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Commentary

Physiological and pharmacokinetic roles of H^+/organic cation antiporters (MATE/SLC47A)☆

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ABSTRACT

Vectorial secretion of cationic compounds across tubular epithelial cells is an important function of the kidney. This uni-directed transport is mediated by two cooperative functions, which are membrane potential-dependent organic cation transporters at the basolateral membranes and H^+/organic cation antiporters at the brush-border membranes. More than 10 years ago, the basolateral organic cation transporters (OCT1-3/SLC22A1-3) were isolated, and molecular understandings for the basolateral entry of cationic drugs have been greatly advanced. However, the molecular nature of H^+/organic cation antiport systems remains unclear. Recently, mammalian orthologues of the multidrug and toxin extrusion (MATE) family of bacteria have been isolated and clarified to function as H^+/organic cation antiporters. In this commentary, the molecular characteristics and pharmacokinetic roles of mammalian MATEs are critically overviewed focusing on the renal secretion of cationic drugs.

1. Introduction

The secretion of drugs and xenobiotics is an important physiological function of the renal proximal tubules. Transport studies using isolated membrane vesicles and cultured renal epithelial cells have suggested that the renal tubular secretion of cationic substances involves the concerted actions of two distinct classes of organic cation transporters: one facilitated by the transmembrane potential difference at the basolateral membranes and the other driven by the transmembrane H^+ gradient (H^+/organic cation antiporter) at the brush-border membranes [1–3]. A prototype substrate, tetraethylammonium (TEA), has been used for the functional characterization of these organic cation transport systems in the kidney.

The first membrane potential-dependent organic cation transporter (OCT1) was isolated from the rat kidney in 1994 [4]. Subsequently, we isolated rat (r) OCT2 cDNA [5]. Currently, there are three isoforms (OCT1-3/SLC22A1-3), and the physiological and pharmacokinetic roles of these transporters have been characterized from various standpoints. There are several excellent reviews documenting the historical developments and recent progress in the understanding of OCT families [6–10].

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Abbreviations: MATE, multidrug and toxin extrusion; MPP, 1-methyl-4-phenylpyridinium; NMN, N^1-methylnicotinamide; OCT, organic cation transporter; OCTN, novel organic cation transporter; SLC, solute carrier; SNP, single nucleotide polymorphism; TEA, tetraethylammonium.

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On the other hand, the molecular identification of H^+/organic cation antiport systems has not been progressed. Although several candidates for H^+/organic cation antiporters such as OCT2p [11], OCTN1 (SLC22A4) [12,13], and OCTN2 (SLC22A5) [14] have been proposed, all reports lacked direct and enough evidences to support the biochemical and physiological characteristics of H^+/organic cation antiport systems. For example, Tamai et al. [12] reported that OCTN1 may serve as a H^+/organic cation antiporter, because it can mediate the pH-dependent transport of TEA, and is localized at the brush-border membranes of renal proximal tubules. However, the following findings may not support that OCTN1 functions as classical H^+/organic cation antiport systems: (i) TEA transport by OCTN1 is electrogenic [13], whereas TEA transport by classical H^+/organic cation antiport systems is electroneutral [15], (ii) the renal expression level of OCTN1 is relatively weak [16], and (iii) OCTN1 has been demonstrated to mediate the Na^+-dependent transport of the fungal antioxidant, ergothioneine with much greater catalytic efficiency than for TEA [17,18]. Thus, no candidate fully satisfies the characteristics of H^+/organic cation antiport systems, and the true molecular nature of this transporter has been veiled for a long time.

2. Cloning of MATE/SLC47

In 1998, Tsuchiya and his colleagues [19] identified a novel multidrug transporter in *Vibrio parahaemolyticus* and its homolog in *Escherichia coli*, named NorM and YdhE, respectively. These two transporters were assigned to a new family of transporters designated as the multidrug and toxin extrusion (MATE) family [20]. Although the overall properties of the MATE family in bacteria have not been elucidated, some transporters mediated the H^+- or Na^+-coupled export of cationic drugs [20–22].

Based on these findings, Moriyama and his colleagues [23] searched for mammalian orthologues of MATE-type transporters using genomic databases, and succeeded in the isolation of cDNAs encoding orthologues of the bacterial MATE family, i.e., human (h) MATE1 (GenBank accession no. NP-060712), hMATE2 (NP-690872), mouse (m) MATE1 (AAH31436), and mMATE2 (XP-354611). Subsequently, we also reported the cDNA cloning of hMATE2-K (AB250364) [24], hMATE2-B (AB250701) [24], and rat (r) MATE1 (AB248823) [25]. Furthermore, other groups have reported the cloning of cDNAs for rMATE1 (AAH88413) [26], rabbit (rb) MATE1 (EF120627) [27], and rbMATE2-K (EF121852) [27]. The MATE family was assigned as the SLC47 family (SLC47A1: MATE1, SLC47A2: MATE2 and MATE2-K) by HUGO Gene Nomenclature Committee in 2007.

