Drug Transporters in Drug Efficacy and Toxicity

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Abstract

Drug transporters are now widely acknowledged as important determinants governing drug absorption, excretion, and, in many cases, extent of drug entry into target organs. There is also a greater appreciation that altered drug transporter function, whether due to genetic polymorphisms, drug-drug interactions, or environmental factors such as dietary constituents, can result in unexpected toxicity. Such effects are in part due to the interplay between various uptake and efflux transporters with overlapping functional capabilities that can manifest as marked interindividual variability in drug disposition in vivo. Here we review transporters of the solute carrier (SLC) and ATP-binding cassette (ABC) superfamilies considered to be of major importance in drug therapy and outline how understanding the expression, function, and genetic variation in such drug transporters will result in better strategies for optimal drug design and tissue targeting as well as reduce the risk for drug-drug interactions and adverse drug responses.

INTRODUCTION

SLC: solute carrier

OCT: organic cation transporter

MATE: multidrug and toxin extrusion

OAT: organic anion transporter

OATP: organic anion transporting polypeptide

ABC: ATP-binding cassette

MRP: multidrug resistance-associated protein

Optimizing drug efficacy and minimizing drug toxicity requires that the drug reach its target at adequate concentration, without excessive accumulation in other tissues. For many drugs in clinical use today, intracellular concentration is determined by the balance in activity of multiple uptake and efflux transporters that facilitate the drugs' movement across biological membranes. Transporters are large, membrane-bound proteins expressed in tissues throughout the body; those found in the epithelia of major organs of absorption and secretion such as liver, intestine, and kidney and in sanctuary sites such as the brain, testes, and placenta are of particular importance in drug disposition (**Figure 1**). Interindividual variation in transporter activity can arise from numerous factors, including genetic heterogeneity, certain disease processes, concomitant medications, and herbals and dietary constituents that may inhibit or induce transporter expression or activity (1–3).

Transporter function has been studied extensively in vitro through the use of cRNA-injected *Xenopus laevis* oocytes and transfected mammalian cell lines. Knockout mice and other animal models have provided significant insights into the role of transporters in vivo, particularly when multiple transporters with overlapping substrate specificities are expressed in the same tissue. However, species-related differences in transporter expression and substrate specificity are relatively common and need to be considered when the results of experiments in rodent models are being interpreted. In humans, the role of transporters in drug efficacy and toxicity has been indirectly shown by inhibition or induction studies both in healthy volunteers and in patients. Naturally occurring genetic polymorphisms cause reduced expression or function of specific transporters, an effect that is not readily achieved by pharmacological inhibitors in most cases. For this reason, studies in human subjects with genetic polymorphisms have been instrumental in defining the clinical relevance of certain transporters to drug disposition and response.

Given the critical role of transporters in mediating the pharmacokinetics of many drugs, transporter studies are an important part of the drug discovery and development process. A recent report from the International Transporter Consortium provides some guidance for the circumstances under which transporter studies may be indicated for a new molecular entity during the drug development process, with the caveat that the proposed decision structures will continue to evolve as the drug transporter field matures (1).

In this review, we focus on transporters with well-defined roles in drug efficacy and toxicity. From the solute carrier (SLC) superfamily, these include the organic cation transporters (OCTs/*SLC22A*), the multidrug and toxin extrusion transporters (MATE transporters/*SLC47A*), the organic anion transporters (OATs/*SLC22A*), and the organic anion transporting polypeptides (OATPs/*SLCO*). Members of the ATP-binding cassette (ABC) superfamily important in drug efficacy and toxicity include P-glycoprotein (MDR1/*ABCB1*), breast cancer resistance protein (BCRP/*ABCG2*), and transporters of the multidrug resistance-associated protein (MRP/*ABCC*) family.

UPTAKE TRANSPORTERS OF THE SOLUTE CARRIER SUPERFAMILY

The SLC superfamily is a large family of membrane-bound transporters that share 20–25% sequence homology. SLC transporters translocate their substrates across biological membranes through numerous mechanisms, including facilitated diffusion, ion coupling, and ion exchange, which, in some cases, is driven by an ion gradient that is maintained by active transporters of the ABC superfamily (4).

