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TRANSPORTER POLYMORPHISMS AFFECT NORMAL PHYSIOLOGY, DISEASES, AND PHARMACOTHERAPY

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Abstract

Drug transporters mediate the movement of endobiotics and xenobiotics across biological membranes in multiple organs and in most tissues. As such, they are involved in physiology, development of disease, drug pharmacokinetics, and ultimately the clinical response to myriad medications. Genetic variants in transporters cause population-specific differences in drug transport and are responsible for considerable inter-individual variation in physiology and pharmacotherapy. The purpose of this review is to provide a broad overview of how inherited variants in transporters are associated with disease etiology, disease state, and the pharmacological treatment of diseases. Given that there are thousands of published papers related to the interplay between transporter genetics and medicine, this review will provide examples that exemplify the broader focus of the literature.

Keywords

ABC; SLC; transporter; clinical pharmacology

INTRODUCTION

The ultimate goal of pharmacogenetics research on transporters is to better understand human diseases and to optimize therapeutics with drug transporters in mind. Pharmacogenetic approaches tailor therapies to patients based on their individual genetic background, and transporters are quintessential to pharmacogenetics research. The present review will: (i) provide a basic background of selected transporters, their polymorphisms, and their inheritance based on racial background; (ii) discuss how transporters mediate clinical pharmacology within various organs based on genetic variation; and (iii) provide a general discussion of how inter-individual variation in transporters influences normal

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physiology, diseases, and clinical pharmacology. Rather than providing a comprehensive overview, examples will be provided to demonstrate how transporter polymorphisms alter drug disposition and outcome.

Background and genetic variation of selected transporters

In general, transporters move substrates in an intracellular to extracellular direction ("efflux" transporters) or vice versa ("influx transporters"). There are a variety of efflux transporters (e.g. the ATP-binding cassette transporter family (ABCs), and multidrug toxin extrusion proteins (MATEs)), and influx transporters (e.g., the organic anion transporters (OATs and OATPs), organic cation transporters (OCTs), oligopeptide transporters (PEPTs), etc.), some of which are bidirectional. Moreover, these transporters are often arranged in polarized cells such that they facilitate the movement of substrates at a single membrane, either basolateral or apical, thereby regulating how substrates distribute across epithelial barriers. There is significant genetic variation in nearly every drug transporter, which has various consequences on their expression, mRNA stability, protein folding, intracellular localization, degradation, substrate binding, and/or transport kinetics. Herein we discuss the most commonly characterized polymorphisms and their consequences. For more comprehensive overviews of transporter SNPs see Boivin et al. (2010), Cascorbi (2008), Choi and Song (2008), and Niemi et al. (2011).

ABCB1/MDR1—ABCB1 is the most thoroughly studied efflux transporter. It is expressed in most human and rodent tissues with the greatest expression at the apical surface of enterocytes, the canalicualar plasma membrane of hepatocytes, and the proximal renal tubule (Fojo *et al.*, 1987; Schellens *et al.*, 2000; Schinkel *et al.*, 1997; Sharom, 2011; Thiebaut *et al.*, 1987). In these tissues ABCB1 serves to modulate the absorption, distribution, metabolism and excretion (ADME) of a multitude of exogenous substrates (Leslie *et al.*, 2005) (Table 1). ABCB1 is also expressed in hematopoietic stem cells, the blood-brain barrier (BBB), the heart, nerves, testes, and placenta. ABCB1 effluxes substrates away from these tissues, and therefore limits the penetration of toxins (Chaudhary *et al.*, 1992; Eichelbaum *et al.*, 2004; Fromm, 2004; Meissner *et al.*, 2002; Rao *et al.*, 1999; Saito *et al.*, 2001). For example, ABCB1 expression in pre-term placentas is crucial in protecting the placental cells and fetus, both of which are more vulnerable in early pregnancy (Ni & Mao, 2011).

ABCB1 contains at least 66 coding SNPs of which 24 are synonymous and 42 are non-synonymous (Wolf *et al.*, 2011). Two of the synonymous SNPs and 12 non-synonymous SNPs are associated with altered function or expression of the ABCB1 protein. *1236C>T*, *3435C>T*, and *2677G>T/A* have been well characterized. These SNPs may be associated with altered mRNA levels, mRNA stability (Cascorbi, 2006), protein folding (Kimchi-Sarfaty *et al.*, 2007) and drug pharmacokinetics (Longo *et al.*, 2010); however, others have found no association between these SNPs and ABCB1 function (Sissung *et al.*, 2010).

Haplotype analysis revéals an additive effect of these SNPs on *ABCB1* function. There are at least 64 *ABCB1* haplotypes, including the common haplotype, *ABCB1*13*, that contains the three previously mentioned SNPs; thus, haplotype structure may denote larger scale linkage

with other functional polymorphisms (Kroetz *et al.*, 2003). Interestingly, functional changes in ABCB1 were only detected when *2677G>T* and either *1236C>T* or *3435C>T* were present in combination, not *2677G>T* alone. This change in function may be due to minor differences in the tertiary structure of the protein (Kimchi-Sarfaty *et al.*, 2007).

Frequencies of *ABCB1* SNPs and haplotypes vary across races. Kroetz et al. (2003) found 16 variants specific to African Americans, 8 to Caucasians, and 3 to Asian-Americans (Kroetz *et al.*, 2003). Though variant allele frequencies are generally higher in African Americans (Wang *et al.*, 2005), the three SNPs previously listed are twice as common in Caucasians as in African Americans. Likewise, frequency of *ABCB1**1 was race-specific (Caucasians = 0.32, African Americans = 0.05, Asian-Americans = 0.266, Mexican-Americans = 0.35, Pacific Islanders = 0.333) (Kroetz *et al.*, 2003). Therefore, ABCB1 substrates may be transported differently depending on racial backgrounds.

ABCC2/MRP2—ABCC2, also known as MRP2, is expressed in several tissues, including the liver, intestine, kidney, BBB, and placenta and is localized to the apical membrane of epithelial cell. It actively exports anionic drug conjugates as well as many unconjugated substances and thus is an important part of drug detoxification (Table 1). Additionally, ABCC2 plays a major part in the transport of anticancer drugs (Cascorbi, 2006). For example, *in vitro* studies indicate that ABCC2 is expressed at higher levels in tamoxifen-resistant breast cancer cells, suggesting a role for ABCC2 in transporting the active metabolites of tamoxifen (Kiyotani *et al.*, 2010).

Most *ABCC2* polymorphisms are quite rare in the general population, however, −24C>T in the 5'-UTR, 1249G>A, and 3972C>T are all relatively common in healthy individuals. Their respective frequencies in Japanese were 0.18, 0.12, and 0.21 (Ito *et al.*, 2001), versus 0.18, 0.21, and 0.34, in healthy German volunteers (Haenisch *et al.*, 2008). The −24C>T and 3972C>T variants are also in linkage disequilibrium (Itoda *et al.*, 2002; Suzuki & Sugiyama, 2002).

The functional importance of *ABCC2* polymorphisms remains unclear. Cascorbi (2006) argued that *ABCC2* SNPs are only of minor importance for drug availability (Cascorbi, 2006). Likewise, Hirouchi et al. (2004) found that 1249G>A did not affect ABCC2 transport function (Hirouchi *et al.*, 2004).

We did not cover *ABCC1* because few studies assessed consequences of polymorphisms in this gene and those that have failed to find any functionally significant effects (Cascorbi, 2006; Letourneau *et al.*, 2005).

