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The Roles of Membrane Transporters on the Oral Drug Absorption

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Oral drug absorption is usually dependent on drug's physicochemical properties, formulation design and physiological conditions of gastrointestinal tract [1]. It is well known that physicochemical properties of drugs, like molecular weight, crystal structure, lipophilicity, pKa could generally determine the absorption mechanism [2]. Physiological conditions of gastrointestinal tract, i.e., expression level of drug metabolizing enzymes (polymorphism), empty/transit of GI tract, food effect, and drug-drug interaction caused by induction or inhibition of metabolism all contributed to the rate and extent of oral drug absorption [3,4]. In the last decade, progress on transporter studies showed increasingly significance of carrier-mediated absorption in drug development and clinical applications [5,6]. With more understanding of drug transporters, many previous puzzles on clinical pharmacokinetics and drug-drug interaction could be well explained. Furthermore, targeting on transporters also provided unique strategy to improve drug absorption or overcome unfavorable absorption barrier. This editorial aimed to briefly outline the major transporters and their roles on oral drug absorption, especially to efflux transporters.

Passive Diffusion

From mechanism perspective, passive diffusion and carrier-mediated absorption are the two major absorption pathways. Passive diffusion, the most common absorption pathway, can be further divided into two categories: paracellular and transcellular pathway [7]. In paracellular pathway, many hydrophilic (usually Log P<0) and small molecules (usually Mw<200) diffuse through the aqueous pores at the tight junctions between intestinal enterocytes [8] whereas lipophilic molecules traverse in transcellular pathway. However, it has to be noted that paracellular absorption is the minor pathway due to tight junctions of enterocytes and much small surface areas compared to transcellular pathway [9]. The rate of passive diffusion is mainly determined by the physicochemical properties of the drugs. Lipinski's 'rules of five' is a well known criterion to evaluate whether the compound has good oral absorption [2].

Carrier-Mediated Absorption

Based on energy requirement carrier-mediated absorption can be divided into facilitated and active transport. Facilitated transport follows the concentration gradient without energy expenditure whereas active transport requires energy (usually from ATP hydrolysis) and can transport against concentration gradient during absorption. For example, GLUT (glucose transporter) is the facilitated transporter while SGLT (sodium-dependent glucose transporters) is the active transporter for glucose transport. Transporters are the gatekeepers for all cells and organelles, controlling uptake and efflux of endobiotics and xenobiotics. Membrane transporters can be further divided into two main classes: solute carrier family (SLC) and ATP-binding cassette (ABC) transporters.

Solute Carrier Transporter

The solute carrier transporters (SLC) contains more than 300 members with 47 families [10] and they are mainly responsible for the uptake (some exceptions of efflux) of amino acids, peptides, ions, xenobiotics, endobiotics, sugars and other biologically active compounds [11]. Solute carrier transporters are widely expressed in various tissues, including intestine, liver, kidney, lung and etc. There are compelling evidences that these transporters are involved in drug absorption in clinical studies [5]. The most important SLC transporters include 1) expressed in the apical side of intestinal epithelia: organic anion transporting polypeptide (OATP) family, peptide transporter 1 (PEPT1), and apical sodium/bile acid co-transporter (ASBT); 2) expressed in the basolateral side of human hepatocytes: sodium/taurocholate co-transporting peptide (NTCP), OATP1B1, 1B3 and 2B1, organic anion transporter 2 (OAT2), OAT7 and OCT1; 3) expressed in the kidney proximal tubules: OAT4, PEPT1, PEPT2, urate transporter 1 (URAT1), organic cation/ergothioneine transporter (OCTN1, OCTN2) and OAT1, OAT2 and OAT3; 4) expressed in brain capillary endothelial cells contributing to the functions of the blood-brain barrier: OATP1A2 and OATP2B1 [5]. FDA issued guidelines for assessing transporter mediated drug interaction for five SLC transporters with demonstrated clinical significance: OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 [5]. In the recent International Transporter Consortium Second Workshop in 2012, MATEs (SLC47A) were proposed for prospective investigation in drug development [12].

ATP-Binding Cassette (ABC) Efflux Transporters

ABC transporters play a critical role in the development of multi-drug resistance in cancer cells and it is well accepted that their roles are to facilitate efflux of their substrates and to serve as rate-limiting step for oral absorption of therapeutical drugs [13]. ABC transporters move a wide range of substrates out of cells. The common feature of all ABC transporters is that they all consist of the transmembrane domain (TMD) and the nucleotide-binding domain (NBD). The TMD, embedded in the membrane bilayer, recognizes a variety of substrates and undergoes conformational changes to transport the substrate across the membrane whereas the NBD is the ATP binding site located in the cytosol side. Their substrates include: lipids and sterols, ions, small molecules, drugs and large polypeptides. The human genome contains 49 ABC genes, which are further classified into seven distinct subfamilies from ABCA to ABCG based on sequence and organization of their ATP-binding cassette domains [14]. The important ABC transporters in human include P-gp (ABCB1), MRP (ABCC), BCRP (ABCG2), cholesterol transporter (ABCG5/8) and bile salt efflux pump transporter (BSEP). P-gp and BCRP are two ABC transporters that FDA requires routine drug interaction assessment [5].