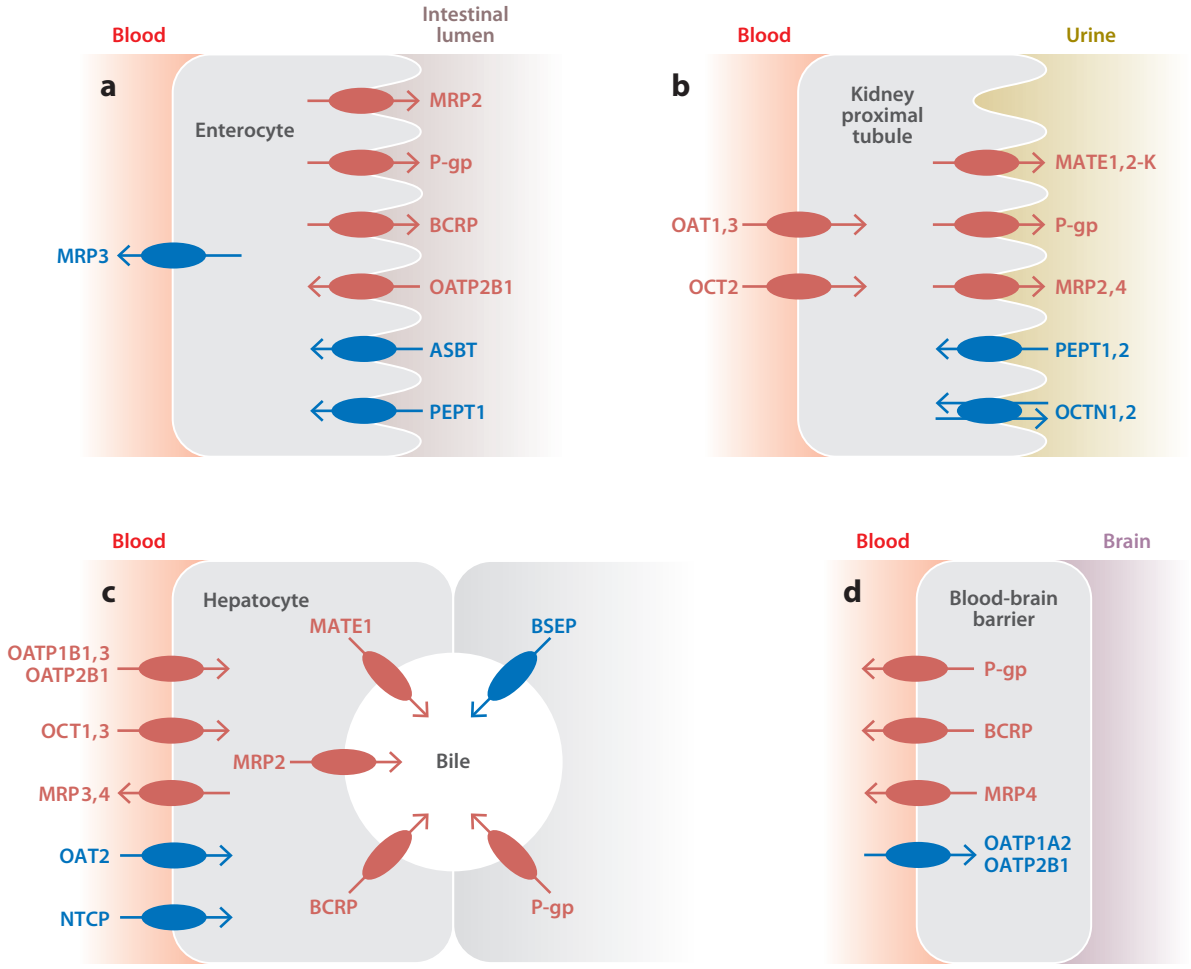

Figure 1

Expression of transporters with major roles in drug efficacy or toxicity in (*a*) human intestinal epithelia, (*b*) kidney proximal tubule epithelia, (*c*) hepatocytes, and (*d*) brain capillary endothelial cells. Transporters discussed in the text are colored red. NTCP, ASBT, and BSEP are bile acid transporters. PEPT1 and PEPT2 transport small peptide fragments. OCTN1 and OCTN2 transport organic cations and carnitine. Abbreviations: ASBT, apical sodium-dependent bile acid cotransporter; BCRP, breast cancer resistance protein; BSEP, bile-salt export pump; MATE, multidrug and toxin extrusion; MRP, multidrug resistance-associated protein; NTCP, sodium-dependent taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; PEPT, peptide transporter; P-gp, P-glycoprotein.

Organic Cation Transporters

Organic cation transporters (OCTs/*SLC22A*) identified in humans include OCT1 (*SLC22A1*) and OCT2 (*SLC22A2*), which are predominantly expressed on the basolateral membranes of hepatocytes and kidney proximal tubules, respectively, and OCT3 (*SLC22A3*), which is more widely expressed in tissues throughout the body. OCTs are uptake transporters that control cellular entry of small, positively charged compounds, including endogenous substrates, such as monoamine neurotransmitters and creatinine, and numerous drug substrates, including the platinum-containing antineoplastics, the antidiabetic metformin, and the histamine H2 receptor

antagonist cimetidine (5–7). OCT expression is highly variable among individuals, which may be a result of genetic variants or disease processes: A study of OCT1 and OCT3 expression in 150 livers from Caucasian subjects revealed significant variation that was associated with genetic polymorphisms and cholestasis (8).

SNP: single-nucleotide polymorphism

Organic cation transporters in efficacy. The importance of cation transport in drug efficacy has been appreciated as a result of studies of metformin, a commonly prescribed antidiabetic whose clinical response is highly variable. Metformin lowers blood glucose primarily by reducing hepatic glucose production and enhancing peripheral insulin sensitivity and is eliminated by the kidney unchanged (9). A large number of functional single-nucleotide polymorphisms (SNPs) in genes encoding OCTs have been identified and characterized in vitro (10–16), and subsequent studies have demonstrated a role for *SLC22A1* and *SLC22A2* polymorphisms in mediating metformin pharmacokinetics and response in healthy volunteers (17–21; **Table 1**). The relative contribution

Table 1 Transporter polymorphisms involved in metformin pharmacokinetics and response

Transporter/polymorphism	Population studied	Experimental approach	Effect of polymorphism	Reference(s)
OCT1 R61C (rs12208357) G401S (rs34130495) 420del (rs72552763) G465R (rs34059508)	Healthy subjects ($n = 20$)	Candidate gene; Full pharmacokinetics profile	Increased C_{max} and AUC	20
	Healthy subjects ($n = 21$)	Candidate gene; Oral glucose tolerance test	Higher plasma glucose levels	19
	Polycystic ovary syndrome patients ($n = 150$)	Candidate gene; Prospective population cohort study	Reduced effect on total cholesterol, triglycerides, and insulin levels	29
OCT1 (rs622342)	Diabetic patients ($n = 102$)	Candidate gene; Retrospective population cohort study	Less reduction in HbA1c measurement	28
OCT2 c.808G>T (rs316019) and others	Healthy subjects	Candidate gene; Full pharmacokinetics profile	Reduced metformin renal clearance; Increased C_{max} and AUC	17, 18, 21
OCT1, *OCT2*, *OCT3*, *OCTN1*, and *MATE1*	Healthy subjects ($n = 103$)	Candidate gene; Full pharmacokinetics profile	Renal secretion increased by OCT variants	22
MATE1, *MATE2-K*	Diabetic patients ($n = 48$)	Candidate gene; Sparse pharmacokinetics profile	No effect	50
MATE1 (rs2289669)	Diabetic patients ($n = 116$)	Candidate gene; Population cohort study	Increased HbA1c reduction	51
	Diabetic patients ($n = 98$)	Candidate gene; Population cohort study	Increased HbA1c reduction in patients with OCT1 rs622342 polymorphism	52

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; MATE, multidrug and toxin extrusion; OCT, organic cation transporter.

of each of the cation transporters to the distribution of shared substrates such as metformin remains to be determined. Genetic variation in genes encoding OCT1, OCT2, OCT3, and MATE1 was investigated in a large cohort of 103 subjects, and in this analysis, only reduced-function *SLC22A1* polymorphisms were associated with increased renal clearance of metformin. OCT1 was localized to the apical membrane of the kidney in this study, suggesting that reduced renal reuptake may be the mechanism underlying their observations (22).

