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REVIEW

Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics

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The renal organic cation transport system mediates the tubular secretion of cationic compounds including drugs, toxins and endogenous metabolites into urine. It consists of a membrane potential-dependent organic cation transporter at the basolateral membrane and an H^+/organic cation antiporter at the brush-border membrane. In 2005, human multidrug and toxin extrusion MATE1/SLC47A1 was identified as a mammalian homologue of bacterial NorM. Thereafter, human MATE2-K/SLC47A2 and rodent MATE were found. Functional characterization revealed that MATE1 and MATE2-K were H^+/organic cation antiporter, mediating the renal tubular secretion of cationic drugs in cooperation with the basolateral organic cation transporter OCT2. Recently, substrate specificity, transcription mechanisms, structure, polymorphisms, *in vivo* contributions and clinical outcomes on MATE have been investigated intensively. In this review, we summarize recent findings on MATE1/SLC47A1 and MATE2-K/SLC47A2 and discuss the importance of these transporters to the pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics of cationic drugs.

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Abbreviations
AhR, aryl hydrocarbon receptor; CAR, constitutive androstane receptor; DAPI, 4′, 6-diamidino-2-phenylindole; FCCP, carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone; KO, knockout; MATE, multidrug and toxin extrusion; MDCK, Madin–Darby canine kidney; MPP, 1-methyl-4-phenylpyridinium; Nrf2, NF-E2-related factor 2; OAT, organic anion transporter; OCT, organic cation transporter; PPARα, peroxisome proliferator-activated receptor α; PXR, pregnane x receptor; TEA, tetraethylammonium

Introduction

The renal tubular secretion of organic compounds including drugs, toxins and endogenous metabolites is an essential physiological function. The secretory process is performed by two distinct classes of transporters: one located at the basolateral membranes to mediate the cellular uptake of substrates from blood and the other at the brush-border membranes to mediate the efflux of cellular substrates into the tubular lumen. More than 25 years ago, using membrane vesicles, the

Table 1
Species differences in the tissue distribution of MATE and OCT

Transporter	Tissue distribution Human	Rat	Mouse
MATE1/SLC47A1	Kidney > adrenal grand > liver, skeletal muscle, testis, etc	Kidney, placenta > pancreas, spleen, etc	Kidney, liver > heart, etc
MATE2-K/SLC47A2	Kidney	Testis (MATE2)	Testis (MATE2)
OCT1/SLC22A1	Liver > small intestine	Liver, kidney > small intestine	Liver, kidney > small intestine
OCT2/SLC22A2	Kidney	Kidney	Kidney
OCT3/SLC22A3	Ubiquitous	Ubiquitous	Ubiquitous

transport mechanisms for a typical organic cation, tetraethylammonium (TEA), were characterized in rat renal brush-border and basolateral membranes (Takano *et al.*, 1984). TEA uptake by basolateral membrane vesicles was stimulated by an inside negative potential, whereas its uptake by the brush-border membrane vesicles was driven by an outwardly directed H^+ gradient. These results indicated that the renal organic cation transport system consists of a membrane potential-dependent organic cation transporter in the basolateral membrane and an H^+/organic cation antiporter in the brush-border membrane.

In 1994, a potential-dependent organic cation transporter OCT1 was identified in the rat kidney (Grundemann *et al.*, 1994). In 1996, kidney-specific OCT2 was also found (Okuda *et al.*, 1996). Human OCT1/SLC22A1 and OCT2/SLC22A2 are expressed mainly in the liver and kidney, respectively (Table 1), and mediate the uptake of cationic drugs (Inui *et al.*, 2000; Koepsell *et al.*, 2007). Ten years later, multidrug and toxin extrusion MATE was identified as an H^+/organic cation antiporter. Several research tools, probe drugs, specific inhibitors, transfected cells and knockout mice were established, and subsequently the substrate specificity, transcription mechanisms, structure, polymorphisms and *in vivo* contributions have been intensively investigated. Furthermore, clinical information has been collected.

