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Evaluation of transporters in drug development: Current status and contemporary issues☆

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ABSTRACT

Transporters govern the access of molecules to cells or their exit from cells, thereby controlling the overall distribution of drugs to their intracellular site of action. Clinically relevant drug-drug interactions mediated by transporters are of increasing interest in drug development. Drug transporters, acting alone or in concert with drug metabolizing enzymes, can play an important role in modulating drug absorption, distribution, metabolism and excretion, thus affecting the pharmacokinetics and/or pharmacodynamics of a drug. The drug interaction guidance documents from regulatory agencies include various decision criteria that may be used to predict the need for *in vivo* assessment of transporter-mediated drug-drug interactions. Regulatory science research continues to assess the prediction performances of various criteria as well as to examine the strength and limitations of each prediction criterion to foster discussions related to harmonized decision criteria that may be used to facilitate global drug development. This review discusses the role of transporters in drug development with a focus on methodologies in assessing transporter-mediated drug-drug interactions, challenges in both *in vitro* and *in vivo* assessments of transporters, and emerging transporter research areas including biomarkers, assessment of tissue concentrations, and effect of diseases on transporters.

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Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC, area under concentration-time curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; C_{max}, maximal plasma concentration; DDI, drug-drug interaction; EMA, European Medicines Agency; FDA, Food and Drug Administration; GI, gastrointestinal; IC_{50}, concentration at 50% of maximal inhibition; ITC, International Transporter Consortium; MATE, multidrug and toxin extrusion protein; MRP, multidrug resistance-associated protein; NME, new molecular entity; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically-based pharmacokinetics; PD, pharmacodynamics; P-gp, P-glycoprotein; PK, pharmacokinetics; PMC, postmarketing commitment; PMDA, Pharmaceuticals and Medical Devices Agency; PMR, postmarketing requirement; SGLT2, sodium-glucose co-transporter 2; URAT1, uric acid transporter 1.

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1. Introduction

Membrane transporters are expressed in various tissues throughout the human body, controlling the movement of endogenous and exogenous substances in and out of cells at various sites in the body. More than 400 transporters have been identified, and approximately 30 transporters are known to play a role in drug transport [1,2]. Over the past 20 years, research activities have generated a vast amount of data on the interaction of drugs with transporters.

Some drugs interact with transporters either as substrates or modulators (inhibitors or inducers). For drugs (or metabolites) that are transporter substrates, transporters can govern their absorption, distribution, metabolism and excretion (ADME), and consequently their safety and efficacy profiles. One example in the literature is related to a dose-limiting toxicity of SN-38, a metabolite of irinotecan. In the enterohepatic circulation path of SN-38 production and elimination following intravenous administration of irinotecan, organic anion transporting polypeptide (OATP) 2B1 was suggested to play a role in the uptake of SN-38 in the gut, contributing to the late-onset diarrhea, a potentially life-threatening toxicity [3]. A drug (or metabolite) may also interact with a particular transporter by altering its expression or activity, resulting in altered absorption or disposition of endogenous or exogenous compounds that are substrates for that transporter. Modulation of transporters is one of the important mechanisms to be considered for understanding drug-drug interactions (DDIs) in addition to those mediated by metabolizing enzymes. For example, loperamide is a peripherally acting mu-opioid receptor agonist marketed as an antidiarrheal agent with minimal effect on the central nervous system (CNS). Coadministration of loperamide (a P-gp substrate) with quinidine (a P-gp inhibitor) increased the systemic exposure to loperamide, and possibly also increased undesirably the opioid effect of loperamide in the CNS [4,5]. Another example is ZEPATIER®, a fixed-dose combination drug product containing elbasvir and grazoprevir approved by the FDA for the treatment of hepatitis C virus (HCV) infection [6]. A drug interaction study showed that cyclosporine (an OATP1B1/1B3 inhibitor) increased the systemic exposure to grazoprevir (a substrate for OATP1B1/1B3) to >15-fold on average, raising the risk of alanine aminotransferase (ALT) elevations. The ZEPATIER® labeling states that inhibitors of OATP1B1 and/or OATP1B3 that are known or expected to significantly increase grazoprevir plasma concentrations are contraindicated in patients receiving ZEPATIER®, because increased grazoprevir exposure could lead to liver toxicity [6]. To date, transporter modulation has been known to contribute to many DDIs that require risk mitigation strategies (Table 1).

In addition to their roles in DDIs, transporters have increasingly been studied as drug targets to treat diseases [7]. For example, several new drugs were approved recently that targeted transporters, including a potentiator of cystic fibrosis transmembrane conductance regulator (CFTR; ABCC7) for the treatment of cystic fibrosis [8], inhibitors of sodium-glucose co-transporter 2 (SGLT2; SLC5A2) for glucose control in Type II diabetes [9–11], and an inhibitor of uric acid transporter 1 (URAT1; SLC22A12) for reducing renal tubule reabsorption of uric acid in gout treatment [12]. Furthermore, a drug may interact with nutrient transporters causing serious adverse events such as the reported case of fedratinib, a Janus Kinase (JAK) inhibitor being developed for myelofibrosis. In a Phase 3 trial, Wernicke's encephalopathy was observed in approximately 2% of patients receiving fedratinib, which resulted in termination of the development of the drug [13]. Fedratinib inhibits the thiamine transporter (hTHTR2, SLC19A3) *in vitro*, and purportedly interferes with thiamine absorption resulting in Wernicke's encephalopathy [14].

2. Evaluation of transporter-mediated drug interactions

Evaluation of transporters during drug development and post-approval is an integral part of risk assessment for the optimal use of therapies in targeted patient populations [1,15–18]. Regulatory guidance documents on drug interactions from the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) as well as the U.S. Food and Drug Administration (FDA) have all included recommendations on how to evaluate transporter-mediated DDIs during drug development [19–21].

2.1. Regulatory considerations on transporter studies

In general, the regulatory guidances on transporter studies focus primarily on transporter-mediated DDIs that result in altered systemic concentrations, which can be readily assessed [19–21]. The aim is to use an integrated approach (*in vitro*, *in vivo* and *in silico*) to assess the DDI potential so that appropriate measures can be taken to minimize the risk of toxicities and to enhance the effectiveness. The DDI potential assessments also provide mechanistic insights which can help elucidate the DDI liability for unstudied concomitant use scenarios. Beyond DDIs at the systemic level, there is recognition that safety assessment of a drug may include investigation on modulation of transporters which govern the transport of particular endogenous compounds (see