Review

The transporters of intestinal tract and techniques applied to evaluate interactions between drugs and transporters

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A B S T R A C T

Most drug products on the global pharmaceutical market are administered orally. The absorption of oral drug in the intestine is an important factor to determine the drug bioavailability. There are many intestinal transporters expressed on the small intestine and the transporters can be classified into two major families, SLC family and ABC family. They mediate drug absorption, distribution, excretion and drug–drug interaction. Understanding the transport mechanism can improve the effectivity and safety of drug and guide clinical rational use of drugs. The roles of drug transporters can be assessed in vitro and in vivo, using techniques spanning from cellular expression systems to gene knockout animals. The purposes of this article were to introduce the main transporters in the intestinal tract, to explain the transport mechanism and to compare the limitations and applications of techniques used to evaluate interactions of drugs and transporters.

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1. Introduction

In 1980s, studies of membrane vesicles and cultured epithelial cell lines were introduced into the research field of drug transport and the biochemical characterization of transporters advanced remarkably. Then many drug transporters have been recognized [1–3]. The transporters play important roles in drug disposition, drug targeting, drug–drug interactions (DDI), and drug-induced toxicity. Uptake (SLC family) and efflux (ABC family) transporters interact with the pharmacokinetics and pharmacodynamics of drugs. There are many transporters expressed on the intestine (Fig. 1). They are responsible for the absorption of drugs. The roles of drug transporters can be assessed in vitro and in vivo, using techniques spanning from cellular expression systems to gene knockout animals. In this article, we provide an overview of the basic characteristics of major drug transporters of the intestine. And this review also provides a broad overview of the current in vitro and in vivo models that are used to evaluate the interaction between a drug candidate and transporters.

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2. Main transporters expressed on the intestine

2.1. ABC (ATP-binding cassette) transporters

2.1.1. P-gp (P-glycoprotein, MDR1, ABCB1)

P-gp belongs to the ABC transporter family and involved in the pharmacokinetics of a wide range of drugs and xenobiotics. It was first isolated from cancer cells where it extrudes drugs out of the cell thereby leading to multidrug resistance. The amino acid sequence of P-gp has been deduced from full-length or partial cDNA sequences of human, mouse, or Chinese hamster P-gp genes. The human MDR1 gene encodes a protein of 1280 amino acids which consists of two highly homologous halves. The molecular weight of P-gp is 170–180 kDa. This molecule contains 12 transmembrane domains (TMD) and two putative ATP binding sites. P-gp is encoded by two genes in humans (MDR1 and MDR3), and three in rodents (MDR1a, MDR1b and MDR2) [1]. It is expressed at brush border membranes of enterocytes, where it functions as the efflux pump for xenobiotics before they can access the portal circulation. It is a frequent cause of treatment failure in cancer patients.

The substrates of P-gp include anticancer drugs (such as vincristine, vinblastine, doxorubicin, daunorubicin, etoposide, and paclitaxel), immnosuppressants (such as cyclosporin A), verapamil, digoxin, and steroids (such as aldosterone and cortisole) [4]. What’s more, P-gp can interact by some other drugs. The AUC of talinolol was significantly decreased when coadministered with P-gp inducer rifampicin [5]. At some times, P-gp and CYP3A4 were suggested to cooperate in the intestinal absorption of drugs. Van Waterschoot RA et al. reported that ritonavir increased lopinavir oral bioavailability by inhibiting CYP3A, and MDR1 [6].

2.1.2. MRP2 (multidrug resistance-associated protein 2, ABCC2)

MRP family is one of the main families of ABC transporter. In the same manner, MRP2 is the main transporter of MRP family. MRP2 encodes a 190–200 kDa polytopic transmembrane protein comprising 1545 amino acids and belongs to ABC transporter subfamily C [7]. MRP2 was first functionally characterized as a canalicular multispecific organic anion transporter in canalicular membranes of hepatocytes. MRP2 has 2 hydrophobic TMDs (TMD1 & TMD2) and 2 cytoplasmic NBDs. The NBDs are responsible for the ATP binding/hydrolysis that drives drug transport, and their structures are conserved independently of the degree of primary-sequence homology [8]. The amino acids of MRP2 have 49% identity with MRP1 [9]. The location of MRP2 is unique, as it is present on the apical plasma membranes of the intestine [10,11], while other MRPs are all located on basolateral membrane of polarized cells.