ABCG2/BCRP/MXR—Similar to ABCB1, ABCG2 (BCRP, MXR) is highly expressed in the placenta, the central nervous system (brain and BBB), liver, adrenal gland, testes, large and small intestine where it effluxes substrates across the apical membrane. In the gastrointestinal tract, ABCG2 limits the intestinal uptake of certain substrates, including antibiotics, quercetin, sulfasalazine, and dietary carcinogens (Robey *et al.*, 2009). In the kidney and liver, ABCG2 is involved in both renal drug excretion and biliary excretion, respectively.

Several SNPs and at least one insertion-deletion variant have been identified (Choudhuri & Klaassen, 2006). The association between these SNPs and ABCG2 expression levels, cellular localization, and pharmacokinetics is unclear. The most commonly implicated SNPs are Q141K and V12M. The *ABCG2 421C>A* (Q141K) SNP has been linked to a reduction in ABCG2 transport activity while the V12M (G34A) SNP is related to aberrant transporter membrane localization (Generaux *et al.*, 2011). However, others failed to confirm these findings (Honjo *et al.*, 2002; Porcelli *et al.*, 2009).

OATP1B1/SLCO1B1—OATP1B1 is a hepatic influx transporter (Niemi *et al.*, 2011). To date, over 40 nonsynonymous SNPs have been indentified on *SLCO1B1* (encoding OATP1B1) (Boivin *et al.*, 2010; Niemi *et al.*, 2011). Several of these SNPs have been associated with functional changes in the transporter. Some variations result in changes in the structure of the transmembrane-spanning domains (217T>C, 245T>C, 521T>C, and 1085T>C), while others alter the extracellular loop 5 (1294A>G, 1385A>G, and 1463A>C) (Tirona *et al.*, 2001). The 521T>C variant was associated with reduced membrane expression of OATP1B1, lower levels of transport activity, and changes in the maximum transport velocity of OATP1B1 substrates (Niemi *et al.*, 2011).

Functional analysis of *OATP1B1* haplotypes showed that transport activity was significantly lower in variants *2, *3, *5, *6, *9, *10, *12, and *13 compared with the reference allele (Tirona *et al.*, 2001). However, these functional changes did not coincide with changes in protein expression, except for the variant *2 in which expression was reduced. The reduction in transport activity may instead be associated with reduction in plasma membrane expression of OATP1B1 haplotypes. In addition, some haplotypes were associated with changes in pharmacokinetics (Tirona *et al.*, 2001). There are contradictory findings regarding the effects of the four 388A>G haplotypes (*1A, *1B, *5, and *15) on transport activity which may be due to substrate-specificity (Niemi *et al.*, 2011).

The most common SNP across populations was 388A>G, though the frequencies varied considerably between races (sub-Saharan Africa = 79%, East Asia = 74%, Oceania = 66%, America = 63%) (Pasanen *et al.*, 2008; Tirona *et al.*, 2001). Some SNPs, however, were race-specific. The variant 10499A>C was found primarily in Europeans and 1086C>T and 1463G>C were specific to sub-Saharan African populations (Pasanen *et al.*, 2008). Other relatively common variants were 2000A>G (0.34) and 1463G>C (0.09) in African Americans and 463C>A (0.16) and 521T>C (0.14) in European Americans (Tirona *et al.*, 2001).

Frequencies of *OATP1B1* haplotypes also varied by geographical region (Pasanen *et al.*, 2008). For example, the *1B haplotype was the most common in North Africa, sub-Saharan Africa, East Asia, Oceania and America, whereas the *1A haplotype was the most common in the Middle East, South/Central Asia and Europe. The frequency of the *15 haplotype was 24% in American, 16% in North African and European, 15% in Middle Eastern, 12% in Asian, 9% in South/Central Asian, and 2% in sub-Saharan African populations. It was not observed in Oceania. The *5 variant was more race-specific and only found in the Middle East (5%), North Africa (2%), and Europe (2%) (Pasanen *et al.*, 2008).

OATP1B3/SLCO1B3—Like OATP1B1, OATP1B3 is a liver-specific influx transporter that moves substrates across the basolateral membrane into the hepatocytes for metabolism and elimination (Svoboda *et al.*, 2011). Forty-one *SLCO1B3* (encoding OATP1B3) polymorphisms, most of which are located in regulatory regions, have been indentified along with a variety of haplotypes (Boivin *et al.*, 2010). Two clusters of deletions at −7 to −4 and −28 to −1 in the 5'-UTR that may result in reduced mRNA stability or problems with initiation of translation have been reported (Boivin *et al.*, 2010). Fourteen SNPs, six of which are nonsynonymous, have been found in coding regions of *OATP1B3* (Schwarz *et al.*, 2011). Functional analysis indicates that variants 699G>A, 1559A>C,1679T>C, and the haplotype 334T>G and 699G>A alter transport levels and kinetics of OATP1B3; however, the change appears to be substrate-specific (Schwarz *et al.*, 2011). Interestingly, 767G>C, 1559A>C, and 1679T>C were associated with lower total OATP1B3 protein expression. However, 669G>A expression was not different from that of wild-type and 334T>G and 439A>G variants had slightly increased expression. The SNPs 1559A>C and 1679T>C displayed lower levels of cell surface expression than wild-type (Schwarz *et al.*, 2011). SNPs at 334T>G, 1564G>A, and the rare variant 1564G>T were associated with changes in cellular localization and transport properties of OATP1B3 (Letschert *et al.*, 2004). Structural modeling suggests that 1679T>C faces the putative central pore of the transport protein that is thought to be necessary for the translocation of substrates (Schwarz *et al.*, 2011).

The most common *OATP1B3* polymorphisms in individuals of all racial backgrounds were 699G>A (Hispanic-Americans=0.833, Chinese-American=0.795, Caucasian-Americans=0.779, African Americans=0.478) and 334T>G (Hispanic-Americans=0.711, Chinese-Americans=0.620, Caucasian-Americans=0.523, African Americans=0.386). 1679T>C and 439A>G were specific to African-Americans (3.6% and 1.1% respectively) (Schwarz *et al.*, 2011).

OCT1 and OCT2—The organic cation transporter (OCT) family of transporters includes but is not limited to OCT1, encoded by *SLC22A1*, and OCT2, encoded by *SLC22A2*. OCT1 and OCT2 are both influx transporters isolated on the the basolateral membrane. OCT1 is expressed in hepatocytes, whereas OCT2 expression is generally limited to kidney proximal tubules (Choi & Song, 2008). To date, 19 non-synonymous *SLC22A1* and 10 non-synonymous *SLC22A2* SNPs have been identified. In OCT1, 41C>T, 181C>T, 292T>C, 566C>T, 659G>T, 848C>T, 859C>G, 1022C>T, 1201G>A, 1256delATG, and 1393G>A have all been associated with functional changes which result in alterations in pharmacokinetics of its substrates (Choi & Song, 2008; Ciarimboli, 2011). Six OCT2 SNPs, 495G>A, 596C>T, 602C>T, 808G>T, 1198C>T, and 1294A>C were associated with phenotypic variation.

Among OCT1 polymorphisms, 4 were specific to Caucasians, 5 to African-Americans, and 3 to Asians (Choi & Song, 2008). In OCT2, 2 SNPs were found exclusively in Caucasians, 4 in African-Americans, and three in Asians. Some SNPs were common across races, but their frequencies varied. For example, in OCT1, the frequency of the variant 1022C>T was 8.2% in African Americans and 16% in Asians. In OCT2, the 808G>T variant allele frequency was 15.7% in Caucasians, 11% in African Americans, and 15% in Asians.