In addition to genetic polymorphisms, functional inhibition of OCTs may account for some of the variability observed in metformin pharmacokinetics. In vitro studies of OCT1 transport demonstrated that inhibition of OCT1-mediated metformin uptake by commonly used medications such as amitriptyline and verapamil was genotype dependent, suggesting that individuals harboring certain polymorphisms may be at greater risk for OCT1-mediated drug-drug interactions (23). Induction of OCTs may also be important in the pharmacokinetics of cationic compounds. Recently, concomitant administration of the pregnane X receptor agonist rifampicin was demonstrated to increase the glucose-lowering effect of metformin in healthy subjects, possibly owing to increased OCT1 expression and hepatic uptake of metformin (24).

Whether changes in pharmacokinetics caused by altered OCT expression or function lead directly to a change in response is an important question. Oct1$^{-/-}$ mice exhibited changes in both metformin pharmacokinetics and metformin response, as liver accumulation of metformin was reduced 30-fold compared with wild-type animals (25) and as plasma glucose-lowering response was eliminated (19). Oct1$^{-/-}$ mice were also protected from metformin-induced lactic acidosis, implicating the liver as the primary organ responsible for this potentially fatal side effect of metformin use (26). In humans, OCT1, but not OCT2, expression was observed in subcutaneous and visceral adipose tissue, and OCT1 expression was increased in samples from obese subjects, suggesting that metformin action in these tissues may account for better metformin response in obese individuals (27). Analysis of a cohort study revealed a modest association between the *SLC22A1* polymorphism rs622342 and reduced metformin effect as measured by HbA1c levels in diabetic patients (28). In a study of 150 women receiving metformin to treat polycystic ovary syndrome, the presence of two or more *SLC22A1* polymorphisms was associated with a reduced effect of metformin on total cholesterol, triglycerides, and insulin levels (29). A study of *SLC22A1* and *SLC22A2* polymorphisms in a small number of metformin responders and nonresponders identified *SLC22A1* variants that were weak predictors of response (30), but a larger study failed to find an association between *SLC22A1* variants and metformin response (31). Loss-of-function polymorphisms in *SLC22A1* were also associated with higher plasma concentrations and increased clinical efficacy of the antiemetic drugs tropisetron and ondansetron, presumably owing to reduced hepatic uptake and subsequent reduction in metabolic inactivation of the drugs by the liver (32).

OCTs are also increasingly recognized for their importance in delivery of antineoplastics to target tissues. OCT1 was identified as a major contributor to the uptake of the tyrosine kinase inhibitor imatinib in chronic myeloid leukemia cells (33). The association of OCT1 mRNA expression and polymorphisms with responses to imatinib has not been consistently replicated; however, ex vivo assays of OCT1 activity in peripheral blood mononuclear cells may predict imatinib response (34, 35). Cytotoxicity induced by the platinum-based anticancer drug oxaliplatin was dependent on OCT1 and OCT2 expression in vitro (36). Studies in Oct1$^{-/-}$ mice did not show a change in oxaliplatin pharmacokinetics; however, this result may be due to species-dependent differences in substrate specificity (37). Thus, OCT expression may contribute to the efficacy of anticancer agents such as imatinib and oxaliplatin and has been proposed as a biomarker for choosing appropriate therapeutic agents.

Organic cation transporters in toxicity. The platinum-based antineoplastic cisplatin is a widely used treatment for solid tumors. However, cisplatin-induced nephrotoxicity and ototoxicity are often dose-limiting side effects. The reduced-function *SLC22A2* SNP rs316019 was associated with reduced nephrotoxicity from cisplatin in cancer patients (38). This observation is supported by studies of cisplatin pharmacokinetics in Oct1$^{-/-}$ and Oct2$^{-/-}$ mice. Oct1 and Oct2 are both highly expressed in mouse kidney, whereas in human kidney, OCT2 expression is dominant. Oct1$^{-/-}$ and Oct2$^{-/-}$ mice showed no difference in cisplatin pharmacokinetics; however, in Oct1/2$^{-/-}$ mice, reduced urinary excretion and nephrotoxicity was observed (38). Oct1/2$^{-/-}$ mice were also protected from cisplatin-induced ototoxicity (39). Oct2 mRNA was observed in murine cochlear hair cells, suggesting that OCT inhibition may be useful in protecting against hearing loss. In this study (39), mRNA from pediatric tumors did not express OCTs, suggesting that OCT inhibition would not affect tumor cisplatin uptake and thus may be a feasible approach. The use of OCT inhibitors to prevent cisplatin toxicity has been studied in other rodent models. Administration of the OCT substrate imatinib in combination with cisplatin prevented nephrotoxicity caused by renal accumulation of platinum in rats (40), and concomitant administration of cimetidine inhibited cisplatin-induced nephrotoxicity in mice (41). A case of severe arrhythmia caused by reduced renal clearance of the antiarrhythmic pilsicainide was postulated to be caused by inhibition of P-glycoprotein or OCT2 by the antihistamine cetirizine (42). This suggests that there may be additional drug substrates of OCTs, particularly OCTs expressed in an organ-specific fashion such as OCT1 and OCT2, which are involved in OCT-mediated hepatic or renal drug elimination and interactions.

Multidrug and Toxin Extrusion Transporters

The multidrug and toxin extrusion transporters (MATE transporters/*SLC47A*) are among the most recently identified transporters of functional importance in cation transport, although the existence of a renal efflux transport system had been known for some time (43). MATE1 (*SLC47A1*) is expressed throughout the body, but predominantly in the liver and kidneys, where it is localized to the canalicular membrane of hepatocytes and the luminal membrane of proximal tubule cells, respectively (44, 45). In contrast, MATE2-K, the protein form of MATE2 (*SLC47A2*) that has been functionally characterized, is expressed specifically in the kidney proximal tubule and is localized to the luminal membranes. Many of the substrates and inhibitors of MATE transporters overlap with those of OCTs; therefore, the role of MATE transporters in mediating cation transport and drug-drug interactions in the kidney may have been underestimated in the past (5, 7).