MRP2 could play a major role in cancer chemotherapy and in the pharmacokinetics of substrate drugs [12]. It is responsible for the efflux of drugs and endogenous compounds. In mice lacking Mrp2, drug level fosinopril was reduced in the intestine by 1.5-fold [13]. The substrates of Mrp2 include cisplatin, BQ-123, etoposide, vinca alkaloids, anthracyclines, camptothecins, MTX, lopinavir and olmesartan [14]. The inhibitors of Mrp2 include MK571 and probenecid.

2.1.3. BCRP (breast cancer resistance protein, ABCG2)

Human BCRP encodes a 655 amino acid, containing a single N-terminal ATP binding cassette, followed by 6 putative TMDs [15]. BCRP are thought to have a protective role in the intestinal tract by preventing toxic substances absorption. It is a pharmacologically important ABC drug efflux transporters located at the apical part of the plasma membrane in polarized cells such as epithelia, and they influence the pharmacokinetics and tissue distribution of drugs [15]. BCRP mediates concurrent resistance to chemotherapeutic agents, presumably by pumping drugs out of the cell, thereby resulting in concentrations lower than cytotoxic levels. The substrates of BCRP transporter include mitoxantrone, etoposide doxorubicin and methotrexate [16].

2.2. Organic ion transporters

2.2.1. OCTs (organic cation transporter, SLC22A)

In 1994, the first member of the SLC22 family, OCT1, was first identified from a rat kidney cDNA library by expression cloning [17]. Then OCT2 was identified from rat in 1996 [18]. OCTs contain 12 TMDs and they mediate intracellular uptake of a broad range of structurally diverse organic cations with molecular masses generally lower than 400 Da [19]. Substrates of OCT1 include endogenous compounds, such as choline, creatinine, and monoamine neurotransmitters; clinically used drugs, such as metformin, oxalipatin and cimetidine; and a variety of xenobiotics, such as tetraethylammonium (TEA, model cation), N-methylquinine, and 1-methyl-4-phenylpyridinium (MPP+) [20,21].

2.2.2. OCTNs (novel organic cation transporter, SLC22A)

OCTN1-3 are the new members of OCT family. The amino acids of OCTNs have 30% identity with OCTs. OCTNs encode a 551
amino acid, containing 12 TMDs. OCTN2 is highly expressed in the human intestine from the jejunum to colon [22]. OCTN2 is clinically important because deficiency of the OCTN2 gene in humans causes systemic carnitine deficiency (SCD) [23]. OCTN2 is involved in the distribution of endogenous and exogenous substrates, including drugs such as quinidine, verapamil, and some β-lactam antibiotics [24,25].

2.2.3. OATPs (organic anion-transporting polypeptide, SLCO)

OATPs families were first isolated from rats [26]. So far 36 OATPs have been identified in humans, rat and mouse [27]. All members contain between 643 and 722 amino acids and they contain 12 TMDs [28,29]. Although some OATPs are selectively involved in the hepatic clearance of albumin-bound compounds from portal blood plasma, most OATPs are expressed in multiple tissues including the blood–brain barrier (BBB), choroid plexus, lung, heart, intestine, kidney, placenta and testis [26,30]. OATP-B is widely expressed on the apical side of the intestinal epithelial cells, mediating intestinal absorption of drugs by pH-dependent [31].

OATPs family mediates the Na+-independent transport of a wide range of amphipathic organic compounds, including bile salts, organic dyes, steroid conjugates, thyroid hormones, anionic oligopeptides, numerous drugs, and other xenobiotic substances [29,32]. Grapefruit juice was also reported to inhibit OATP transporter thus reducing the blood levels of OATP substrates [33].

2.3. **PEPT1 (H+/peptide cotransporter, SLC15A1)**

The cDNA of PEPT1 was firstly identified by expression cloning using a rabbit small intestinal cDNA library [34]. Homologous cDNAs were then found in human, rat, mouse, cow and chicken [35]. PEPT1 consists of 707–710 amino acid residues, with several putative glycosylation and phosphorylation sites. It contains 12 TMDs, with both the C- and N-terminal localized inside the cell [35]. PEPT1 is a low-affinity H+/peptide cotransporter that is primarily expressed in the brush border membrane of the small intestine [36]. Currently, PEPT1 can be divided into two types; i.e., the one localized at the brush-border membranes of epithelial cells, and the other one at the basolateral membranes. The former one plays a major role on the transport of the substrates [37].