In this review, we summarize recent findings on MATE1/SLC47A1 and MATE2-K/SLC47A2 and discuss the importance of these transporters to the pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics of cationic drugs.

Cloning and nomenclature

Multidrug and toxin extrusion (MATE) transporters were originally identified in *Vibrio parahaemolyticus* and *Escherichia coli*, and named NorM and YdhE. In 2005, MATE1 was identified as a human orthologue of the bacterial NorM, suggesting that MATE1 mediates H^+-coupled electroneutral exchange of organic cation (Otsuka *et al.*, 2005; Omote *et al.*, 2006). Based on the functional characterization, MATE was revealed to be an H^+/organic cation antiporter (Terada *et al.*, 2006; Tsuda *et al.*, 2007; Terada and Inui, 2008). The MATE family was assigned as the SLC47 family.

Human MATE2 was also cloned as a homologue of human MATE1 (Otsuka *et al.*, 2005). Thereafter, two alternatively spliced variants of MATE2, MATE2-K and MATE2-B, were found (Masuda *et al.*, 2006). They exhibit a different splicing pattern between exon 6 and exon 7. MATE2-K mRNA has a deletion of 108 bases in exon 7, compared with MATE2 mRNA. A 154-base intron between exon 6 and exon 7 is not spliced in MATE2-B, where there is a stop codon. MATE2, MATE2-K and MATE2-B consist of 602, 566 and 219 amino acids respectively. Among them, MATE2-K is predominantly expressed in human kidney and is the active form of the *SLC47A2* gene (Masuda *et al.*, 2006). Physiological roles of MATE2 and MATE2-B are unclear.

Animal orthologues of the human MATE have also been found, although the nomenclature and classification are confusing. Human MATE2-K and rodent MATE2 exhibit only low mutual sequence identity (38. 1%) and different expression patterns (Table 1), although the characteristics of human MATE1 and rodent MATE1 are similar (Otsuka *et al.*, 2005; Ohta *et al.*, 2006; Omote *et al.*, 2006; Terada *et al.*, 2006; Terada and Inui, 2008). Rabbit MATE2-K shows similar features to human MATE2-K (Zhang *et al.*, 2007). In fact, the counterparts of human MATE2-K have not been identified in rats and mice, and the counterpart of rodent MATE2 has not been found in humans (Omote *et al.*, 2006; Terada and Inui, 2008). The phylogenetic tree of mammalian MATE-type transporters clearly suggested that rodent MATE2 is classified into MATE3 family but not MATE2 family (Figure 1) (Hiasa *et al.*, 2007). To avoid the misunderstanding, it would be reasonable to rename mouse and rat MATE2 as MATE3.

Tissue distribution

Human MATE1 is highly expressed in the kidney, adrenal gland, liver, skeletal muscle and several other tissues (Masuda *et al.*, 2006). MATE2-K exhibits a kidney-specific expression. MATE1 and MATE2-K mRNA are detected at similar levels in the kidney, and these proteins are similarly localized in the brush-border membrane of proximal tubules. Therefore, both MATE1 and MATE2-K could play a role in the renal tubular secretion of cationic drugs in human (Figure 2). MATE1 also acts as an efflux transporter in other tissues.

Species differences in the tissue distribution of organic cation transporters were demonstrated (Figure 2 and Table 1).

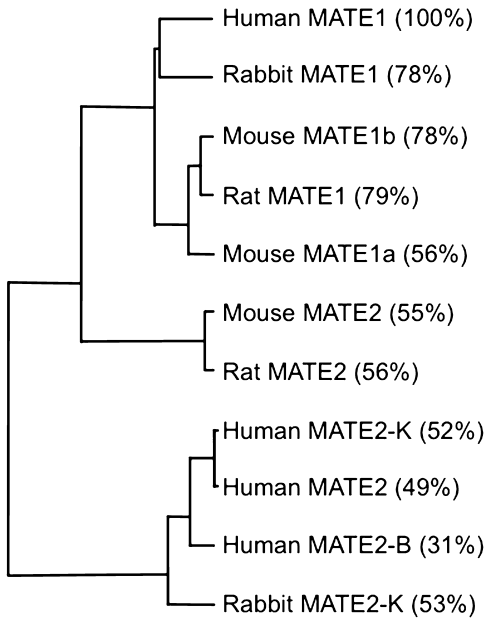

Figure 1

Phylogenetic tree of human, mouse, rat and rabbit MATE. Amino acid identity compared with human MATE1 is shown.