Multidrug and toxin extrusion transporters in efficacy. Several polymorphisms in genes encoding MATE transporters have been identified and functionally characterized (46–49). Many of these variants exhibit changes to transport activity in vitro; however, the influence of these polymorphisms in vivo remains to be seen. In one study of diabetic patients, heterozygous *SLC47A1* and *SLC47A2* variants did not alter the pharmacokinetics of metformin (50), although another study found an association between the *SLC47A1* SNP rs2289669 and increased HbA1c reduction in patients taking metformin (51). A third study found that the effect of the *SLC47A1* polymorphism on metformin-mediated HbA1c levels was larger in patients homozygous for the *SLC22A1* polymorphism rs622342 than in individuals with the *SLC22A1* reference allele, thus illustrating an example of a MATE1-OCT1 genotype interaction (52).

Multidrug and toxin extrusion transporters in toxicity. Pharmacokinetic studies in Mate1$^{-/-}$ mice have provided some insight into the potential for MATE transporter–mediated changes

in substrate clearance and incidence of toxicity. Metformin concentration in kidney, liver, and plasma was increased in Mate1$^{-/-}$ compared with wild-type mice following intravenous administration, whereas urinary excretion was reduced (53). Reduced urinary excretion and increased renal concentration of the antibiotic cephalexin was observed in Mate1$^{-/-}$ mice compared with wild-type animals (54). Following cisplatin exposure, the life span of Mate1$^{-/-}$ mice was significantly shorter, with a higher plasma and renal concentration in the knockout mice compared with control animals (55).

A transporter-mediated interaction between a drug and an endogenous substrate was identified in a study of the novel antibacterial agent DX-619 in healthy volunteers (56). This study showed that the elevated serum creatinine levels caused by this compound resulted from inhibition of OCT2, MATE1, and MATE2-K and from the subsequent reduced tubular secretion of creatinine. To date, MATE transporter–mediated potential drug-drug interactions that have been studied in vitro include cimetidine inhibition of fexofenadine transport (57) and the ability of tyrosine kinase inhibitors to inhibit MATE transporter function (58).

Organic Anion Transporters

The organic anion transporters (OATs/*SLC22A*) move small organic anions against their concentration gradient using a Na^+ gradient maintained by Na^+/K^+-ATPase. Of particular importance in drug disposition are OAT1 (*SLC22A6*), which is predominantly expressed on the basolateral membrane of proximal renal tubules, and OAT3 (*SLC22A8*), which is predominantly expressed throughout the kidney and in the choroid plexus, although both OAT1 and OAT3 are expressed in other tissues in the body. In the kidney, OAT1 and OAT3 facilitate the uptake of compounds from the blood and share a broad and partially overlapping substrate specificity. OAT substrates include steroid hormones, biogenic amines, and drugs such as the angiotensin converting enzyme inhibitors captopril and quinaprilat, the angiotensin II receptor blocker olmesartan, and numerous antibiotics and antivirals. Many drugs in clinical use are inhibitors of OAT transport in vitro, including antibiotics, antivirals, and nonsteroidal anti-inflammatory drugs (NSAIDs) (59, 60).

Oat1$^{-/-}$ and Oat3$^{-/-}$ mice have provided some insight into the role of OATs in vivo. In Oat3$^{-/-}$ mice, clearance of the antibiotics penicillin G (61) and ciprofloxacin (62) was reduced, and brain concentration of the active form of the anti-influenza drug oseltamivir, Ro64–0802, was higher than that of wild-type controls (63). The loop and thiazide diuretics likely rely on Oats for their secretion into the kidney proximal tubules, as demonstrated in Oat1$^{-/-}$ and Oat3$^{-/-}$ mice given furosemide or bendroflumethiazide (64).

Inhibition of OAT-mediated kidney proximal tubule secretion by coadministered anionic drugs has been implicated in numerous drug-drug interactions that may have desirable or undesirable consequences. A classic example is the probenecid and β-lactam antibiotic interaction, whereby probenecid inhibits penicillin secretion, likely at OAT3, resulting in increased penicillin exposure (59). Conversely, NSAID inhibition of OAT transport may result in a potentially life-threatening exposure to methotrexate when these two compounds are administered together (65, 66). In addition, the nephrotoxic effects of antivirals such as adefovir may be attenuated by coadministration with NSAIDs, which inhibit their OAT-mediated uptake in vitro (67).

To date, genetic variants in genes encoding OATs have not been associated with changes in drug disposition (1), although a polymorphism in the intergenic region between *SLC22A6* and *SLC22A8* (rs10792367) was recently found to be modestly associated with blood pressure response to hydrochlorothiazide (68). The large number of substrates and inhibitors of the OATs means that they continue to be transporters of interest in drug disposition and response.

Organic Anion Transporting Polypeptides

The organic anion transporting polypeptides (OATPs/*SLCO*) have a wide substrate specificity for amphipathic molecules, including endogenous compounds such as bile acids, thyroid hormones, sulfated and glucuronidated hormones, and drug substrates including rifampicin, methotrexate, antidiabetics, and statins (69–71).

Organic anion transporting polypeptides in efficacy. Of the human OATPs, OATP1B1 (*SLCO1B1;* previously known as OATP-C, OATP2, and LST-1) has been studied most extensively, owing to the prevalence of clinically relevant polymorphisms (72). OATP1B1 is expressed exclusively on the basolateral membrane of the liver and is thought to be the driving force for hepatic uptake of statins and certain antidiabetic drugs that target the liver as their site of action. *SLCO1B1* is highly polymorphic (72, 73); the most extensively characterized variant is the loss-of-function polymorphism c.521T>C (rs4149056), which has a frequency of approximately 15% in Asian and Caucasian populations. Aberrant cell surface trafficking of this allele may result in reduced hepatic uptake of OATP1B1 substrates in affected individuals.

Given that statins target the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme in the liver, it might be expected that reduced hepatic uptake by OATP1B1 would be accompanied by reduced efficacy, as the statin does not reach sufficient concentration in the liver to inhibit the enzyme effectively. This was demonstrated in studies that showed the *SLCO1B1* c.521T>C polymorphism was associated with the lipid-lowering effect of statins in healthy volunteers (74–76) and in a small group of patients (77), but the association of *SLCO1B1* c.521C>T with reduced statin efficacy has not been convincingly demonstrated in large patient cohorts.

