cell line.[2] In that cell line, as well as in mice in vivo, P-gp was found to be a determining factor in the induction of CYP3A by rifampicin.[3] From these early studies and hypothesis, three aspects of the interdependence of transport and metabolism appeared to emerge:

(1) impact and cooperation in drug absorption and disposition;
(2) regulation by common nuclear receptors;
(3) control, by transporters, of intracellular levels of substrates (inhibitors or inducers) of drug metabolizing enzymes.

These three mechanisms and the cellular localization of transporters and enzymes create a setting in which, in addition to their combined effects on drugs, inhibition or induction of one of the players (transporter or enzyme) has an impact not only on its own activity but also on the observed effect or expression of the other. This, in turn, can either reinforce or counteract the activity on their substrates. This multifaceted codependence between transporters and drug metabolizing enzymes is described as the *interplay*.

These mechanisms of interplay, to which can be added the influence of genetic variants of enzymes and transporters, have been studied extensively and have gained greater attention. It is also now clear that, besides CYP3A and P-gp, additional efflux transporters, such as BCRP (ABCG2) or MRP2 (ABCC2), and uptake transporters (e.g., OATPs), can interact with other CYPs and phase II enzymes such as UGT or GST.

The recognition of the transport−metabolism interplay has also helped in understanding and reinterpreting absorption and disposition studies of marketed drugs and drug−drug interactions (DDI). In drug discovery and development, the appreciation of the impact of the transporter−metabolism interplay on hepatic clearance is also changing the approaches and tools used for the prediction of clearance and the assessment of potential DDI. While the mechanism and specificity of transporters and enzymes can be studied separately using in vitro methods, both systems need to be integrated to assess the relative contribution of transporters and enzymes on drug elimination and to predict DDI by inhibition of transporters, enzymes or both. Although cell-based or whole organ assays can provide mechanistic insight, this challenge can best be addressed through modeling and simulations based on experimental expression and activity data.

This special issue of *Molecular Pharmaceutics*, "Transport−Metabolism Interplay", highlights these various approaches. The review by Benet describes the progress made in uncovering and understanding the interplay between CYP3A and P-gp as well as uptake transporters through in vitro, animal and human studies. It also details the interpretation and impact of the interplay on drug absorption and elimination. Meyer zu Schwabedissen and Kim discuss the importance of hepatic uptake transporters in drug disposition and their central role in regulating the intracellular level of CAR and PXR ligands, which can then influence the expression of drug metabolizing enzymes. The potential impact of SNPs of CAR and PXR on the expression of their target genes (enzymes and transporters) is also reviewed. The third review, by Soars et al., describes in detail the models used for the prediction of hepatic clearance, their underlying assumptions and the impact of uptake

(1) Wacher, V. J.; Wu, C. Y.; Benet, L. Z. *Mol. Carcinog.* **1995**, *13* (3), 129–34.
(2) Schuetz, E. G.; Beck, W. T.; Schuetz, J. D. *Mol. Pharmacol.* **1996**, *49* (2), 311–8.
(3) Schuetz, E. G.; Schinkel, A. H.; Relling, M. V.; Schuetz, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93* (9), 4001–5.

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transporters on hepatic metabolism. Methodologies for incorporating drug uptake in the predictions of hepatic clearance and DDI are also presented.

Complementing the review on nuclear receptors and OATPs by Meyer Zu Schwabedissen and Kim, a study in HepG2 cells shows for the first time a link between LXRα and ABCC2 expression (Adachi et al.).

The combined effects of conjugation and efflux transport are illustrated by Vaidya et al., who investigated glutathione conjugation and MRP-mediated efflux in human placental tissues, and Xu et al., who studied the glucuronidation and transport of naringenin in rat intestine.

Integrating in vitro parameters from transporters and enzymes, PBPK models can be powerful tools in gaining a better understanding of rate limiting processes and allowing, through simulations, greater insight into the impact of physiological changes on transport and metabolism. Three contributions explore the use of such models. Poirier et al. describe the modeling of fexofenadine and napsagatran hepatic uptake and the predictions of their clearance and plasma and liver concentrations.

The review by Pang et al. examines the transporter−enzyme interplay in cell systems, isolated organs and animal models using catenary and PBPK models, and proposes reinterpretations of some findings from the literature.

Using simulations, Endres et al. study the effects of inhibition of transporter or enzyme activity on hepatic clearance. The authors discuss the interpretations of data under such conditions, and whether the alterations observed represent an "apparent interplay".

Finally, an article submitted by Zhang et al. from the Food and Drug Administration provides examples of DDI that can be attributed to alterations of both drug metabolizing enzymes and transporters. They point out the challenges in anticipating such interactions and discuss strategies for their prediction and investigation.

Numerous drugs are substrates to both enzymes and transporters and thus likely "victims" of the transport−metabolism interplay. The hypotheses, results and models described in this issue contribute to an improved understanding of their absorption, disposition and potential toxicity. These and additional tools, such as cell lines transfected with relevant transporters and enzymes and transgenic or knockout animals, in conjunction with PBPK modeling, will continue to shed more light on the interaction between transport and metabolism and help predict the pharmacokinetics of drugs and possible DDI.

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