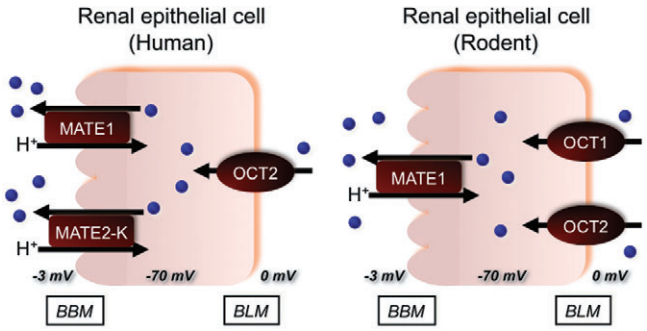

Figure 2

Organic cation transport systems in the proximal tubular epithelial cells of human and rodent kidneys. BBM, brush-border membrane; BLM, basolateral membrane.

In rats, MATE1 mRNA is expressed abundantly in the kidney and placenta, slightly in the spleen but not in the liver (Terada *et al.*, 2006). In mice, MATE1 is highly expressed in the kidney, liver, heart and several tissues (Hiasa *et al.*, 2007). The tissue distribution of MATE1 in mice is generally consistent with that in human. However, MATE2-K is not expressed in mice. In addition, the basolateral organic cation transporters OCT1 and OCT2 are expressed in the rodent kidney, although only OCT2 was found in the human kidney (Inui *et al.*, 2000; Koepsell *et al.*, 2007). Therefore, OCT1/2 double-knockout mice have been used to examine the role of OCT in the tubular secretion of cationic drugs (Jonker *et al.*, 2003). In the case of MATE, MATE1 knockout mice could represent a model of MATE1 and MATE2-K deficiency in humans (Tsuda *et al.*, 2009a).

Pharmacology

Substrate specificity

Substrates for MATE1 and MATE2-K are typical organic cations, TEA, 1-methyl-4-phenylpyridinium (MPP), metformin, cimetidine, procainamide and so on (Table 2) (Tanihara *et al.*, 2007). These compounds are also transported by OCT2 (Inui *et al.*, 2000; Koepsell *et al.*, 2007). K_m values of cationic drugs for MATE1 and MATE2-K are similar and higher than the plasma concentrations in clinical use. In addition, the anionic compounds estrone sulphate, acyclovir and ganciclovir are also substrates for MATE1 and MATE2-K (Tanihara *et al.*, 2007). However, most anions para-aminohippuric acid, ochratoxin A, dehydroepiandrosterone sulphate, uric acid, salicylic acid, indomethacin, prostaglandin F2 alpha, valproic acid, adefovir, cidofovir and tenofovir were not transported. Further study showed that 4′, 6-diamidino-2-phenylindole (DAPI), a fluorescent probe, was a substrate for MATE1 and MATE2-K and useful for the assay of the MATE activity (Yasujima *et al.*, 2010). In addition, the transport of paraquat and agmatine, an L-arginine metabolite, by MATE1 was reported, but transport by MATE2-K has not been examined (Chen *et al.*, 2007; Winter *et al.*, 2011). Furthermore, human OCT and MATE double-transfected Madin–Darby canine kidney (MDCK) cells were established as an *in vitro* model of human organic cation transport systems, and represented the vectorial transcellular transport of cationic drugs (Sato *et al.*, 2008; König *et al.*, 2011). These reports