In total, the influence of *SLCO1B1* polymorphisms on the pharmacokinetics of more than 20 clinically used drugs has been studied (72); these drugs include fexofenadine (78), irinotecan (79, 80), lopinavir (81, 82), methotrexate (83), and repaglinide (84–86). In addition, *SLCO1B1* c.521T>C has been associated with toxic side effects caused by the anticancer drugs irinotecan (87, 88) and methotrexate (89). Not all in vitro substrates of OATP1B1 appear to be affected by OATP1B1 polymorphisms in vivo, suggesting that for certain substrates, additional transporters may compensate for loss of OATP1B1 function. For example, bosentan was described as a substrate of OATP1B1 and OATP1B3 (90); however, it does not appear that polymorphisms in either of these transporters significantly influence bosentan pharmacokinetics in vivo (91).

OATP1B3 (*SLCO1B3;* previously known as OATP8 and LST-2) is also expressed on the basolateral membrane of human hepatocytes. In addition to transporting many of the same compounds transported by OATP1B1, OATP1B3 transports taxanes and numerous small peptides. Polymorphisms in *SLCO1B3* have been identified and assessed for transport activity (92, 93), although evidence for the clinical importance of these polymorphisms is less clear than for *SLCO1B1*. Genetic variants in *SLCO1B3* were not associated with paclitaxel or docetaxel pharmacokinetics in Caucasian cancer patients, despite evidence for OATP1B3-mediated transport of these drugs in vitro (94–96). *SLCO1B3* variants were, however, associated with docetaxel-induced leukopenia in Japanese cancer patients (97), and *SLCO1A/1B*$^{-/-}$ knockout mice had a twofold increased exposure to paclitaxel compared with wild-type animals (98). Thus, the role of OATP1B3 in taxane transport is not fully understood, although it is interesting that OATP1B3 is overexpressed in colorectal and breast cancers and that its transport activity may be important in drug entry to tumor cells (99).

The other OATP expressed on the basolateral membrane of human hepatocytes, OATP2B1 (*SLCO2B1;* previously known as OATP-B), is also expressed on the apical membrane of enterocytes, where it may be involved in the intestinal uptake of its substrates. Reduced plasma levels of the leukotriene receptor antagonist montelukast were associated with the nonsynonymous *SLCO2B1*

polymorphism c.935G>A (rs12422149); individuals with this polymorphism also experienced less improvement in their symptoms compared with wild-type individuals (101). Reduced exposure to the OATP2B1 substrate aliskiren following ingestion of apple, orange, or grapefruit juice is postulated to result from inhibition of intestinal OATP2B1-mediated transport (102, 103). For montelukast, orange juice consumption had an effect on plasma exposure for wild-type carriers but not for *SLCO2B1* c.935G>A carriers; the latter had reduced montelukast exposure regardless of treatment (104).

Oatp1b2 was the first murine Oatp to be studied in a knockout mouse model and is the closest ortholog of the human OATPs expressed in the liver, OATP1B1 and OATP1B3. *Slco1b2*$^{-/-}$ mice had lower liver-to-plasma ratios of the prototypical OATP1B substrates pravastatin, lovastatin, and rifampicin compared with wild-type controls (105, 106), indicating the importance of Oatp1b2 in mediating the hepatic uptake of these compounds. Reduced hepatic uptake of the toxins phalloidin and microcystin-LR in *Slco1b2*$^{-/-}$ mice resulted in protection against hepatotoxicity induced by these compounds (107). There are additional Oatps of the Oatp1a family that are expressed in mouse but not human liver, and compensation by these transporters in *Slco1b2*$^{-/-}$ mice may not fully reflect the effect of OATP1B loss in humans. *Slco1a/1b*$^{-/-}$ mice with deletion of Oatp1b2, Oatp1a1, Oatp1a4, Oatp1a5, and Oatp1a6 expression demonstrate significantly reduced hepatic concentrations and elevated plasma levels of methotrexate and fexofenadine (108) and provide a model to further elucidate the combined role of the Oatp1a and Oatp1b families in drug disposition.

Organic anion transporting polypeptides in toxicity. Numerous studies of statin pharmacokinetics in healthy individuals have demonstrated that reduced-function *SLCO1B1* polymorphisms, particularly c.521T>C, increase the area under the curve of plasma exposure to nearly all the statins, including atorvastatin (109, 110), pravastatin (111–117), pitavastatin (118–120), rosuvastatin (109, 121, 122), and simvastatin acid (123) (**Table 2**). Increased systemic statin exposure is thought to be one component of risk for muscle toxicity, a side effect associated with statin use that can range from mild to life-threatening in its severity. In 2008, a genome-wide association study identified a variant in complete linkage disequilibrium with *SLCO1B1* c.521T>C to be the single best predictor of myopathy risk in individuals on high doses of simvastatin (124). Subsequently, the *SLCO1B1* c.521T>C variant was found to be a modest risk predictor for cerivastatin-induced rhabdomyolysis in a candidate gene study of 185 cases matched to controls (125). In another study, *SLCO1B1* c.521T>C was associated with severe myopathy induced by simvastatin, but not atorvastatin (126). Analysis of 509 subjects who were randomized to receive low-dose atorvastatin, simvastatin, or pravastatin followed by higher doses of the same drug demonstrated an association between the same polymorphism and adverse events such as discontinuation, myalgia, or creatine kinase elevation following the dose escalation (127). Most recently, the incidence of less severe forms of statin intolerance, as manifested by adjusting the dose or switching to another statin, was associated with the *SLCO1B1* c.521T>C polymorphism in a study of more than 4,000 diabetic patients (128). Finally, OATP2B1 was identified as a statin transporter present in muscle tissue, indicating a potential role for statin entry into muscle tissue as part of the mechanism of statin-associated muscle toxicity (129).