Expression and function of transporters in excretory organs and biological barriers

While a diverse set of organs and tissues are regulated by transporters, there are some similarities in how transporters function. Efflux transporters expressed on the basolateral side of epithelia extrude drugs from organs back into plasma, while basolateral influx transporters move drugs from the blood into the epithelia (Figures 1–3). Apical efflux transporters extrude drugs into the excrete (i.e., bile or urine) or into tissues, while apical influx transporters bring drugs from the lumen of the excretory organs into the epithelia or out of tissues into the epithelia. In this way, both influx and efflux transporters influence ADME and disposition of endogenous substrates (Leslie *et al.*, 2005). Endothelial and hematopoietic transporters also act as gatekeepers that regulate the tissue concentrations of drugs and primarily serve a protective function by limiting tissue exposure to certain substrates.

Gut—The gut wall is composed of several transporters that are expressed on the luminal membrane of enterocytes, including efflux transporters (e.g. ABCB1, ABCG2, ABCC2) and influx transporters (e.g. PEPT1, OATP2B1, OATP1A2) although uptake transporters are rather poorly characterized (Figure 1). Efflux transporters limit the absorption of various toxins in the gut lumen while influx transporters increase absorption of certain drugs. The interplay between these transporters, however, is complex. For instance, a decrease in fexofenadine exposure was observed when orally administered fexofenadine was administered with grapefruit juice (Cvetkovic *et al.*, 1999; Dresser *et al.*, 2005). This observation was unexpected given that fexofenadine is a substrate of ABCB1 and inhibition of ABCB1 with grapefruit juice was thought to increase fexofenadine exposure by blocking its efflux into the lumen of the gut. It was later determined, however, that grapefruit juice also blocks the influx transporter OATP1A2 thereby decreasing the oral absorption of this drug. However, little is known about how genetic variation in SLCO1A2 (encoding OATP1A2) affects the pharmacokinetics and therapeutic effects of its substrates (Franke *et al.*, 2009).

Drug substrates can also induce ABCB1 expression in the gut. For instance, long-term levothyroxine treatment induces enterocellular ABCB1 expression. Consequently, patients with hyperthyroidism may require larger-than-normal doses of multiple drugs, including (but not limited to): digoxin (Frye & Mathews, 1987), cyclosporine A (Jin *et al.*, 2005), and propanalol (Wells *et al.*, 1983); albeit, mulitiple transporters and enzymes in multiple organs may also be involved. Transporter expression in the gut is therefore based on pharmacotherapy and may influence relationships between polymorphisms and inter-individual variation in drug disposition and outcomes.

Genetic variation in transporters also affects the systemic exposure of a variety of drugs by altering the influx or efflux of drugs between the intestinal epithelial barrier and the gut lumen thereby influencing intestinal absorption. ABCG2 limits the oral bioavailability of its substrates by effluxing drugs back into the intestinal lumen. *In vitro* studies have shown that in ABCG2-deficient mice, the intestinal uptake, and thus oral bioavailability of quercetin and dietary carcinogens such as aflatoxin, was increased (Robey *et al.*, 2009). Additionally, the *ABCG2 421C>A* SNP is associated with decreased plasma membrane expression,

decreased transport, and a profound increase in oral bioavailability and plasma levels of sulfasalazine. The activity of sulfasalazine in ulcerative colitis (UC) depends on minimal absorption in the upper GI tract but decreased ABCG2 activity increases sulfasalazine absorption in the upper GI tract (Urquhart *et al.*, 2008).

Liver—In the liver, influx transporters of the SLC family act to uptake drugs into hepatocytes where metabolism occurs. Efflux transporters, primarily ATP-dependent transporters that are located at the canalicular or sinusoidal membrane of hepatocytes, then act to export these drugs and their metabolites back into the blood or into the bile (Muller & Fromm, 2011) (Figure 2). Both influx and efflux transporters play a critical role in drug metabolism and clearance. For instance, statin metabolism and elimination is largely governed by how rapidly the liver is able to uptake, metabolize, and then clear these drugs (Rodrigues, 2010).

Genetic variation in these transporters is a source of inter-individual variability of liver processing of drugs. For example, it was previously shown that in ABCG2-deficient mice, biliary excretion of various drugs, such as the antibiotics nitrofurantonin, ciprofloxacin, grepafloxacin, and ofloxacin was very low. Expression of transporters in the hepatocyte and other excretory organs can also influence ADME. For instance, individuals with certain *ABCG2* SNPs experience more extensive reductions in low-density lipoprotein cholesterol (LDL-C) after treatment with rosuvastatin because they have reduced capacity to remove statins from the liver and have increased GI-uptake due to reductions in ABCG2 activities (Generaux *et al.*, 2011). As a second example, individuals with certain SLCO1B1 polymorphism have a reduced rate of statin uptake resulting in slower metabolism and elimination of certain statins (Niemi *et al.*, 2004). Therefore, hepatocellular transport of drugs is a key facilitator of the metabolism and elimination of drugs.

Kidney—Proximal tubule epithelia express tight junctions that limit substrate diffusion; thus transporters are essential mediators of renal elimination pathways. Influx transporters, including OATPs, OATs, and OCTs transport substrates into the renal epithelial cell while various MRPs transport substrates back into the bloodstream (Figure 3). Equilibrative nucleoside transporters (ENTs) function as bidirectional receptors at the basolateral membrane. Lumenal efflux transporters, such as ABCs, MRPS, and MATEs, efflux substrates into the lumen. Other transporters, such as OATPs, OATs, OCTNs, CNTs, PEPTs and others, either pump drugs into the lumen, remove drugs from the lumen, or function as bidirectional pumps.

Transporter SNPs modulate the renal elimination of drugs. For example, OCT1 and OCT2 polymorphisms are related to altered uptake of metformin in the proximal-renal tubule (Shu *et al.*, 2001; Takane *et al.*, 2008; Wang *et al.*, 2008). More recent findings suggest that MATE1 is related to the elimination of metformin into the lumen, and polymorphisms in MATE contribute to the coordinate function of both transporters (Meyer zu Schwabedissen *et al.*, 2010).

Transporter SNPs can also influence organ-specific toxicities. For instance, cisplatin-induced nephrotoxicity is caused by increased uptake of cisplatin by OCT2 into the

proximal-renal tubular cells that are unable to eliminate cisplatin into the urine. A polymorphism in OCT2 that decreases renal uptake, 808G>T, is associated with lessened renal toxicity because less cisplatin is sequestered in the proximal tubule epithelia (Filipski *et al.*, 2009).

Endothelial barriers—There are multiple blood-tissue barriers that shelter various tissues from circulating blood (Poduslo *et al.*, 1994). Perhaps the best-known barrier is the BBB, which significantly limits the penetration of myriad substances into the CNS (Miller, 2010). The BBB is quite impermeable to the penetration of drugs, due to the presence of tight junctions between cells and the high expression of efflux transporters (i.e. P-glycoprotein) on the luminal membrane of the endothelial cells. Other blood-tissue barriers, however, can be more readily penetrated by various drugs. For instance, the blood-nerve-barrier (BNB) is composed of the endoneurial microvasculature and the innermost layers of the perineurium. Peripheral nerve microvascular endothelial cells (PnMECs) constitute the main interface between the peripheral nerves and the blood. PnMECs express P-glycoprotein, however, alterations to P-glycoprotein activity greatly increase drug penetration into the nerve, whereas the brain is less affected by decreased P-glycoprotein activity and remains highly impermeable to drugs (Saito *et al.*, 2001). Similarly, P-glycoprotein is expressed in the endothelium of the heart and other tissues that are more permeable toward circulating ABCB1 substrates (Meissner *et al.*, 2004; Meissner *et al.*, 2002).