Table 2

Substrate specificity of MATE1 and MATE2-K

	Specificity	Compounds
Substrate	MATE1 = MATE2-K	Tetraethylammonium, 1-Methyl-4-phenylpyridinium (MPP), Cimetidine, Metformin, Creatinine, Guanidine, Procainamide, Thiamine, Topotecan, Estrone sulphate, Acyclovir, Ganciclovir, 4′, 6-Diamidino-2-phenylindole (DAPI), Paraquat[#], Agmatine[#]
	MATE1 > MATE2-K	Cephalexin, Cephradine, Fexofenadine, PNU-288034
	MATE1 < MATE2-K	Oxaliplatin
Inhibitor	MATE > OCT	Cimetidine, Pyrimethamine

[#]Transport by MATE2-K was not examined.

indicated that MATE1 and MATE2-K mediated the efflux of several cationic compounds in the apical membrane of epithelial cells.

The zwitterionic drugs cephalexin and cephradine are mainly transported by MATE1 (Tanihara *et al.*, 2007; Watanabe *et al.*, 2010). As they were transported by organic anion transporters OAT, but not OCT (Zhang *et al.*, 2010), cephalexin and cephradine are likely eliminated by tubular secretion via OAT and MATE1. Similarly, fexofenadine and the oxazolidione antibiotics N-({(5*S*)-3-[4-(1,1-dioxidothiomorpholin-4-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (PNU-288034) were found to be substrates for MATE1 and OAT3, although they were not transported by MATE2-K (Matsushima *et al.*, 2009; Lai *et al.*, 2010). In addition, fluoroquinolones such as ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, norfloxacin, pazufloxacin and tosufloxacin were also transported by rat MATE1 (Ohta *et al.*, 2009a). Thus, MATE1 can transport some substrates for OAT. On the other hand, oxaliplatin was a specific substrate for MATE2-K, although other platinum agents were hardly recognized by MATE2-K (Yonezawa *et al.*, 2006; Yokoo *et al.*, 2007). MATE1 and MATE2-K are very similar, but not completely the same, in substrate specificity.

Inhibitors of drug–drug interaction

Some compounds were reported to be specific inhibitors of MATE, although OCT and MATE are common in substrate specificity (Table 2). The affinity of cimetidine for MATE1 and MATE2-K is much stronger than that for OCT2 (Matsushima *et al.*, 2009; Ohta *et al.*, 2009b; Tsuda *et al.*, 2009b). IC_{50} values for MATE1 and MATE2-K are 1–10 μM, comparable to plasma concentrations (Tsuda *et al.*, 2009b). Clinical drug–drug interactions have been previously reported between cimetidine and cationic drugs, metformin (Somogyi *et al.*, 1987), procainamide (Somogyi *et al.*, 1983; Christian *et al.*, 1984), triamterene (Muirhead *et al.*, 1986), pilsicainide (Shiga *et al.*, 2000) and varenicline (Feng *et al.*, 2008). The K_i value (147 μM) of cimetidine for OCT2 as a competitive inhibitor is higher than plasma concentrations (Tsuda *et al.*, 2009b). Therefore, it was suggested that cimetidine would inhibit MATE1 and MATE2-K activities and decrease the tubular secretion of cationic drugs. In addition, two other histamine H2 receptor antagonists, famotidine and ranitidine, also inhibit MATE more than OCT, but their clinical concentrations are lower than their IC_{50} values (Tsuda *et al.*, 2009b). Furthermore, the anti-malaria agent pyrimethamine is a potent inhibitor of MATE1 and MATE2-K (Ito *et al.*, 2010). In mice, the coadministration of pyrimethamine and metformin increased the renal concentration of metformin at clinical doses. Cimetidine and pyrimethamine are useful probe inhibitors of MATE.