EFFLUX TRANSPORTERS OF THE ATP-BINDING CASSETTE SUPERFAMILY

ATP-binding cassette (ABC) transporters use energy from the hydrolysis of ATP to move their substrates across biological membranes and against their concentration gradients, thereby limiting

Table 2 Transporter polymorphisms involved in statin pharmacokinetics and response

Statin	Transporter/ polymorphism	Population studied	Experimental approach	Effect of polymorphism	Reference(s)
Atorvastatin	*SLCO1B1* c.521T>C (rs4149056)	Healthy subjects	Candidate gene; Full pharmacokinetics profile	Increased AUC and C_{max}	109, 110
		Patients ($n = 509$)	Candidate gene; Dose escalation	Increased incidence of muscle toxicity	127
		Patients (25 cases, 84 controls)	Candidate gene; Case-control study	No association with muscle toxicity	126
	ABCG2 c.421C>A (rs2231142)	Healthy subjects ($n = 32$)	Candidate gene; Full pharmacokinetics profile	Increased AUC	169
Rosuvastatin	*SLCO1B1* c.521T>C	Healthy subjects	Candidate gene; Full pharmacokinetics profile	Increased AUC and C_{max}	109, 121, 122
	ABCG2 c.421C>A	Healthy subjects ($n = 32$)	Candidate gene; Full pharmacokinetics profile	Increased AUC and C_{max}	169
		Patients ($n = 386$)	Candidate gene (61 genes)	Enhanced LDL-C-lowering response	174
		Hypercholesterolemic patients ($n = 305$)	Candidate gene	Enhanced LDL-C-lowering response	175
		Myocardial infarction patients ($n = 601$)	Candidate gene (6 genes); Substudy of RCT	Enhanced LDL-C-lowering response	176
Simvastatin	*SLCO1B1* c.521T>C	Healthy subjects ($n = 32$)	Candidate gene; Full pharmacokinetics profile	Increased AUC and C_{max}	123
		Patients (85 cases, 90 controls)	Genome-wide association study; Substudy of RCT	Increased incidence of muscle toxicity	124
		Patients (25 cases, 84 controls)	Candidate gene; Case-control study	Increased incidence of muscle toxicity	126
		Patients ($n = 509$)	Candidate gene; Dose escalation	Increased incidence of muscle toxicity	127
		Diabetic patients ($n = 4,196$)	Candidate gene; Population cohort study	Increased incidence of statin intolerance	128

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.

cellular accumulation of their substrates. Members of this large family are identified by the presence of a highly conserved ATP-binding motif (3).

P-glycoprotein

P-glycoprotein (MDR1/*ABCB1*) is an ABC transporter with an important role in protecting tissues from xenobiotics. The protein was originally identified in cells selected for multidrug resistance

(130) and has subsequently been studied extensively in the context of normal physiology and tumor biology (131). Of particular importance in drug disposition is the expression of P-glycoprotein in the apical membrane of enterocytes, hepatocytes, and kidney proximal tubules, and in the endothelial cells of the blood-brain barrier (131).

As it became apparent that P-glycoprotein was not the only molecule capable of conferring a multidrug-resistant phenotype, two other ABC transporters involved in multidrug resistance were cloned: multidrug resistance-associated protein 1 (MRP1/*ABCC1*) (132) and breast cancer resistance protein (BCRP/*ABCG2*) (133–135). Expression of these transporters, along with their functional genetic polymorphisms, has been implicated in drug response and prognosis for numerous tumor types and chemotherapeutic agents. Many detailed reviews of ABC transporters and anticancer therapy have been published (136, 137).

P-glycoprotein has broad substrate specificity for structurally divergent compounds; in general, its substrates are hydrophobic and may be cationic. Substrates of P-glycoprotein include HIV protease inhibitors, calcium channel blockers, and anticancer drugs of the vinca alkaloid, anthracycline, and taxane classes. P-glycoprotein is inhibited by numerous compounds including verapamil, ritonavir, and cyclosporine (131). A great deal of effort has been expended to identify potent and selective P-glycoprotein inhibitors that may be used to overcome multidrug resistance, but these efforts have not been as successful as hoped (138). Mouse P-glycoprotein was recently the first mammalian ABC transporter to be crystallized and characterized at a high resolution (139). The identification of substrate and inhibitor binding sites will contribute to an understanding of the mechanism of ABC transporters in general and assist the effort to design molecules that inhibit P-glycoprotein in order to overcome multidrug resistance.

The role of P-glycoprotein in reducing the absorption of xenobiotics can be directly examined by comparing oral drug exposure in Mdr1a/1b$^{-/-}$ mice with wild-type controls. This model proved to be particularly helpful in outlining the likely in vivo impact of this transporter on the observed oral bioavailability of substrate drugs such as HIV protease inhibitors, topotecan, etoposide, tacrolimus, ivermectin, and loperamide (140).

In addition to limiting oral bioavailability, the expression and function of this efflux transporter in the endothelial cells that constitute the blood-brain barrier appear to be critical to limiting the central nervous system (CNS) entry of many substrate drugs, including those predicted to have brain accumulation on the basis of physicochemical properties such as lipophilicity (141). Endoxifen, the active metabolite of the estrogen receptor antagonist tamoxifen, is a newly identified P-glycoprotein substrate, with significantly higher endoxifen concentrations observed in the brains of Mdr1a/1b$^{-/-}$ mice (142, 143). Expression of P-glycoprotein at the blood-brain barrier has also been implicated in anticonvulsant therapy failure, although its clinical relevance remains controversial (144). Conversely, limited CNS entry by third-generation antihistamines that are P-glycoprotein substrates, such as fexofenadine, has proven to be a desirable property as it reduces the side effect of sedation (145).

For some drugs that are substrates of BCRP, P-glycoprotein alone does not fully limit CNS drug entry, and only when both transporters are absent is the magnitude of CNS drug accumulation significantly enhanced. This has been shown through the use of the Mdr1a/1b/Bcrp$^{-/-}$ mice for tyrosine kinase inhibitors such as lapatinib, imatinib, sunitinib, and tandutinib, which are substrates of P-glycoprotein and BCRP (146–149). Species differences in the brain uptake of radiolabeled P-glycoprotein substrates have been observed by positron emission tomography, and although the mechanisms for these differences are not well understood, they may be a consideration for animal studies conducted in preclinical drug development (150).

ABCB1 is highly polymorphic; however, the in vivo role of these polymorphisms has not been consistently demonstrated. To date, hundreds of studies in genotype-defined subjects have been

conducted with numerous P-glycoprotein substrates, and the results have been mixed (131, 151). The *ABCB1* c.3435T>C (rs1045642) variant in particular has received a great deal of attention but the data are conflicting. These inconsistent findings may result from different experimental conditions, inadequate sample sizes, or heterogeneity of the sample population studied. Many substrates that are used as probes for transporter function are also substrates for drug-metabolizing enzymes or other transporters. For example, transport studies with cyclosporine and tacrolimus may be complicated by the involvement of CYP3A metabolism, and, in addition to being transported by P-glycoprotein, fexofenadine is also a substrate of OATPs (152). Thus, metabolism and transport by proteins other than P-glycoprotein may contribute significantly to the observed variability in drug disposition. Future studies from current resequencing efforts with larger sample sizes and more detailed genetic information may help clarify the influence of genetic polymorphisms in *ABCB1*.