Genetic polymorphisms in transporters influence the degree to which the nervous system is exposed to various compounds. Few studies have characterized ABCB1 expression in endothelial cells based on genetic variation, but two evaluated ABCB1 SNP effects on expression in cardiac endothelium (Meissner *et al.*, 2002). Contrary to most other tissues, patients carrying variant alleles at *2677G>T* and *3435C>T* actually express higher levels of ABCB1 in the endocardium and are more protected from cardiotoxic drugs (Meissner *et al.*, 2004; Sissung *et al.*, 2011). We previously demonstrated that patients carrying ABCB1 variants have a greater propensity to distribute drugs into extrahepatic tissues if they carry variant alleles (i.e., less ABCB1 function) (Sissung *et al.*, 2008). While, it is currently unclear how ABCB1 variants influence endothelial expression of ABCB1, ABCB1 does protect various tissues from toxic substances, and *ABCB1* alleles influence the degree to which these substances enter tissues (Sissung *et al.*, 2008).

Hematopoietic cells—Nearly all hematopoietic cells express drug transporters that regulate various endobiotic processes, (Table 2) alter paracrine signaling, and can confer resistance to therapeutics in normal and diseased (e.g., HIV-infected or cancerous) cells (Kock *et al.*, 2007). In normal lymphocytes ABCB1 expression ranges from 20–80% of B-cells and 30–100% of T-cells (Kock *et al.*, 2007), whereas approximately 40–65% of leukocytes express ABCB1 (Chaudhary *et al.*, 1992). Monocytic expression of ABCB1 has been problematic for HIV therapeutics that are substrates of ABCB1; this is especially true for antiretrovirals that induce ABCB1 expression in target cells (Kock *et al.*, 2007). ABCB1 overexpression is also a problem in the treatment of leukemia. Some estimate that 45% of patients with newly diagnosed AML overexpress ABCB1, while 65% of patients with refractory AML overexpress ABCB1 (Robey et al., 2009). ABCB1 effluxes multiple

therapeutics used to treat AML (Kock *et al.*, 2007). However, ABCB1 also protects hematopoietic cells from cytotoxicity of certain anticancer therapies. For instance, taxanes can cause severe neutropenia, and higher ABCB1 expression appears to have a protective effect (Sissung *et al.*, 2008; Sissung *et al.*, 2006).

Polymorphisms in *ABCB1* and *ABCG2* have been linked to differential transport of substrates in hematopoietic cells (Hitzl *et al.*, 2001). These studies consistently found that carriers of *ABCB1* variant alleles have lower expression and function of ABCB1 in multiple cell populations (Hitzl *et al.*, 2001). Studies in mice lacking various ABC transporters demonstrated that normal physiological processes were interrupted while certain hematopoietic cells were more susceptible to drug-induced toxicity (Kock *et al.*, 2007). Therefore, ABCB1 variants alter the physiology, disease, and treatment with agents that target or cause undesirable toxicity in hematopoietic cells.

Transporter pharmacogenetics in normal physiology and pathophysiology

Transporter genetic variation is responsible for a variety of effects of pharmacotherapy on different organ systems and tissues. However, the ultimate measure of the complexities of transporters is how an individual patient responds to drug therapy. Transporter genetics can influence disease etiology, disease progression, and the disposition towards endogenous substrates, drug clearance, drug distribution, and drug resistance; all of these factors then influence the response to treatment. Therefore, transporter pharmacogenetics is very complex with a single variant potentially influencing a variety of processes involved in diseases and treatments. Consequently, there is considerable heterogeneity in the literature and few true pharmacogenetic tests are currently available that inform therapy decisions.

Transporter genetics affect physiological substrates—Studies are emerging suggesting that commonly inherited transporter polymorphisms can affect inter-individual variation in normal physiology. For instance, polymorphisms in transporters are related to sterol homeostasis, lipid metabolism, uric acid elimination, conjugated bilirubin extrusion into the bile, and others (Ueda, 2011). For example, the *ABCG2 421C>A* SNP that encode Q141K is strongly associated with hyperuricemia (i.e., gout) such that ~10% of gout cases in whites are attributable to this SNP (Dehghan *et al.*, 2008; Dresser *et al.*, 2005; Woodward *et al.*, 2009). ABCG2 is localized to the brush border of the proximal tubule where it plays a role in renal filtration of urate, and Q141K results in a 53% reduction in the rate of urate efflux (Woodward *et al.*, 2009).

Transporter expression is also affected by physiologic substrates that interact with various nuclear receptors (i.e., PXR, CAR, MR, GR, FXR, VDR, etc.). PXR is involved in the expression of a wide array of transporters and metabolizing enzymes (Tirona, 2011). PXR is activated by myriad substrates such as xenobiotics, glucocorticoids, antibiotics, and bile acids; these substrates bind to PXR resulting in its nuclear localization and transcription of its target genes (Tirona, 2011).

PXR expression was very low in endoscopic biopsies of patients with ulcerative colitis (UC), resulting in reduced expression of PXR-induced detoxification enzymes and drug transporters (Langmann *et al.*, 2004; Ufer *et al.*, 2009). Several investigators have studied

ABCB1 and PXR genetic variation in UC. Four studies investigated the role of PXR SNPs in adult UC so far with three confirming a relationship between PXR SNPs and UC (Andersen *et al.;* Dring *et al.*, 2006; Martinez *et al.*, 2007), and one not confirming the relationship (Choudhuri & Klaassen, 2006), though in the latter study, SNP frequency differed in the control population, not the patient population. Multiple studies (Ardizzone *et al.*, 2007; Fiedler *et al.*, 2007; Ho *et al.*, 2005; Ho *et al.*, 2006; Huebner *et al.*, 2009; Juyal *et al.*, 2009; Martinez *et al.*, 2007; Ostergaard *et al.*, 2009; Osuga *et al.*, 2006; Tahara *et al.*, 2008; Urcelay *et al.*, 2006) and two meta-analyses (Annese *et al.*, 2006; Onnie *et al.*, 2006) have demonstrated that *ABCB1* variants are related to the risk of UC, with few demonstrating no relationship (Fischer *et al.*, 2007; Oostenbrug *et al.*, 2006; Palmieri *et al.*, 2005). Martinez et al. ((Martinez *et al.*, 2007) detected significant interaction between *ABCB1* and *PXR* in UC. This suggested an epistatic interaction whereby *PXR* And *ABCB1* allelic variation influences *ABCB1* expression in the UC gut, and therefore both alleles contribute to disease susceptibility by altering *ABCB1* expression. Moreover, the *3435C>T* SNP has recently been related to UC therapy with tacrolimus due to local uptake deficiencies (Herrlinger *et al.*, 2011). Therefore, it appears that breakdown of the gut detoxification system, merely by altering the expression of the ABCB1 transporter, is involved in UC etiology and treatment.