Studies have demonstrated that many peptide-like drugs are absorbed by the H+-coupled peptide transporter, PEPT1. For example, β-lactam antibiotics [38], the anti-cancer agent Bestatin [39], renin inhibitors [40], and several angiotensin converting enzyme (ACE) inhibitors [41] were all reported to be recognized by PEPT1.

3. Techniques used to evaluate the interaction of drugs and transporter

3.1. **In vitro methods**

3.1.1. Brush border membrane vesicles (BBMV)

Under ether anesthesia, rapidly removed the jejunum of rats and flushed with ice-cold saline, then the mucosa was scraped. BBMV were prepared by the calcium precipitation method. Prepared BBMV were suspended in 100 mM D-mannitol, 100 mM KCl and 10 mM Hepes/Tris (pH 7.5) and stored at −80 °C. Purity of BBMV was evaluated by comparison of the activities of alkaline phosphatase (a marker enzyme of the brush border membrane) and Na+/K+ ATPase (a marker enzyme of the basolateral membrane) with those of the initial homogenate [42,43]. The model of BBMV is shown in Fig. 2. Our previous study indicated that the anti-hepatitis drug JBP485 can be transported by Pept1 by using rat BBMV technique [44]. BBMV can only measure the top side of the intestinal membrane transport and has low survival rate. All these shortcomings limit the use of BBMV in the experiment.

3.1.2. Everted intestinal sac

The abdomen of rats was opened by a midline incision, and the jejunum was removed by cutting across the upper end of the duodenum (i.e., ~2 cm distal to the ligament of Treitz) and the lower end of the ileum and manually stripping the mesentery. The small intestine was washed out carefully with cold normal oxygenated saline, using a syringe equipped with a blunt end. Intestinal segments (10 ± 1 cm) were everted according to the conventional technique described by Wilson and Wiseman (1954) with modifications. The everted intestine was placed in glucose-saline at room temperature in a flat dish. A thread ligature was tied around one end to facilitate subsequent identification and to check for perforation. The empty sac was filled with 1 ml of Krebs–Ringer buffer (KRB)
same manner, our previous study also used the Caco-2 cells to maintain the epithelial permeability of intestine [52]. Intestinal permeability is a basic parameter that can be easily assessed using a nonabsorbable marker [45,46]. The distended sac was placed in incubation medium containing drugs. The incubation medium was surrounded by a water jacket maintained at 37 °C. A gas mixture of 95% O2 and 5% CO2 was bubbled through the external incubation medium during the incubation period. At the end of the incubation period, the serosal fluid was drained through a small incision into a test tube.

Everted intestinal sac is an excellent in vitro model to evaluate the absorption of drugs by transporters. The advantages of using this system for transport studies are (a) drug transport across the basolateral and apical membrane can be measured separately, (b) buffers inside and outside vesicles can be changed easily. But there also have some limitations such as compounds with high nonspecific binding and high passive diffusion which may result in false negative results.

3.1.3. Caco-2 cells method

Caco-2 cells are derived from human colorectal adenocarcinomas and form monolayer (like human intestinal epithelium) under conventional culture conditions. They have been widely used as a potent in vitro model to predict drug absorption in humans, to explore mechanisms of drug absorption, and to identify substrates or inhibitors of transporters [47,48]. These cells exhibit remarkable morphologic and biochemical similarity to the small intestinal columnar epithelium; they are extremely useful for mechanistic studies of drug absorption and are widely used by pharmaceutical companies in absorption screening assays for preclinical drug selection [49].