Breast Cancer Resistance Protein

Breast cancer resistance protein (BCRP/*ABCG2*) is expressed on the luminal membrane of enterocytes, with greatest expression observed in the duodenum; it is important for limiting the oral bioavailability of its substrates (153). BCRP is also expressed on the canalicular membrane of hepatocytes, where it is involved in facilitating biliary excretion, and found in sanctuary sites such as the blood-brain barrier, placenta, and testes. BCRP substrates include numerous anticancer agents, such as the topoisomerase II inhibitor etoposide, the camptothecin derivatives topotecan and irinotecan, and the tyrosine kinase inhibitors imatinib and gefitinib. Other substrates of BCRP include statins, antibiotics, numerous environmental toxins, and endogenous substrates such as conjugated steroid hormones, folates, and uric acid (154–156).

Bcrp1$^{-/-}$ mice have been useful in elucidating the relative contribution of Bcrp1 to drug absorption, distribution, and excretion in tissues where other ABC transporters with overlapping function may be present. The first in vivo evidence for another transporter active along with P-glycoprotein was the observation that the oral bioavailability of topotecan, a shared P-glycoprotein and Bcrp1 substrate, was significantly increased when the Bcrp1 and P-glycoprotein inhibitor GF120916 was coadministered with topotecan to *Mdr1a/1b*$^{-/-}$ mice (157). Since these early results, many studies in Bcrp1$^{-/-}$ mice have been conducted to better elucidate the role of BCRP in drug penetration of the CNS and in oral bioavailability (158).

Comparison of single ABC transporter gene knockout mice with multiple ABC transporter gene knockout mice may be useful in understanding the overlapping functions of BCRP and P-glycoprotein with members of the MRPs, as demonstrated by studies of methotrexate pharmacokinetics in double and triple knockout animals. For example, plasma concentration of the toxic metabolite 7-hydroxymethotrexate was not significantly different in Bcrp1$^{-/-}$ mice, but 6.2-fold increased in Mrp2$^{-/-}$ mice and 12.4-fold increased in Mrp2;Bcrp1$^{-/-}$ mice compared with wild-type animals. These results indicate that both Mrp2 and Bcrp1 are important determinants of methotrexate distribution but that Mrp2 is better able than Bcrp1 to compensate for the loss of the other transporter (159). Triple knockout Mrp2;Mrp3;Bcrp1$^{-/-}$ mice retained 67% of an intravenous dose of methotrexate in their livers 1 h after administration compared with wild-type mice that had only 7% of the dose remaining. These results highlight the overlapping functional roles of Mrp2, Mrp3, and Bcrp1 in biliary excretion of toxic metabolites (160).

BCRP is expressed in lactating mammary glands and has a demonstrated role in active efflux of xenobiotics into milk. Levels of topotecan, the H_2 blocker cimetidine, and the antibiotic nitrofurantoin, as well as the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

(PhIP), were significantly lower in milk from Bcrp1$^{-/-}$ mice than from wild-type mice (161, 162). The involvement of BCRP in the secretion of toxic compounds into breast milk is counterintuitive for a transporter that otherwise plays a protective role, and avoidance of BCRP substrates may be a consideration for nursing women. BCRP was demonstrated to concentrate riboflavin (vitamin B12) into breast milk, an observation that may provide some insight into its physiological function in the mammary gland (163).

Reduced-function polymorphisms in *ABCG2* have been identified, and from the known function and location of BCRP, they would be expected to increase the bioavailability of BCRP substrates owing to reduced efflux from enterocytes and reduced biliary excretion. Exposure to sulfasalazine was significantly increased in healthy volunteers with one or more *ABCG2* variants following oral administration of the drug (164, 165). These findings were consistent with increased oral bioavailability and reduced excretion of sulfasalazine in Bcrp1$^{-/-}$ mice (166). These results raised the possibility of using sulfasalazine as an in vivo probe of BCRP activity, an especially attractive tool given that expression of both mRNA and protein is highly variable in human intestinal samples and that this variation is independent of common genetic variants (164, 167). However, a recent pharmacokinetic study of sulfasalazine in 36 healthy volunteers failed to reproduce these results because the presence of the *ABCG2* c.421C>A (rs2231142) polymorphism or coadministration of the BCRP inhibitor pantoprozole showed no effect on sulfasalazine plasma exposure or maximum plasma concentrations (168). Thus, more work is needed to validate the utility of sulfasalazine as an in vivo probe of BCRP activity.

The total exposure to atorvastatin and rosuvastatin is higher in individuals with the *ABCG2* c.421T>C polymorphism (169, 170), consistent with reduced biliary excretion of rosuvastatin in Bcrp1$^{-/-}$ mice (171) (**Table 2**). Conversely, pitavastatin pharmacokinetics were not influenced by the *ABCG2* c.421C>A polymorphism in healthy volunteers (119) despite the involvement of Bcrp1 in biliary excretion of pitavastatin in mice (172). Another study linked the *ABCG2* polymorphism to the pharmacokinetics of fluvastatin and simvastatin lactone, but not to the pharmacokinetics of pravastatin or simvastatin acid (173). BCRP appears to be particularly important for the distribution of rosuvastatin, as multiple studies have now associated reduced-function *ABCG2* polymorphisms with increased lipid-lowering response to rosuvastatin therapy in patients (174–176), presumably a result of increased exposure to rosuvastatin, which mimics the effect of increasing the statin dose.