Disease biology can also influence transporter interactions with physiologic substrates. For example, we identified a testosterone-transporting function of OATP1B3 in which commonly inherited polymorphisms (i.e. S112A and M233I) influenced the degree to which testosterone was imported into cells (Hamada *et al.*, 2008). Although OATP1B3 was originally considered a liver-specific transporter, we also showed that OATP1B3 was aberrantly expressed in a variety of tumors, including prostate cancer (Hamada *et al.*, 2008; Pressler *et al.*, 2011). We then determined that polymorphisms in *SLCO1B3* were associated in the duration of the response to androgen-deprivation therapy (ADT), and overall survival from diagnosis in men with prostate cancer (Hamada *et al.*, 2008; Sharifi *et al.*, 2008; Yang *et al.*, 2011). This has since been confirmed by others (Wright *et al.*, 2011). It remains to be determined if prostate tumors are more susceptible to certain OATP1B3 substrate drugs based on their increased expression at the site of the tumor.

The physiological and pathophysiological role of transporter polymorphisms is poorly studied in comparison to their role in drug disposition. It is therefore crucial that future investigations focus on how inherited genetic variation in transporters influences the etiology, disease-state, and treatment of different illnesses that are treated with pharmacological substances that are themselves substrates of drug transporters. Such research will make the application of transporter pharmacogenetics in personalized medicine more likely.

Transporter pharmacogenetics in clinical pharmacology

Transporter genetics in drug pharmacokinetics—Transporter genetic variants are heavily linked to inter-individual variation in drug pharmacokinetics. Initial reports indicated that the *ABCB1 3435C>T* polymorphism was related to lowered ABCB1 expression and higher digoxin concentrations (Hoffmeyer *et al.*, 2000). In addition, the

ABCB1 2677G>T/A and *3435C>T* haplotype was more strongly related to digoxin pharmacokinetics (i.e. variants had high AUC) (Johne *et al.*, 2002; Verstuyft *et al.*, 2003). Other studies of the relationship between *ABCB1* SNPs and drug pharmacokinetics have been largely inconsistent (reviewed in (Cascorbi, 2006; Eichelbaum *et al.*, 2004; Haufroid, 2011; Sakaeda, 2005)).

This inconsistency is largely due to the multiple functions of ABCB1. For example, ABCB1 also regulates absorption of drugs through the gut wall (oral drugs), limits drug biodistribution into a variety of extrahepatic tissues, transports drugs into the cerebro-spinal fluid, eliminates drugs through both the renal and hepatobilliary routes, and mediates enterohepatic recirculation. Moreover, a single variant in *ABCB1* can produce opposite effects on transporter expression in different tissues (Hoffmeyer *et al.*, 2000; Meissner *et al.*, 2004) and there are a number of synergistic compensatory transport pathways for certain drugs (Zhou *et al.*, 2009). As such, the contribution of *ABCB1* pharmacogenetics towards drug ADME is extremely complex and is largely dependent upon the properties of each individual drug. Adding to the complexity of these studies is the heterogeneity of patient populations undergoing a variety of therapies and cotherapies.

As an example, multiple studies have showed that docetaxel pharmacokinetics is related to *ABCB1* alleles, whereas other studies failed to confirm these findings (Baker *et al.*, 2009; Bosch *et al.*, 2006; Chew *et al.*, 2011; Fajac *et al.*, 2010; Sissung *et al.*, 2008; Tran *et al.*, 2006). This is likely because intravenous docetaxel is biodistributed differently in the extrahepatic tissues of patients carrying different genetic variants, is eliminated by ABCB1 to a different extent, and undergoes enterohepatic recirculation. Each of these events can alter the plasma pharmcokinetic profile of docetaxel and each event is likely influenced by ABCB1 SNPs differently. In addition, docetaxel is heavily transported by ABCB1, and ABCC2 may compensate for deficiencies in ABCB1-mediated transport. Therefore, it is exceedingly difficult to ascertain a true mechanism behind the contribution of *ABCB1* polymorphisms to changes in drug pharmacokinetics.

In summary, ABCB1 is poorly understood for the following reasons: (i) high genetic variation in different populations (i.e. different haplotypes) that are poorly understood; (ii) variability in a given SNPs influences on expression/function in different organ systems; (iii) compensatory transporters; (iv) expression in multiple organs influences several biological processes involved in absorption, distribution, elimination, and enterohepatic recirculation; (v) ABCB1 transports myriad substrates; and (vi) physiological and disease influences on drug transport.

SNPs in other transporters clearly influence drug therapy. These transporters tend to be expressed in fewer tissues and regulate fewer biological processes. For example, the OATP1B1 is almost exclusively expressed in hepatocytes where it is involved in the uptake of bile acids, eicosanoids, DHEA, estrogens, and other endogenous compounds (Niemi *et al.*, 2011). Thus, OATP1B1 is primarily involved in influxing compounds into the liver where they are subsequently metabolized, not in multiple other biological pathways relating to drug pharmacokinetics. OATP1B1 is known to transport all statins in current clinical use, and the *SLCO1B1* (encoding OATP1B1) *521C>T* SNP was initially related to increased

AUC of pravastatin (Niemi *et al.*, 2004) and the unfavorable plasma pharmacokinetics of cholesterol synthesis biomarkers (Niemi *et al.*, 2005). A comparison of all statins demonstrated that simvastatin pharmacokinetics was heavily influenced by *SLCO1B1 521C>T* (3.2-fold increase in AUC in *521CC* carriers) followed by atorvastatin, and pravastatin or rosuvastatin. Fluvastatin AUC was not affected by *SLCO1B1 521C>T* presumably because fluvastatin is influxed into liver by several other uptake transporters (Niemi *et al.*, 2011).

Therefore, transporter SNPs are important determinants of inter-individual variation in the pharamcokinetic profiles of a multitude of agents. However, plasma pharmacokinetics is typically derived from plasma concentration vs. time profiles that are insufficient to detect the multiple contributions of transporters to bodily functions that affect the various aspects of pharmacokinetics. Therefore, multivariate pharmacokinetic models must incorporate well-studied genetic variants to better represent the contribution of transporters to the ADME properties of drugs.

Drug efficacy—Multiple studies have investigated how transporter polymorphisms are related to the benefit of various agents (Sissung *et al.*, 2010). For instance, evidence suggests that the anti-platelet activity of clopidogrel is linked to *ABCB1 3435C>T* (reviewed in (Ellis *et al.*, 2009; Johnson *et al.*, 2011)). An initial study determined that patients carrying two variant alleles at *ABCB1 3435C>T* had a higher event rate at 1 year than those carrying wild-type alleles. Those carrying variant alleles in both *CYP2C19* And *ABCB1* had the highest risk of events (HR(95%CI)=5.31(2.13–13.20)) (Simon *et al.*, 2009). This finding was not replicated in a GWAS study of the healthy Amish population, although it is unclear why the two studies present different findings (Shuldiner *et al.*, 2009). In a larger study of patients with acute coronary syndromes, *ABCB1 3435C>T* was again strongly related to increased cardiovascular death, MI, or stroke during clopidogrel therapy (HR(95%CI) = 1.72(1.22–2.44)), but did not have increased risk of reduced prasugrel efficacy (Mega *et al.*, 2010). This same study demonstrated that healthy volunteers receiving clopidogrel had a 7.3% reduction in maximum platelet aggregation if they carried *3435TT* genotypes. A more recent study conflicted with these results (Wallentin *et al.*, 2010).