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P-Glycoprotein (ABCB1)

P-glycoprotein consists of 1280 amino acids with molecular weight (Mw) of 170 kDa, and its gene name is MDR1, also called ABCB1. Humans have two genes from MDR family (MDR1 and MDR3) whereas rodents have three Mdr genes (Mdr1a, Mdr1b, and Mdr2). The P-gp encoded by human MDR1 and mouse Mdr1a/1b are responsible for drug efflux, whereas human MDR3 and mouse Mdr2 encoded P-glycoprotein are functional in phospholipid transport [14]. Some results also suggest MDR3 P-glycoprotein is able to transport drugs, like digoxin, paclitaxel and vinbalstine in addition to phospholipids [15].

P-gp consists of 12 transmembrane domains and 2 nucleotide binding domain. The mouse P-gp crystal structure revealed an inward facing conformation that is believed to be important for binding substrate along the inner leaflet of the membrane. Additional structures binding with two different cyclic peptides revealed poly-specific drug binding site and the promiscuous binding pocket of P-gp is lined with aromatic amino acid side chains [16]. There are several proposed molecular mechanism of transport, including hydrophobic vacuum cleaner model, flippase model and phospholipid flip-flop within the lipid bilayer, but the in-depth understanding of its mechanism remains to be revealed [14]. P-gp is one of the most prevalent efflux transporters expressed in multidrug resistance cancer cells and in several organs such as intestine, liver, kidney and the blood-brain barrier [17]. P-gp plays an important role in limiting the intestinal absorption of its substrates *in vivo* and inhibition of P-gp leads to the improvement of bioavailability of orally administrated drugs and therapeutical agents [18-21].

In human intestine, P-gp is expressed in apical membrane of enterocytes and its mRNA level is highest in jejunum, followed by ileum and colon [22]. In contrast, protein level of P-gp in mice is highest in colon, followed by ileum and jejunum [23]. In liver, P-gp is highly expressed on the canalicular membrane of hepatocytes to facilitate the biliary excretion of many P-gp substrates, like daunomycin and doxorubicin.

P-gp has broad substrate specificity, recognizing hundreds of compounds including lipids, steroids, xenobiotics, chemotherapeutics, peptides, glycosides, biliruin, etc. The molecular weight ranges from 250 Daltons (cimetidine) up to several thousand Daltons (cyclosporine A). Although most of the drugs transported by P-gp are basic or uncharged compounds, there are many exceptions [24]. One common feature is that most P-gp substrates are hydrophobic and partition into the lipid bilayer [24,25]. Other studies have shown that both the lipophilicity and number of hydrogen bonds of compounds are the most important parameters to be recognized as substrates of P-gp [26].

Multidrug-Resistance Associated Proteins (MRPs/ABCC)

So far 12 members have been identified in human ABCC subfamily which consists of ABCC1 through ABCC12, and nine of them are MRP transporters [14]. ABCC1 (MRP1), ABCC2 (MRP2/cMOAT), ABCC3 (MRP3), ABCC6 (MRP6), and ABCC7 (CFTR) are the larger MRPs containing three transmembrane domains (TMDs) whereas ABCC4 (MRP4), ABCC5 (MRP5), ABCC8 (SUR1), and ABCC9 (SUR2) contain two TMDs. MRP2 is one of the most studied transporter among MRP family due to well reported clinical significance. It is the largest MRP with a MW of 190 kDa and 1545 amino acids. MRP2 is highly expressed in various normal tissues, such as the apical side of enterocytes, the canalicular membrane of the liver and the brush-border membrane of proximal tubule epithelial cells [27-29]. The substrate of MRP2 includes a variety of drugs such as doxorubicin, mitomycin C, cisplatin, 5-fluorouracil, etoposide as well as endogenous compounds and metabolites [30-32]. Unlike P-gp, MRP2 substrates have been shown to include many hydrophilic compounds, i.e., phase II metabolites of endogenous and exogenous compounds such as bilirubin glucuronides and flavonoids glucuronides. Highly expressed MRP2 in intestine and liver may decrease drug absorption and facilitate its excretion, consequently cause low oral bioavailability. Other MRP members, like MRP3 and MRP4 are located on the basolateral side of enterocytes and hepatocytes, and apical side of renal tubular cells. Knockout of MRP3 and MRP4 was reported to lead low plasma level of glucuronides of morphine and bilirubin indicating they are responsible for excreting metabolites into blood [33,34].

