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Special topic: Emerging role of transporters in drug interaction and delivery

To date, over 400 membrane transporters have been identified and characterized in human cells at both the molecular level and functional level. These transporters are classified into two families: ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters. They are well-recognized determinants of drug disposition and metabolism, even in the development of some diseases. Due to the biological function and tissue-specific expression, transporters play a potent role not only in drug disposition but also in drug-drug/drug-food interaction, and hold great potential to be utilized as targets for drug delivery. In 2019, we published a printed book entitled *Drug Transporters* (PMPH 2019; ISBN 978-7-117-28219-2) in Chinese. The content of the PMPH 2019 book included the basic transporter information and its role in diseases, drug-drug interaction, and drug delivery. However, the printed PMPH 2019 book was started in 2015. The field is growing so fast that several new emerging areas were uncovered in the book, which motivated us to propose a special issue that focuses on the latest advances of drug transporters in drug interaction and delivery. In this issue, we would like to invite several contributors to discuss the emerging findings regarding transporters and drugs.

The main reason for transporter-based drug interaction is supposed to be the broad and overlapping substrate spectra of transporters. All statins can be transported by OATP1B1, OATP1B3, and OATP2B1, and some of them are even characterized as substrates of efflux transporters, including P-gp, MRP2 and BCRP. As for the clinical investigation of drug interactions, OATP1B1 and OATP1B3 are specifically mentioned in EMA and FDA guidelines. Here, in this issue, Dr. Ogura and co-authors summarized the acute facilitating drug interaction via OATP2B1 and highlighted the key role OATP2B1 in the adverse drug events [1]. In addition, genetic polymorphisms of transporters also affect the in vivo behavior of stains. Prof. Cui and co-authors investigated the impact of genetic polymorphism in drug metabolism enzymes and transporters on fluvastatin pharmacokinetics [2]. Organic anion transporters (OATs) could also transport stains, and Prof. Liu et al. studied the drug-drug interaction between imipenem and cilastatin mediated by OATs [3].

Based on their important roles in drug disposition, transporters have drawn considerable attention for drug delivery. Prof. Chen et al. introduced the important role of SLCs in the blood-brain barrier, astrocytes, and neurons from the physiological, pathological, and pharmacological views, and underlined the potential of these transporters as targets for improved drug delivery to the brain [4]. Transporter-targeted prodrugs have achieved a successful record in industry pharmaceutics. The most remarkable examples are valacyclovir and valganciclovir, the prodrugs of acyclovir and ganciclovir, respectively. Both prodrugs could target enterocytes expressed PEPT1 and $ATB^{0,+}$ for enhanced oral absorption. In addition, the strategy using transporter-targeting nanoparticles is also of research importance for optimal drug delivery. Dr. Luo and co-authors reviewed recent advances of tumor-related amino acid transporters for drug delivery by prodrugs and nanoparticles [5]. Dr. Wang already made significant achievements in OCTN2 and MCT1-based drug delivery. In this issue, he and co-authors compressively introduced OCTN2 and MCT1-targeted drug delivery by using prodrugs and nanoparticles and emphasized the potential of a dual transporter-targeting strategy [6]. While ABC transporters expressed on biological barriers always block the therapeutic effects, Prof. Yu et al. reviewed the recent advances of using novel micro/nano drug delivery systems to overcome the efflux transporters-mediated treatment failure [7].

Furthermore, transporter biochemistry is implicated in important pathological events. Breast cancer resistant protein (BCRP), also called ABCG2, was recognized as one of the most important resistance proteins. The mutations of ABCG2 could decrease the excretion of uric acid, leading to hyperuricemia and an increased risk of gouty arthritis. Prof. Ganapathy et al. elucidated the rationale of ABCG2 as a target for gout and summarized the potential FDA-approved drugs and nutrients for gout treatment via ABCG2 [8]. Currently, we have a deepening understanding about the altered tumor metabolism. Besides Warburg effect, glutaminolysis, which indicates that cancer cells have an increased demand for glutamine, is one of the specific metabolism pathways. Prof. Indiveri summarized the identified glutamine transporters

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and discussed the key points from function to drug design by targeting glutaminolysis [9]. The redox balance with high levels of ROS and GSH is another specific feature in tumor pathology resulting from the altered metabolism. Dr. Kou and co-authors introduced the relationship between cancer metabolism and redox homeostasis and highlighted the recent advancements of redox-modulated nanomedicines for cancer treatment, especially by targeting xCT/SLC7A11 [10]. Further, Dr. Bhutia et al. investigated the potential role of xCT/SLC7A11 in the promotion of epithelial-mesenchymal transition and cancer development upon exposure to excess iron and emphasized the potential of xCT/SLC7A11 as a target for cancer therapy [11]. The emerging understanding of transporter biochemistry opens new possibilities in pharmacology and pharmaceutical science.

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Longfa Kou
Zhonggui He
Jin Sun

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