Drug toxicity—Statin-induced myopathy is directly related to the AUC of circulating active statin metabolites. As such, the *SLCO1B1* SNPs that influence the exposure to active statin metabolites are also associated with statin-induced myopathy (Niemi, 2010). However, not all pharmacogenetic relationships with toxicity are due to plasma exposure-related differences. For instance, the aforementioned blood-endothelial barriers polymorphically exclude certain drugs from different tissues. For instance, we previously showed that taxane-induced neutropenia and peripheral neuropathy were associated with SNPs in *ABCB1*; however, these same SNPs were not related to overall exposure to docetaxel in the plasma (Baker *et al.*, 2009; Bosch *et al.*, 2006; Chew *et al.*, 2011; Fajac *et al.*, 2010; Sissung *et al.*, 2008; Tran *et al.*, 2006). We have also shown that intracardiac romidepsin exposure and QT-interval were increased in mice lacking *ABCB1*, although the plasma pharmacokinetics was unchanged (Sissung *et al.*, 2011). Humans have polymorphic expression of ABCB1 in the cardiac endothelium (Meissner *et al.*, 2004), and those carrying

alleles associated with low intracardiac ABCB1 expression had the highest QT-interval prolongation following romidepsin (Sissung *et al.*, 2011). Therefore, since ABCB1 expression in hematopoietic cells and endothelial blood-tissue barriers varies with inherited ABCB1 polymorphisms, these polymorphisms also alter the exposure of certain tissues independently of the plasma.

Drug-drug interactions—Many drugs are substrates of multiple transporters and are also metabolized by similar cytochrome P450. This has complicated the evaluation of drug-drug interactions with transporters because genetic variation in a single transporter is unlikely to alter the ADME properties of a given drug consistently among a large group of patients with various comorbidities and cotherapies. Nonetheless, inhibition of polymorphic transporters clearly influences several drug-drug interactions. For instance, certain drugs (e.g., gemfibrozil) inhibit multiple transporters and cytochrome P450s in the liver and elsewhere (Muller & Fromm, 2011). The hepatocyte is the site for the pharmacological action of statin drugs while the plasma exposure to statins and their metabolites is responsible for statin-induced myotoxicity (Rodrigues, 2010). Since OATP1B1 is mainly a liver influx transporter, inhibition of OATP1B1 increases the myotoxic effects of statins while reducing their activity as HMG-CoA reductase inhibitors.

CONCLUSION

Transporter pharmacogenetics is an important source of inter-individual variation in organ function, physiology, disease, and drug treatment. Despite the large number of studies devoted to transporter pharmacogenetics and transporters in general, there has been relatively little progress in using germline genetic markers in transporters in the clinic. Future studies must be broadened in order to capture the intricacies of how a single variant can influence the entire spectrum of bodily functions and drug disposition/activity.

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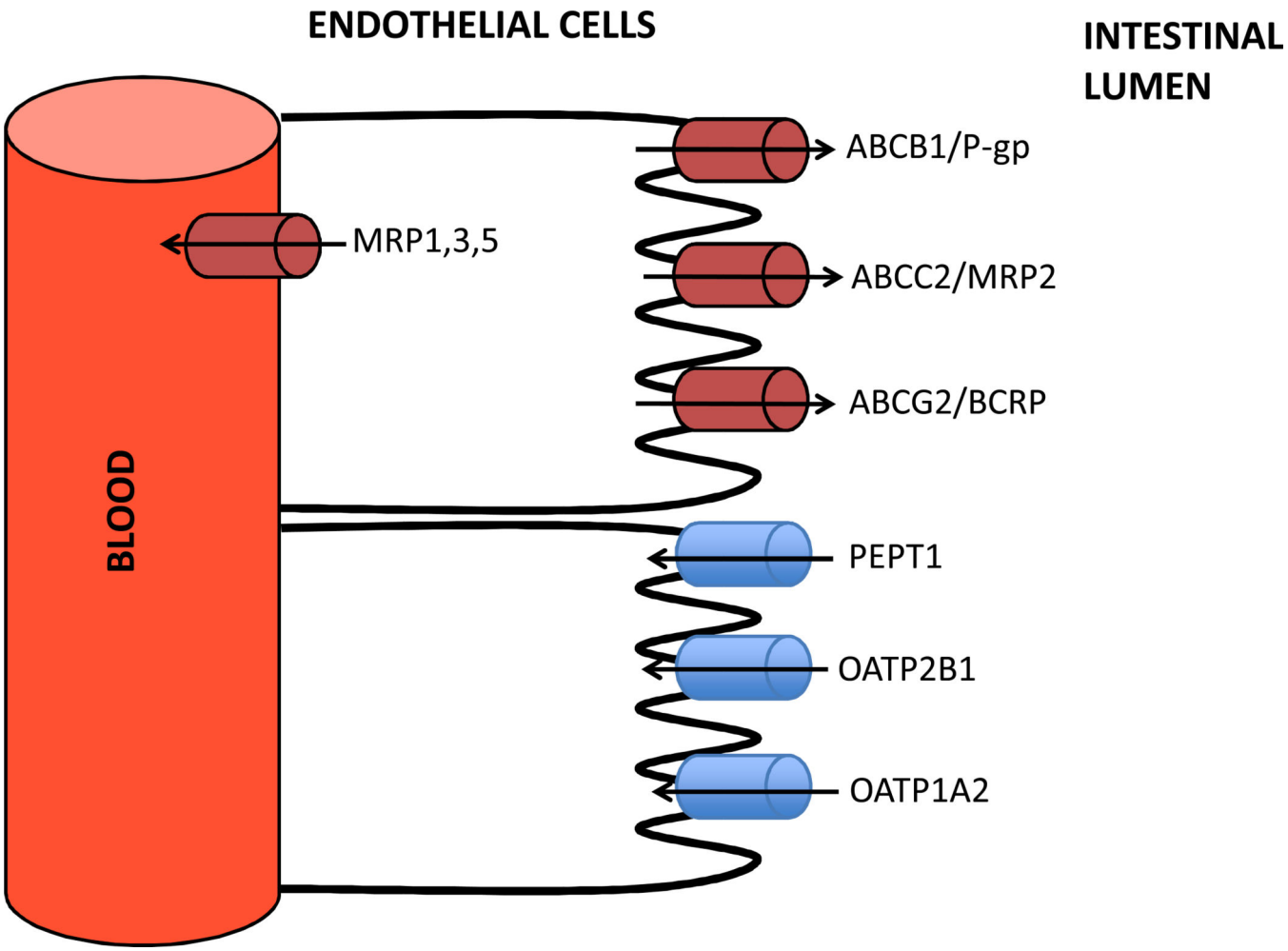

Figure 1.

Select transporters expressed in the gastrointestinal (GI) tract. Efflux transporters (red) efflux substrates back into the intestinal lumen, while influx transporters (blue) influx substrates from the intestinal lumen into the blood. PEPT: peptide transporter.