Caco-2 cells were plated on 24-well dishes at a density of 5 × 10⁵ cells/well. The cell monolayers were given fresh medium every other day and were used on the 15th day for uptake experiments. Hank’s balanced salt solution (HBSS: 145 mM NaCl, 3 mM KCl, 1 mM CaCl₂, and 0.5 mM MgCl₂) containing 5 mM D-glucose and 5 mM MES (for pH 6.0) was used as the uptake medium. HBSS containing 5 mM D-glucose and 5 mM HEPES (for pH 7.4) was used as the rinse medium. The culture medium was removed on the day of experiment, and the Caco-2 cell monolayers were rinsed twice with HBSS (pH 7.4). After washing, the monolayers were preincubated with HBSS (pH 7.4) for 15 min at 37 °C. The medium was removed after the preincubation period and uptake was initiated by adding 1 ml of the preincubated drug solution. The drug solution was aspirated at the appropriate time to terminate uptake, and the cells were then quickly rinsed four times with ice-cold rinse medium (pH 7.4). The amount of drug uptake was determined by lysing the cells with 0.3 ml of 0.1% Triton X-100, and the cell lysate was then transferred to a plastic vial for quantitation.

Ogihara, T’ et al. indicated that the antivirus drug Oseltamivir is a substrate of PEPT1 by using Caco-2 cells [50]. In the same manner, our previous study also used the Caco-2 cells to investigate the uptake characters of JBP485 by PEPT1 [51].

Caco-2 cells system is also a useful model to estimate the epithelial permeability of intestine [52]. Intestinal permeability is a basic parameter that can be easily assessed using a variety of experimental models and it can be linked mechanistically to the pathways of drug absorption as well as to the overall absorption rate constant for drug absorption into the body.

Transepithelial transport studies were conducted using Caco-2 cell monolayers grown for 21 days on 24-well transwell inserts (Fig. 3). The cell monolayers were given fresh complete medium every other day. Monolayers formed after 2 weeks of culture. The integrity of the cell layer was evaluated by measuring the transepithelial electrical resistance (TEER) using Millicell-ERS equipment. Monolayers with TEER values (>250 Ω cm²) were used for the experiments. The monolayer cells were rinsed gently three times with HBSS (pH 7.4). The TEER values of the monolayer were measured before and after addition of an assay sample to the insert. Then the buffer added to the apical or basal side was replaced by the test solutions maintained at 37 °C and the plate was incubated at 37 °C for the appropriate time. The apparent permeability values (Papp) were calculated in all experiments according to the equations:

\[
P_{\text{app}} = \frac{dQ/dt}{AC_0}
\]  

where dQ/dt is the slope of the cumulative amount transported during the time course of the period studied, A is the area of the inserts, and C₀ is the starting concentration.

Permeability direction ratios (PDR) were calculated according to the following equation:

\[
PDR = \frac{P_{\text{app(AP-BL)}}}{P_{\text{app(BL-AP)}}}
\]

where AP-BL is the apical-to-basolateral transport and BL-AP is the basolateral-to-apical transport. This equation will be reversed if transporter is localized on the basolateral cell membrane.

The transport assay is the most direct assay for evaluating a given transporter’s function and measuring the permeability of a test compound across cell monolayer. And the Caco-2 system has now become the gold standard for investigating drug permeability in oral drug absorption.

3.1.4. Transfected cells

Although Caco-2 cells system has many advantages, there also include some limitations such as the long (21 day) cell culturing time, heterogeneity, and non-specificity due to the
expression of multiple transporters. The heterogeneity of Caco-2 cells can be caused by different origins, culture conditions and number of cell passages [53]. Thus cells stably expressed drug transporters were constructed to study the transport characters. The transfected cells can ensure the cells expressing high level of a single transporter. This approach can be more intuitive to analyze the effects of transporters on drugs. For generation of stable transfectants, the cells were transfected with the plasmid using Lipofect-AMINE 2000 reagent, and were grown in G418 in DMEM (high glucose) for 4 weeks [54]. Ten surviving cell colonies were randomly selected and examined by immunostaining and western blot [55]. One cell colony that exhibited the highest expression of plasmid was chosen for the following experiments. Knutten, I et al. transfected PEPT1 into human retinal pigment epithelial cells and confirmed the affinity of 14 different vascular converting enzyme inhibitors for PEPT1 [41]. In the same manner, double-transfected cells system is also an effective method to identify the substrates and inducers of transporters. Iwai, M. et al. assessed the interaction of YM155 with P-glycoprotein (MDR1/A/B/C1) using double-transfected cells system: LLC-OCT1/MDR1 cell line [56]. They get the conclusion that YM155 is a substrate of MDR1, and that MDR1 may play an important role in the pharmacokinetics of YM155. What’s more, Masakazu Horiiuchi et al. successfully constructed OATP1B1/MRP2/MRP3 and OATP1B1/MRP2/MRP4 three-transfected cells to study drug transport through the transporters [57]. Because of the scarcity of human tissue sources, transporter expressing systems will be useful for predicting transporter-mediated drug–drug interactions. In many cases, the endogenous transporter existing in the transfected cells can interfere test results. Appropriate cells should be chosen in the transfection process.