The role of BCRP in cancer treatment efficacy and prognosis has been widely studied owing to the vast number of antineoplastic drugs that are substrates for this efflux transporter. Indeed, *ABCG2* polymorphisms have been associated with increased exposure and/or risk for toxicity for numerous anticancer drugs in clinical use. For example, reduced-function BCRP variants were associated with higher area under the curve and maximum concentration values of the tyrosine kinase inhibitor erlotinib; higher trough erlotinib levels were associated with skin rash (177). Expression of BCRP in cancer cells is generally associated with poor prognosis; however, this association has not been demonstrated for all tumor types. In particular, BCRP expression has been linked to poor prognosis in acute myeloid leukemia in adults and children (178, 179) and to poor prognosis in esophageal squamous cell carcinoma (180). Whether the association of BCRP with reduced survival is a result of increased BCRP-mediated efflux of anticancer drugs or a marker of more complex biology is not fully understood. BCRP is expressed in stem cells, and indeed, some discrepancy in findings may be related to the relative composition of the subtypes of cells in the tissue samples obtained. For a more comprehensive review of the role of BCRP in anticancer drug efficacy, toxicity, and overall prognosis, refer to recent comprehensive reviews (181, 182).

Multidrug Resistance-Associated Proteins

Of the multidrug resistance-associated protein (MRP) family of ABC transporters, MRP1 (*ABCC1*), MRP2 (*ABCC2*), and MRP4 (*ABCC4*) have been most widely studied in the context of drug response and toxicity. In some cancers, their expression may be associated with poor overall prognosis or response to therapy (137).

Multidrug resistance-associated protein 1 in efficacy and toxicity. MRP1 is expressed in tissues throughout the body, including the lung, testis, kidney, cardiac and skeletal muscle, and placenta. As described above, overexpression of MRP1 in cancer cells is associated with multidrug resistance (183). Like P-glycoprotein, MRP1 is capable of transporting structurally diverse compounds. Endogenous substrates of MRP1 include oxidized glutathione, cysteinyl leukotrienes, glucuronide and sulfate conjugates, and drug substrates including anthracyclines, vinca alkaloids, and antivirals. Mice lacking Mrp1 demonstrate increased sensitivity to the topoisomerase II inhibitor etoposide (184, 185). Functional *ABCC1* polymorphisms have been described (186), but to date, *ABCC1* variants have not been associated with striking changes in drug response.

Multidrug resistance-associated protein 2 in efficacy and toxicity. MRP2 is expressed on the canalicular membrane of the hepatocyte and on the apical membrane of renal proximal tubule endothelial cells (187). MRP2 transports a wide range of glutathione, sulfate, and glucuronide-conjugated endo- and xenobiotics. Genetic mutations in MRP2 cause Dubin-Johnson syndrome, a disease characterized by hyperbilirubinemia resulting from reduced transport of conjugated bilirubin into bile (188). Polymorphisms in *ABCC2* have been associated with higher plasma concentrations of some MRP2 substrates (189). The gastrointestinal toxicity associated with the use of some drugs, such as NSAIDs and antibiotics, may result from enterohepatic recirculation of these compounds and their metabolites that is driven, in large part, by MRP2 in the bile canaliculi (190).

Multidrug resistance-associated protein 4 in efficacy and toxicity. MRP4 is located on the basolateral membrane of hepatocytes and choroid plexus epithelium and on the apical membrane of kidney proximal tubule cells and brain capillary endothelium (191). Localization of MRP4 to the basolateral or apical membrane, depending on the polarized cell type, is associated with the expression of the adaptor protein NHERF1 (192). Substrates of MRP4 include numerous endogenous compounds involved in cellular signaling, such as cyclic nucleotides, eicosanoids, urate, and conjugated steroids, as well as folate, bile acids, and glutathione. Drug substrates of MRP4 include cephalosporin antibiotics, nucleotide analog reverse transcriptase inhibitors, and cytotoxic agents such as methotrexate and 6-mercaptopurine (191).

A SNP in *ABCC4* (c.G2269A, rs3765534) caused disrupted membrane localization and reduced MRP4 activity, and it was hypothesized to increase sensitivity to thiopurine-induced myelosuppression as a result of thiopurine metabolite accumulation in hematopoietic cells (193). Polymorphisms in *ABCC4* were reported to be associated with side effects and survival in childhood acute lymphoblastic leukemia patients treated with methotrexate (194); however, the same genotypes did not show any influence on the event-free survival in adult acute lymphoblastic leukemia patients receiving methotrexate (195).

CONCLUSIONS AND FUTURE PERSPECTIVES

The past decade has seen remarkable progress in the field of drug transporters, not only in terms of functional characterization and substrate specificity but also in elucidating the important role

that transporters play in the disposition and efficacy of drugs in clinical use. Drug interactions that target uptake or efflux transporters can often result in unexpected systemic exposure and, in some cases, organ specific toxicity. Interestingly, the same processes that can result in higher tissue drug accumulation can also be utilized to produce a desirable therapeutic effect, as exemplified by the statin class of lipid-lowering drugs that utilize liver-specific uptake transporters to target hepatic HMG-CoA reductase. The next decade holds even greater promise of new discoveries relating to drug transporters. Indeed, as we approach the personal genomics era, the field of drug transporter pharmacogenomics will no doubt prove to be integral to the delivery of personalized medicine. In addition, the systematic inclusion of drug transporter studies in the drug discovery and development process will result in drugs with greater efficacy and reduced side effects.

Finally, the efforts of dedicated drug transporter researchers over the past half century have resulted in a paradigm shift in our understanding of how drugs are handled by the body. What was once thought to be predictable, on the basis of simple physicochemical properties, has given way to our current recognition of the important role that drug transporters play in all aspects of drug absorption, tissue distribution, and elimination. Indeed, drug transporter research has matured and proven to be remarkably significant to human health and optimal therapeutics.

SUMMARY POINTS

1. Drug transporters are ubiquitously expressed, and many are critical for drug entry into and elimination from tissues in the body.
2. Genetic polymorphisms in drug transporters may result in changes in drug pharmacokinetics leading to reduced drug efficacy and increased risk for drug-induced toxicity.
3. Drug transporters are involved in numerous drug-drug interactions; often, this is a result of one drug inhibiting the transport of another.
4. Knockout mouse models have provided valuable insight into the in vivo contribution of numerous transporters; however, these studies are sometimes limited by species differences in transporter expression and substrate specificity.

FUTURE ISSUES

1. Standards for transporter studies in drug discovery and development should be implemented, as described in a recent white paper by the International Transporter Consortium.
2. Better individualization of drug therapy must be provided through the integration of transporter-related genetic and clinical variables into drug choice and dose algorithms.
3. Continued efforts to improve the extrapolation of data from in vitro and in vivo animal experiments to the in vivo human setting and clinical relevance are needed.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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