Driving force

Transport studies in brush-border and basolateral membrane vesicles prepared from the kidney have been successfully utilized to characterize a number of transport systems under well-defined *in vitro* conditions. This is because the ionic composition inside or outside membrane vesicles is easily manipulated, and ion gradients and membrane potential can be provided artificially. In fact, it was clearly demonstrated that organic cation transport systems at the renal brush-border membranes are driven by an oppositely directed H^+ gradient (Takano *et al.*, 1984). By using membrane vesicles from HEK293 cells expressing MATE, it was directly indicated that the driving force of TEA transport by MATE1 and MATE2-K is an oppositely directed H^+ gradient (Tsuda *et al.*, 2007; 2009b). Furthermore, this stimulation disappeared in the presence of a protonophore, carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone (FCCP). These results correspond to previous findings using rat kidney brush-border membrane vesicles and indicated that MATE1 functions as an H^+/organic cation antiporter.

Pharmacokinetic contributions

In the kidney, MATE mediates the efflux of drugs from epithelial cells into urine. Experiments with knockout (KO) mice have revealed the role of MATE1 in the pharmacokinetics of several drugs. In Mate1 KO mice, plasma and renal concentrations of metformin were dramatically increased, and urinary excretion was decreased (Tsuda *et al.*, 2009a). The renal secretory clearance was 14% of that in wild-type mice. These results indicated that MATE plays a predominant role in the tubular secretion of metformin. In heterozygous Mate1 KO mice, the pharmacokinetics of metformin was not significantly different from that in wild-type mice, although the level of MATE1 protein was decreased (Toyama *et al.*, 2010). It was suggested that the rate-limiting step in the excretion of metformin is not the efflux from tubular cells mediated by MATE1, but renal plasma flow, because renal clearance is comparable to renal plasma flow. Furthermore, renal accumulation of the zwitterionic drug cephalexin was much higher in Mate1 KO mice than wild-type mice (Watanabe *et al.*, 2010). Plasma concentrations were slightly increased. Tubular secretion was 35% of the wild-type level. Thus, MATE1 could contribute to the renal tubular secretion not only of cationic drugs but also of zwitterionic drugs. These data are consistent with previous findings using rat renal brush-border membrane vesicles (Inui *et al.*, 1985).

The biliary clearance of metformin was around 100 times lower than the renal clearance, although the hepatic concentration was one-third of the renal concentration (Ito *et al.*, 2010). However, the hepatic concentration and K_p ratio (tissue/plasma) of metformin were significantly higher in Mate1 KO mice and the mice coadministered with the MATE1 inhibitor pyrimethamine than in control mice (Tsuda *et al.*, 2009a; Ito *et al.*, 2010). Therefore, MATE1 is also a determinant of the hepatic concentrations of cationic drugs. In addition, MATE1 is expressed in several tissues. It is possible that MATE can control the tissue concentrations as well as renal excretion of substrates.

Regulation

The regulatory mechanisms for MATE1 expression were characterized, focusing on the basal transcriptional regulation. Sp1 was identified as a general transcription factor of human MATE1 by a deletion analysis, mutational analysis and electrophoretic mobility assay (Kajiwara *et al.*, 2007). In a TATA-less promoter, Sp1 binds to the GC-rich region to recruit

TATA-binding proteins and fixes the transcription start site (Baumann *et al.*, 2010). In the proximal promoter region of the human, rat and mouse *SLC47A1* genes, two Sp1-binding consensus sequences are conserved. It was also reported that transcription of MATE1 was regulated by AP-1 (Ha Choi *et al.*, 2009). The binding site of AP-1 was located at –64 to –70 bp from the translational ATG site, which could be the 5′-UTR region of the *SLC47A1* gene. The ubiquitous transcription factor Sp1 is considered as a constitutive activator of TATA-less genes, which are usually not highly regulated. On the other hand, AP1 activity is induced by several factors, growth factors, cytokines, neurotransmitters, polypeptide hormones, infections and stresses. Therefore, the general transcription factor Sp1 and transcriptional regulator AP-1 could coordinately play a role in the transcriptional regulation of the *SLC47A1* gene.