3.1.5. Xenopus laevis oocytes
The Xenopus laevis oocytes expression system has been used by many scientists to probe different transporters using influx and efflux studies [58,59]. Briefly, surgically removed oocytes from female X. laevis (African Xenopus Facility, Knysna, South Africa) were separated by collagenase treatment and were injected with 30 nl of RNA solution containing 30 ng of cRNA. The two-electrode voltage clamp technique was applied to characterize responses in inward current (I) to substrate addition as described [60]. Current–voltage (I–Vm) relationships were measured in the potential range from −160 to +80 mV. I–Vm measurements were made immediately before and 30 s after substrate application when current flow reached steady state [61]. Knutten I et al. used xenopus laevis oocytes transfected with PEPT1 to investigate the affinity of sartans for PEPT1. They concluded that the sartans tested in the study displayed high-affinity interaction with PEPTs [62]. Due to their relatively large size, they are readily accessible by microinjection. What’s more, the system shows low activity of endogenous transporters and high sensitivity. But the expression system displays a distinct variability in performance between individual oocytes. Quality and quantity of oocytes can vary considerably between individual donor animals [63].

3.1.6. Positron emission tomography (PET)
PET is a molecular and functional imaging technique with sensitivity, which permits repeated, non-invasive assessment and quantification of specific biological and pharmacological processes. Now it is playing an increasing role in both drug discovery and development by assessing their pharmacokinetics and pharmacodynamics. It is noteworthy that many PET tracers used for cancer detection are thought to be substrates of specific transporters [64,65]. To evaluate the functions of P-gp and BCRP in Caco-2 cells, Yamasaki T et al. carried out a small animal PET study using [11C]GF120918. PET results indicated that [11C]GF120918 uptake in the tumor was low, but was significantly increased by treatment with unlabeled GF120918. The study indicated that a PET study combining the administration of [11C]GF120918 with unlabeled GF120918 may be a useful tool for evaluating the functions of P-gp in tumors [66]. PET is thus a promising approach to determine the functional change in transporters associated with drug–drug interactions. However, due to the higher cost of PET, it is not widely used in scientific research.

3.1.7. ATPase assays
The transport function of the ABC efflux pumps depends on the binding and the hydrolysis of cytoplasmic ATP within NBD. The ATPase activity of the ABC-gp, MRP or BCRP expressing in insect cell or mammalian cell membranes is vanadate sensitive and can be stimulated or inhibited by substrates of these transporters [67]. P-gp, exhibits a high-capacity drug-dependent ATP hydrolytic activity that is a direct reflection of its drug transport capability [68]. The drug-stimulated ATPase activity is a useful alternative to conventional screening systems for identifying high-affinity drug substrates of the P-gp. Using this assay system, a variety of drugs have been directly shown to interact with the P-gp [69,70].

The membrane ATPase assay is compound-independent, easy to perform and does not require the use of radiolabeled compounds. Therefore it can easily be applied in a high throughput mode [71]. However, the ATPase assay is not a functional assay and cannot be used to distinguish between substrates and inhibitors. Other drawbacks of this assay include large inter-day or intra-day variations and potential false negative results.