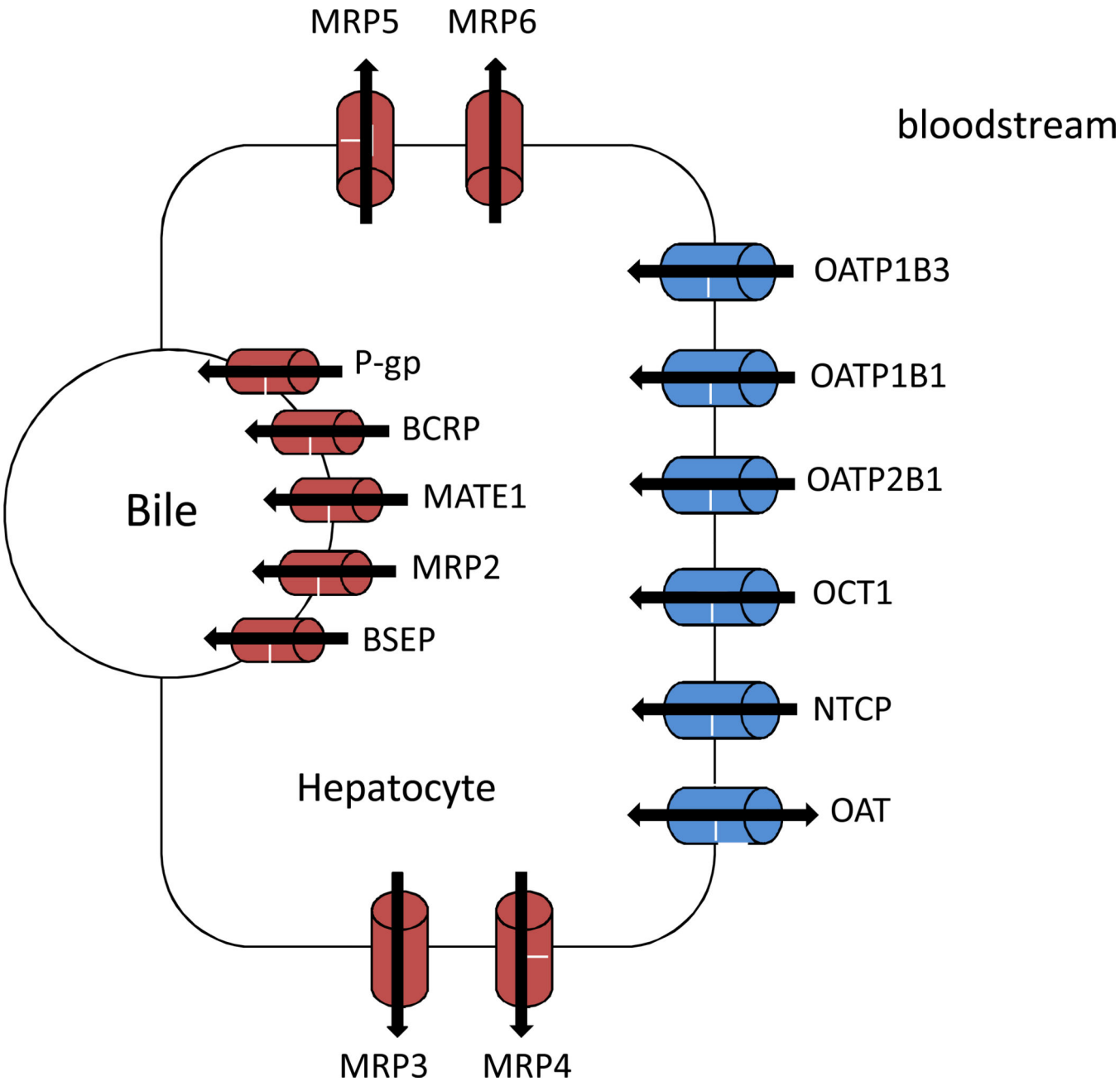

Figure 2.

Select transporters expressed on the canalicular and sinusoidal membrane of hepatocytes. Influx transporters (blue) transport drugs from the blood into hepatocytes where they are metabolized. Efflux transporters (red) then efflux drugs and their metabolites into bile or back into the blood. MATE1: multidrug and toxin extrusion 1 protein; MRP: multidrug resistance protein; NTCP: Sodium/taurocholate cotransporting polypeptide; OCT: Organic cation transporter.

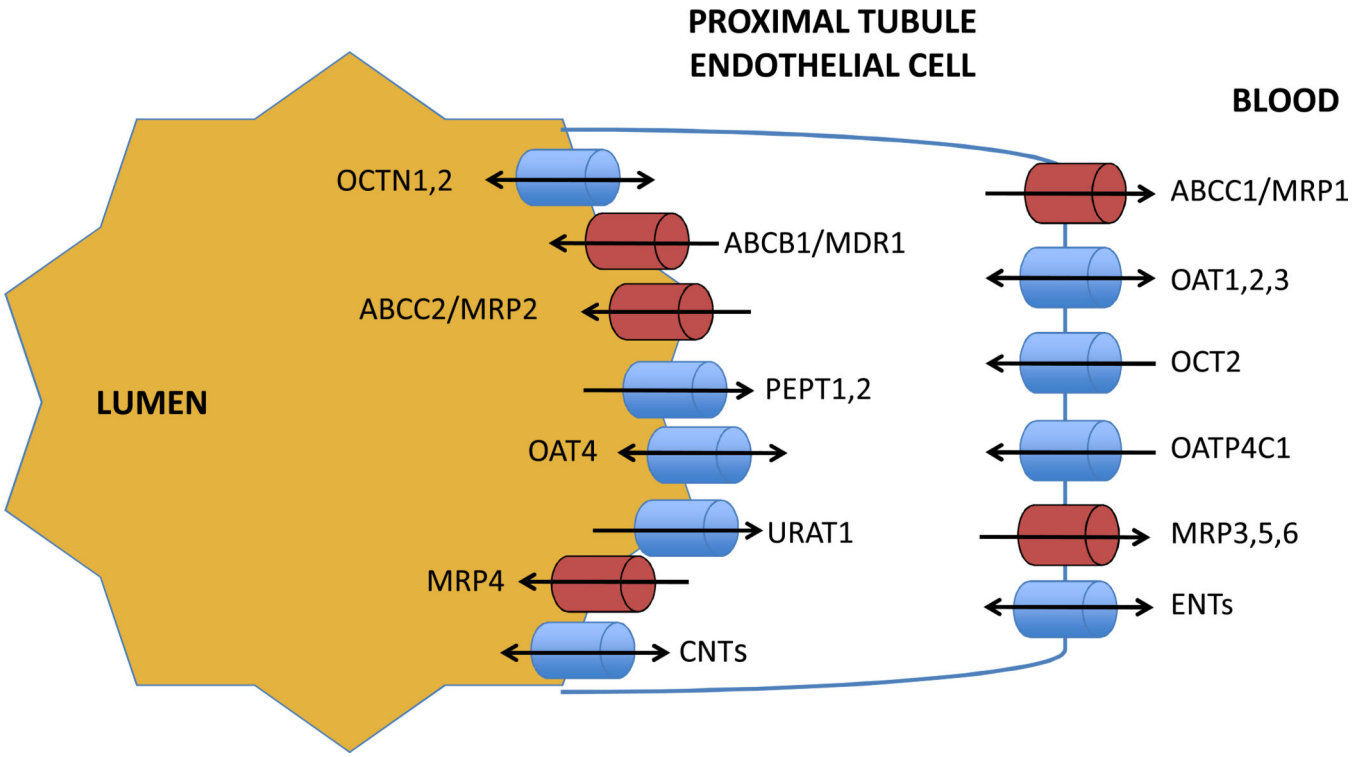

Figure 3.

Select transporters expressed in the renal proximal tubule. Influx transporters on the basolateral membrane (blue) influx substrates from the blood into the renal epithelial cells, while efflux transporters (red) transport substrates back into the blood. On the lumenal membrane, efflux transporters efflux substrates into the lumen, while influx transporters remove drugs from the lumen or act as bidirectional pumps. ENTs: equilibrative nucleoside transporters; CNTs: concentrative nucleoside transporters.