The effect of other transcription factors on MATE1 expression was also examined. Pharmacological examinations suggested that Aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), pregnane x receptor (PXR), peroxisome proliferator-activated receptor α (PPARα) and NF-E2-related factor 2 (Nrf2) did not affect MATE1 levels in mice (Lickteig *et al.*, 2008). Interestingly, MATE1 expression in the liver of HNF4α-null mice dramatically decreased but not MATE2 expression (Lu *et al.*, 2010). Tissue-specific expression, regulations associated with various diseases and inter-individual variations in MATE1 depended on several transcription factors and also DNA methylation. Factors other than Sp1 and AP-1 would also play a role in the transcriptional regulation of MATE1.

Biochemistry and genetics

Topology

MATE1 and MATE2-K were predicted to have 12 or 13 transmembrane domains using *in silico* systems (Otsuka *et al.*, 2005; Terada and Inui, 2008). It had been unclear whether there was a 13th transmembrane domain in MATE. The topology of MATE was examined in detail (Zhang and Wright, 2009). The C-terminal of rabbit MATE1 was tagged by V5, and the accessibility of the COOH terminus to an anti-v5 antibody in permeabilized and non-permeabilized cells was examined. The V5 epitope at the COOH terminus of MATE1 was freely accessible to the external V5 antibody. These results indicated the COOH terminus of MATE1 to have an extracellular location.

Recently, the X-ray structure of the MATE transporter from *Vibrio cholerae* was reported at 3.65 Angstrom resolution (He *et al.*, 2010), revealing an outward-facing conformation with two portals open to the outer leaflet of the membrane and a unique topology of the predicted 12 transmembrane helices. However, the extra C-terminal sequence of human MATE including the 13th transmembrane domain is not conserved in NorM, which is shorter than human MATE1. The structure of NorM matched previous predictions of human MATE1 topology in the 1st to 12th transmembrane domains besides the extra C-terminal. Based on these reports, it was strongly suggested that human MATE1 is a 13-transmembrane protein (Figure 3).

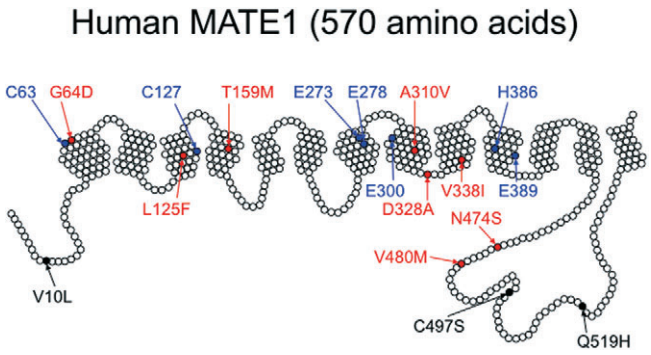

Figure 3

Predicted topology of human MATE1. Red symbols indicate non-synonymous SNPs of MATE1 with a decreased transport activity, and black symbols indicate non-synonymous SNPs with an unchanged transport activity. Blue symbols represent essential amino acid residues in MATE1 activity.

Essential amino acids

Previous studies using rat renal brush-border membrane vesicles have indicated cysteine and histidine residues to be critical to H^+/organic cation antiporter activity (Hori *et al.*, 1987; 1989). Using site-directed mutagenesis and chemical modifiers, some of histidine and cysteine residues in MATE family were identified as essential amino acids for the transport activity (Asaka *et al.*, 2007). Cys-62 and Cys-126 of rMATE1 and the corresponding amino acid residues of hMATE1 (Cys-63 and Cys-127) and hMATE2-K (Cys-59 and Cys-123) were sites of interaction with substrates (Figure 3). Moreover, His-385 of rMATE1 (His-386 for hMATE1 and His-382 for hMATE2-K) acted as a H^+-binding site for a driving force. In addition, the glutamate residues Glu-273, Glu-278, Glu-300 and Glu-389 were also focused, which are conserved in the transmembrane regions in human MATE1, because MATE1 transports many cationic drugs (Matsumoto *et al.*, 2008). When the four residues were substituted with alanine or aspartate, the transport activity decreased. These amino acids should play important roles in the transport activity of the MATE family (Figure 3).