3.2. In vivo methods
3.2.1. In situ jejunal perfusion technique
In situ jejunal perfusion technique is a well-established technique to investigate the intestinal absorption behavior of drugs in which the compound of interest is monitored in perfusate. Rats were anesthetized with an intraperitoneal (i.p.) injection of 25% ethylurethane (0.4 ml/kg), and a heating pad and heating lamp were used to maintain body temperature. Briefly, a laparoscopy was performed, and an inflow annual made of silastic tubing was inserted in the jejunum approximately 1 cm below the ligament of Treitz [38,45,72]. An outflow annual was set up at a distance of 10 cm. The bile duct was ligated to prevent possible enterohepatic circulation. The jejunal segment was then flushed with saline solution (prewarmed to 37 °C) to remove residual intestinal contents [73]. Oxygenated perfusion solution was delivered with a...
The comparisons of the techniques used to study the intestinal transporters.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Limitations</th>
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<tr>
<td>In situ jejunal perfusion</td>
<td>Maintain the nerve intact; high activity of enzyme.</td>
<td>The organ integrity and enzyme activity may become fragile and compromised during long-term perfusions.</td>
</tr>
<tr>
<td>Genetic knockout mice</td>
<td>Meet the real environment of body.</td>
<td>The model is difficult to establish; It is expensive and not suitable for high-throughput screening.</td>
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<tr>
<td>BBMV</td>
<td>Suitable for high-throughput screening.</td>
<td>The survival rate is low; It can only measure the top side of the intestinal membrane transport.</td>
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<tr>
<td>Everted intestinal sac</td>
<td>The cells can receive sufficient oxygen. The concentration of serosal side is high and easy to detect. The experiment cycle is short and can save animals.</td>
<td></td>
</tr>
<tr>
<td>Caco-2 cells</td>
<td>They are similar to small intestinal epithelial cells. The conditions are easy to control. The experiment is economic.</td>
<td>The cells require long-time culture and have multiple transporters expressed. They also lack intestinal mucus layer and certain metabolic enzymes. The expression of transporters is different in different culture conditions. Transected cells have endogenous transporters. The Km or Vmax obtained from transected system may be different from natural cell lines. The cells are lack of regulation way.</td>
</tr>
<tr>
<td>Transfected cells</td>
<td>The transporters are specific and suitable for regulating.</td>
<td>The expression of protein can’t be regulated. Quality and quantity of oocyes can vary considerably between individual donor animals.</td>
</tr>
<tr>
<td>Xenopus laevis oocytes</td>
<td>The activity of endogenous transporters is low. The sensitivity is high.</td>
<td></td>
</tr>
<tr>
<td>PET ATPase assays</td>
<td>High resolution; high accuracy. Easy to operate; saving time.</td>
<td>The instrument is complicated and expensive. The study is indirect and cannot provide dynamic information.</td>
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In situ jejunal perfusion technique would maintain the nerve intact and high activity of enzyme. However the organ integrity and enzyme activity may become fragile and compromised during long-term perfusions. Positive control should be taken to examine the success of the model.

3.2.2. Genetic knockout mice

Genetic knockout mice have become important models in understanding the physiological functions of drug transporters and in evaluating the effects of transporters on the pharmacokinetics and pharmacodynamics of drugs [67]. Schinkel et al. used transgenic technology to build the mdr1a (similar to the human MDR1) gene-deficient mice [76,77], the female Mdr1a/1b(–/–) and Mdr1a(–/–) knockout mice housed in Amsterdam had dramatically increased level of CYP3A, 2B, and 1A proteins and activities.

Table 1 – The comparisons of the techniques used to study the intestinal transporters.

In this review, basic characteristics of major intestinal transporters and techniques applied to evaluate interactions of drugs and transporters are discussed. Then the advantages and limitations of each model are discussed in this review (Table 1). The study of drug transporters can be actually applied to clinical science and drug development; that is, applications of drug delivery, the clarification of DDI, application of personalized pharmacotherapy, and clarification of the relationship of each transporter to particular disease(s). To avoid adverse consequences of such transporter-mediated drug–drug interactions, we need to be more aware of the role played by drug transporters.

4. Conclusion

In this review, basic characteristics of major intestinal transporters and techniques applied to evaluate interactions of drugs and transporters are discussed. Then the advantages and limitations of each model are discussed in this review (Table 1). The study of drug transporters can be actually applied to clinical science and drug development; that is, applications of drug delivery, the clarification of DDI, application of personalized pharmacotherapy, and clarification of the relationship of each transporter to particular disease(s). To avoid adverse consequences of such transporter-mediated drug–drug interactions, we need to be more aware of the role played by drug transporters.

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