Breast Cancer Resistance Protein (BCRP, ABCG2)

Unlike P-gp and MRP2, BCRP is a half-size ABC transporter as it has one NBD at the N-terminus and one TMD containing 6 transmembrane regions at the C-terminus. There are reports showed that BCRP possibly functions as a homodimer [35]. BCRP is not only expressed in many cancer cell lines and solid tumor tissues for its multidrug resistance function [36], but also expressed in various normal tissues, such as the apical membrane of trophoblast cells in placenta, the brush-border membrane of intestinal epithelial cells, canalicular membrane of hepatocytes and the luminal surface of endothelium in brain microvessels [36-38]. BCRP has been reported to confer a variety of drugs for multidrug resistance function such as mitoxantrone, daunorubicin, doxorubicin, cisplatin, SN-38, topotecan and dipyridamole [36,39]. BCRP substrates have also been reported to include many phase II metabolites, especially for sulfation conjugates [40]. Knockout of BCRP was found to increase the bioavailability of its substrates either through improved oral absorption or changed *in vivo* disposition [41,42].

Cholesterol Transporter (ABCG5/G8)

ABCG5 and G8 functions as a sterol efflux heterodimer pump for mediating the secretion of sterols from the liver and efflux of dietary sterols from the gut [43,44]. As the member of G subfamily of ABC transporters, G5 and G8 are also half-transporters and oligomerize to form the functional transporter. They are highly expressed on the apical membrane of hepatocytes and expressed at low levels in the apical membrane of enterocytes in small intestine and colon. It has been reported that net cholesterol absorption correlates with the expression levels of ABCG5/8 in intestine in mice [45]. Biliary cholesterol concentrations were extremely low in Abcg5 Abcg8 (−/−) knockout mice when compared with wild-type mice [46]. Similarly, plasma level of dietary plant sterols are many fold higher in Abcg8 (−/−) knockout mice than wild-type mice Expression of Abcg5 and Abcg8 were regulated by liver X receptor (LXR), and the inducer of LXR, like TO901317 could increase their expression level [47].

Bile Salt Export Pump (BSEP/ABCB11)

Bile salt export pump (BSEP), formerly called sister of p-glycoprotein, belongs to ATP binding cassette B subfamiliy. It is responsible for active transport of bile acids across the hepatocyte canalicular membrane into bile, and recently studies showed that it can also transport non bile acid substrate, like statin-type drugs [48]. In human, BSEP is highly expressed in liver, and also expressed in intestine and kidney in a relatively low level [49].

Targeting Transporters to Improve Oral Absorption

The strategies of transporter-mediated prodrugs for oral delivery have already achieved successes. Several antiviral prodrugs (i.e., Valaciclovir) improved oral bioavailability of the parent drug (Aciclovir) by 3-5 -fold via structure modification of prodrug as the substrate of PePT1 [50]. The prodrug of ganciclovir, valganciclovir, also increase its oral bioavailability through improved binding affinity to PepT1 and PepT2 [51]. The rational drug development to target high-capacity uptake transporters to improve oral absorption demonstrated it is also a viable approach. Extended release of gabapentin enacarbil had been approved by FDA, which is the prodrug of gabapentin. The mechanism of the prodrug is to target high-capacity uptake transporters, monocarboxylate transporter type I (MCT-1) and multivitamin transporter (SMVT), instead of the low-capacity transporter, L-type amino acid transporter for parent drug [52,53].

Specific Inhibitor of drug metabolizing enzymes (CYP3A and 2D6) was approved as pharmacokinetic enhancer (cobicistat in *Stribild*) to be administrated concomitantly with other therapeutic drugs for the treatment of HIV [54]. Inhibitor of efflux transporters and booster of certain uptake transporters have been extensively studied and now in clinical evaluation [55]. Although there are no such approved drugs yet, the trend of finding potent and safe PK enhancer targeting on transporters is continuing.

Reversing Efflux Transport

Efflux transporters play a major role in limiting the intestinal absorption of various xenobiotics. Three generations of P-gp modulators has emerged to overcome this phenotype. The first generation of P-gp inhibitors include verapamil and cyclosporine A, but their clinical studies indicated significant toxicity and low potency after co-administration with other drugs [56,57], which lead to chemical synthesis of the second generations of P-gp inhibitors, like PSC-833. PSC-833 is the derivative from cyclosporine A and showed high potency with lower but not negligible toxicity. The third generation of P-gp inhibitors such as GF120918 and LY335979, showed improved potency with minimal pharmacokinetic interactions. Development of natural compounds as P-gp inhibitors has emerged in the recent ten years [58]. Natural products caught many attentions because of potential inhibitory effects on transporters. Natural products such as curcumine, ginsenosides and some flavonoids showed significant P-gp inhibition effect [40,59]. Most importantly, natural products which have been used for long history have much lower toxicity compared to synthesized reversing agents.

In summary, membrane transporters showed significant impact on the oral absorption of drugs. With more well established methodology and in-depth understanding, targeting on efflux transporters may become a viable approach in future although there are many challenges ahead.

Footnote

Parts of contents were presented in the dissertation of Dr. Zhen Yang at University of Houston in 2012.

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