Polymorphisms and function

In the *SLC47A1* and *SLC47A2* genes, 11 and 2 non-synonymous single nucleotide polymorphisms were found, some of which affect function (Figure 3 and Table 3). The mutations G64D and V480M in MATE1 and G211V in MATE2-K caused a complete loss of function (Chen *et al.*, 2009; Kajiwara *et al.*, 2009). The expression of these variants in membranes was abolished. Therefore, the variants can affect the pharmacokinetics of all substrates. The allelic frequency of the dysfunctional mutations was less than 5%, and homozygous carriers have not been found. In addition, polymorphisms in the promoter region of MATE1 were identified. It was reported that the SNP rs72466470 decreased Sp1 binding and transcription activity (Kajiwara *et al.*, 2007). The allelic frequency of this polymorphism was 3.7%. At the AP-1 binding site, rs2252281 SNP, causing reduced transcriptional activity, was also identified at a relatively high frequency

Table 3
Single nucleotide polymorphisms of MATE1 and MATE2-K

Gene	Location	dbSNP	Nucleotide	Amino acid	Function	Allele frequency (%)	Reference
MATE1/SLC47A1	Promoter	rs72466470	G > A	–	↓	1.9	(Kajiwara *et al.*, 2007)
(NM_018242.2)	5′UTR	rs2252281	T > C	–	↓	23.1–44.5	(Ha Choi *et al.*, 2009)
	Exon 1	rs111060521	G > T	V10L	→	2.2	(Kajiwara *et al.*, 2009)
	Exon 2	rs77630697	G > A	G64D	↓	0.6–2.1	(Chen *et al.*, 2009; Kajiwara *et al.*, 2009; Toyama *et al.*, 2010)
	Exon 4	rs77474263	C > T	L125F	↓	0.7–5.1	(Chen *et al.*, 2009; Toyama *et al.*, 2010)
		rs35646404	T > C	T159M	↓	1	(Meyer zu Schwabedissen *et al.*, 2010)
	Intron 10	rs2289669	G > A	–	N.D.	43	(Becker *et al.*, 2009; 2010)
	Exon 11	rs111060526	C > T	A310V	↓	2.2	(Kajiwara *et al.*, 2009)
		rs111060527	A > C	D328A	↓	0.6–1.0	(Kajiwara *et al.*, 2009; Toyama *et al.*, 2010)
		rs35790011	G > A	V338I	↓	0.4–10	(Chen *et al.*, 2009; Meyer zu Schwabedissen *et al.*, 2010)
	Exon 16	rs111060528	A > G	N474S	↓	0.6	(Kajiwara *et al.*, 2009)
		rs76645859	G > A	V480M	↓	0.8	(Chen *et al.*, 2009)
	Exon 17	rs35395280	G > C	C497S	→	2.4	(Chen *et al.*, 2009)
		rs78700676	G > C	Q519H	→	0.8	(Chen *et al.*, 2009)
MATE2-K/SLC47A2	Exon 2	rs111060529	G > T	K64N	↓	0.6	(Kajiwara *et al.*, 2009)
(NM_152908.3)	Exon 8	rs111060532	GC > TT	G211V	↓	1.7–2.1	(Kajiwara *et al.*, 2009; Toyama *et al.*, 2010)

N.D., no data; ↓, decrease in transcription and transport activity; →, no change in transcription and transport activity.

(23.1–44.5%) (Ha Choi *et al.*, 2009). These non-synonymous and transcriptional polymorphisms could explain the inter-individual variation in the disposition of cationic drugs.

A pharmacokinetic analysis of metformin was conducted in heterozygous carriers of the MATE1 and MATE2-K variants (Toyama *et al.*, 2010). Plasma concentrations and apparent clearance did not differ from control levels. These results corresponded with the data for knockout mice and suggested that heterozygous MATE variants do not influence the disposition of metformin. It was suggested that the rate-limiting step in the excretion of metformin in human is not the efflux from tubular cells mediated by MATE1.