Table 1

Substrates and inhibitors of ABCB1, ABCG2, ABCC2, OATP1B1, OATP1B3 (adapted from Sissung et al., 2010)(Sissung *et al.*, 2010)

ABCB1	**Substrates**	**Inhibitors**
Antibiotics	actinomycin D erythromycin gramicidin D rifampin salinomycin sparfloxacin valinomycin	
Anti-Cancer Drugs	bisantrene daunorubicin diflomotecan docetaxel doxorubicin epirubicin etoposide gefitinib imatinib irinotecan mitoxantrone paclitaxel romidepsin teniposide tipifarnib vinblastine vincristine	sunitinib tamoxifen
Antifungals	itraconazole ketoconazole	ketoconazole
Antihistamines	certirizine fexofenadine loratadine terfenadine	
Antihypertensive Drugs	losartin talinolol	nicardipine quinidine verapamil
CNS Drugs	chlorpromazine clozapine fluphenazine olanzapine quetiapine risperidone	
Flavonoids		biochanin A genistein oroxylin A
Heart Medications	digoxin diltiazem ouabain quinidine verapamil	gallopamil
HIV-1 Protease Inhibitors	abacavir amprenavir aquinavir darunavir indinavir lopinavir nelfinavir ritonavir saquinavir	
Immunosuppressants	cyclosporin A dexamethasone D-penicillamine enkephalin	cyclosporin A valspodar

	FK 506 hydrocortisone prednisolone rapamycin tacrolimus triamcinolone	
Sedatives		midazolam
Statins	atorvastatin cerivastatin lovastatin	
Miscellaneous	asimadoline cimetidine colchicine domperidine eletriptan flesinoxan glabridin ivermectin loperamide ondansetron quinacrine ranitidine topiramate	dexverapamil emopamil JAI-51 quinacrine tariquidar
ABCG2	**Substrates**	**Inhibitors**
Antibiotics	ciprofloxacin erythromycin nitrofurantoin norfloxacin ofloxacin	novobiocin rapamycin
Anti-Cancer Drugs	9-aminocamptothecin bisantrene cladribine daunorubicin diflomotecan doxorubicin epirubicin erlotinib etoposide flavopiridol gefitinib gimatecan homocamptothecin imatinib methotrexate mitoxantrone SN-38 (irinotecan metabolite) teniposide tomudex topotecan	biricodar diethylstilbestrol elacridar fumitremorgin gefitinib ginsenoside ortataxel sunitinib tamoxifen tryprostatin vandetanib
Antihypertensive Drugs	olmesartan	dihydropyridine dipyridamole reserpine
Anti-inflammatory Drugs		chrysin curcumin
Antiplatelets	dipyridamole	
Calcium Channel Blockers	azidopine dipyridamole nitrendipine	nicardapine nimodipine nitrendipine
Flavonoids	seravastatin	acacetin apigenin genistein naringenin quercetin silymarin techochrysin

HIV-1 Protease Inhibitors	abacavir lamivudine nelfinavir zidovudine (AZT)	abacavir amprenavir atazanavir delavirdine efavirenz lopinavir nelfinavir ritonavir saquinavir
Immunosuppressants	cyclosporin A lefunomide sirolimus sulfasalazine tacrolimus	cyclosporin A sirolimus tacrolimus
Specific Inhibitors		GF120918 Ko143 tariquidar (XR9576)
Statins	pitavastatin posuvastatin seravastatin	rosuvastatin
Miscellaneous	glyburide protoporphyrin	pantoprazole
ABCC2	**Substrates**	**Inhibitors**
Antibiotics	ampicillin azithromycin cefodizime ceftriaxone grepafloxacine	azithromycin
Anti-Cancer Drugs	camptothecin cisplatin doxorubicin etoposide irinotecan methotrexate mitoxantrone vinblastine vincristine	BTK lonafarnib
Antihypertensive Drugs	olmesartan	
Antiinflammatory Drugs		curcumin
Blood-Glucose Lowering Drugs		glibenclamide
HIV-1 Protease Inhibitors	adefovir cidofovir indinavir lopinavir nelfinavir ritonavir saquinavir	
Immunosuppressants		cyclosporin A
Statins	pravastatin	
Miscellaneous	temocaprilate valproate	MK-571 furosemide PAK-104P phenobarbital probenecid
OATP1B1	**Substrates**	**Inhibitors**

Antibiotics	benzylpenicillin rifampin	clarithromycin erythromycin hyperforin rapamycin rifampin rifamycin SV roxithromycin telithromycin
Anti-Cancer Drugs	ACU-154 atrasentan Bamet-R2 Bamet-UD2 demethylphalloin dihydromicrocystin-LR irinotecan methotrexate SN-38	antamanide ketoconazole paclitaxel PKI-166 SN-38
Anti-Diabetics		glibenclamide pioglitazone rosiglitazone
Antifungals	caspofungin	clotrimazole
Antihistamines	fexofenadine	
Antihypertensive Drugs	bosentan enalapril olmesartan temocapril valsartan	telmisartan
Antiinflammatory Drugs	valsartan D-penicillamine enkephalin troglitazone sulfate	troglitazone troglitazone sulfate
Blood-Glucose Lowering Drugs	repaglinide	
Fibrates		gemfibrozil gemfibrozil-1-Oglucuronide
Flavonoids		biochanin A
Heart Medications		digoxin
HIV-1 Protease Inhibitors		indinavir nelfinavir ritonavir saquinavir
Immunosuppressants		cyclosporin A tacrolimus
Statins	atorvastatin cerivastatin fluvastatin pitavastatin pravastatin rosuvastatin simvastatin acid	atorvastatin BMS-241423 atorvastatin analogue) BMS-243887 atorvastatin analogue) lovastatin lovastatin acid lovastatin lactone pravastatin simvastatin simvastatin lactone
Miscellaneous	BQ-123 bromosulphophthalein	carbamazepine glycyrrhizin metyrapone mifepristone sildenafil
OATP1B3	**Substrates**	**Inhibitors**

Antibiotics	rifampin	clarithromycin erythromycin hyperforin rifampin rifamycin roxithromycin telithromycin
Anti-Cancer Drugs	demethylphalloin dihydromicrocystin-LR docetaxel imatinib irinotecan methotrexate paclitaxel SN-38	
Antihistamines	fexofenadine	
Antihypertensives	bosentan enalapril olmesartan telmisartan valsartan	
Anti-inflammatory Drugs	D-penicillamine enkephalin	troglitazone sulfate
Blood-Glucose Lowering Drugs	repaglinide	
Heart Medications	digoxin ouabain	
Immunosuppressants		cyclosporin A
Statins	fluvastatin pitavastatin pravastatin rosuvastatin	pravastatin
Miscellaneous	BQ-123 bromosulphophthalein	bromosulphophthalein glycyrrhizin

Table 2

Selected ABC transporters expressed in peripheral blood cells (adapted from Kock et al., 2007) (Kock *et al.*, 2007)

Peripheral Blood Cell	Transporters Expressed
Natural Killer (NK) Cell	P-gp, MRP1, Mini-P-gp
T Cell	P-gp, MRP1, MRP2
B Cell	P-gp, MRP1
Erythrocyte	MRP1, MRP4, MRP5, BCRP, P-gp (?)
Monocyte	P-gp
Neutrophil G	P-gp
Eosinophil G	P-gp
Basophil G	P-gp
Platelet	MRP4, MRP1