Pathology and clinical significance

Pathology

Mate1 KO mice were found to be viable, fertile and of normal body weight (Tsuda *et al.*, 2009a). Histopathological examinations excluded any genotype-related abnormalities in 18 tissues (adrenal, bladder, cerebellum, cerebrum, duodenum, esophagus, heart, ileum, jejunum, kidney, liver, pancreas, pituitary gland, spleen, stomach, testis, thyroid and trachea). Blood biochemical parameters were also changed little in Mate1 KO mice. The disruption of the MATE gene did not have any pathological significance under the specific pathogen-free conditions.

In humans, heterozygous carriers of MATE1 and MATE2-K variants have been found as described above (Chen *et al.*, 2009; Kajiwara *et al.*, 2009; Toyama *et al.*, 2010). Pathological symptoms were not described in these reports. On the other hand, non-synonymous homozygous MATE polymorphisms have not been found in any patients. This may simply be due to a low allelic frequency, but it is also possible that MATE dysfunction affects survival in human.

Change in expression with disease

Changes in MATE expression were observed in several animal models of human diseases. Acute kidney injury models and chronic renal failure models showed decreases in the level of MATE1 protein in the kidney (Nishihara *et al.*, 2007; Matsuzaki *et al.*, 2008; Morisaki *et al.*, 2008; Nakagawa *et al.*, 2010). On the other hand, MATE1 expression was increased in a model of metabolic acidosis (Gaowa *et al.*, 2011). These reports suggested MATE1 expression to be changed under pathological conditions, and the pharmacokinetics of cationic drugs, especially renal accumulation, to be altered. Further clinical study is necessary.

Clinical pharmacology and toxicology

Metformin is an anti-diabetic drug, whose main mechanism of efficacy is the suppression of the gluconeogenesis in the liver. It was reported that OCT1 regulated the hepatic uptake of metformin and polymorphisms of the OCT1 gene affected the efficacy of metformin (Shu *et al.*, 2007). MATE1 transports metformin (Tanihara *et al.*, 2007) and could also be a determinant of its efficacy. The relationship between metformin efficacy and MATE1 SNPs was recently examined in more than 100 diabetic patients (Becker *et al.*, 2009; 2010). One SNP rs2289669 in the 10th intron of the *SLC47A1* gene was significantly associated with a reduction in hemoglobin A1c levels. However, it is unclear whether rs2289669 affects function of MATE1 (Table 3). In addition, its allelic frequency was 43%, much higher than that of any non-synonymous polymorphism found to data (Table 3). Therefore, this intron SNP is not thought to be linked to another polymorphism. As the authors of this manuscript described (Becker *et al.*, 2009; 2010), further replication is necessary.

Furthermore, an anti-cancer platinum agent cisplatin is secreted into urine by tubular secretion, mediated by organic cation transport systems (Yonezawa and Inui, 2011). In Oct1/2 double KO mice, the renal accumulation and toxicity of cisplatin were suppressed (Filipski *et al.*, 2009; Ciarimboli *et al.*, 2010). In Mate1 KO mice, however, cisplatin was markedly accumulated in the kidney and was highly nephrotoxic (Nakamura *et al.*, 2010). In addition, a MATE1 inhibitor pyrimethamine potentiated cisplatin-induced nephrotoxicity. The balance of uptake and efflux by OCT and MATE could determine the renal accumulation and toxicity of cisplatin.

Conclusions

A first mammalian MATE1/SLC47A1 was identified in 2005, based on the bacterial NorM. Human MATE2-K/SLC47A2 and rodent MATE were found thereafter. Functional characterization revealed MATE1 and MATE2-K to be H^+/organic cation antiporter, mediating the renal tubular secretion of cationic drugs in cooperation with OCT2. In addition, roles of MATE1 in the liver and several tissues were clarified. Recent achievements in the study of substrate specificity, transcriptional mechanisms, structure, polymorphisms, *in vivo* contributions and clinical outcomes have demonstrated the importance of MATE to the pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics of cationic drugs. Further clinical study of MATE as well as OCT should help to overcome the inter-individual variation of cationic drugs and establish personalized pharmacotherapy.

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Conflict of interest

The authors declare no conflict of interest.

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