3. Concerns for nomenclature and classification

3.1. *hMATE2, hMATE2-K, and hMATE2-B*

During the course of our cloning process, the original hMATE2 cDNA could not be isolated, alternatively cDNAs for hMATE2-K and hMATE2-B were isolated [24]. As compared to the original hMATE2 cDNA, the hMATE2-K cDNA lacked 108 base pair (bp) in exon 7, and the hMATE2-B cDNA contained an insertion of 46 bp in exon 7. The open reading frame of the hMATE2-K cDNA was 1698 bp long, coding for a 566-amino acid protein. That of hMATE2-B was 660 bp long and encoded a 220-amino acid protein. hMATE2-K, but not hMATE2-B, exhibited the transport activity of TEA. Based on these findings, we originally described hMATE2-K as a splicing variant of hMATE2. However, subsequently, Zhang et al. [27] also isolated rbMATE2-K cDNA instead of rbMATE2 cDNA. So far, transport characteristics of the original hMATE2 remain unclear, whereas those of hMATE2-K and rbMATE2-K were clearly demonstrated [24,27,28]. Although the identification and characterization of the original hMATE2 should be carried out, MATE2-K is currently the only functional isoform in the MATE2 subfamily.

3.2. *mMATE2*

Moriyama's group classified rodent MATE2 (mMATE2 and rMATE2) as MATE3 family based on an amino acid alignment [29,30]. Dog, opossum and chimpanzee MATE3 are also members of MATE3 family [29,30]. This classification may be supported by tissue expression, i.e., human and rabbit MATE2-K are specifically expressed in the kidney, but rodent MATE2 is predominantly expressed in the testis [30]. In addition, based on the genomic database, it was found that there are no rodent isoforms corresponding to hMATE2-K. In order to avoid the misunderstanding of nomenclature, it would be reasonable to rename mMATE2 and rMATE2 as mMATE3 and rMATE3, respectively.

4. Structure

Human, mouse, rat, and rabbit MATE1 consists of 570, 532, 566, and 568 amino acid residues, respectively [23,25–27]. Phylogenetic trees of MATE1 and MATE2-K from various species are shown in Fig. 1A. A comparison of the multiple alignments of these MATE1 sequences revealed a similar overall homology except for the C-terminus of mMATE1 (Fig. 1B). Instead of the original mMATE1 (AAH31436, mMATE1a), another protein with 567 amino acid residues was registered in the NCBI database [CAI25734], which was recently reported as mMATE1b [31]. mMATE1b had almost the same C-terminal amino acid sequence as the other MATE1 proteins (Fig. 1B). In the cDNA of mMATE1b, a nucleotide 1528 ''A'' of the mMATE1a cDNA is deleted. mMATE1b has similar transport properties with mMATE1a and is localized at the renal brush-border membranes [31,32].

Hydropathy analysis in the original paper suggested that the hMATE1 protein contains 12 transmembrane domains, with both the C- and N-terminal located inside the cell. The secondary structure of various MATEs was examined by using transmembrane domain (TMD)-predicting programs such as SOSUI (http://sosui.proteome.bio.tuat.ac.jp/~sosui/proteome/sosuiframe0.html), TopPred (http://www.sbc.su.se/~erikw/toppred2/), TMHMM (http://www.cbs.dtu.dk/services/TMHMM-2.0/), and HMMTOP (http://www.enzim.hu/

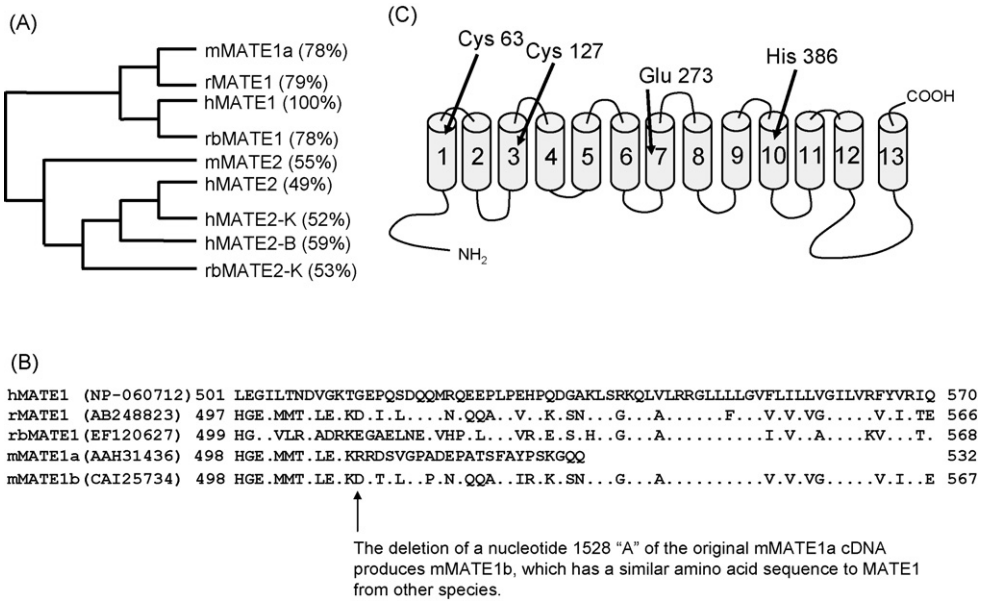

Fig. 1 – Structural characteristics of MATEs. (A) Phylogenetic trees of MATE1 and MATE2-K from various species. (B) Comparison of C-terminal amino acid sequence among the various MATE1 proteins. mMATE1b protein had almost the same C-terminal amino acid sequence as the other MATE1 proteins, but the original mMATE1a did not. (C) Secondary structure of hMATE1. Three different transmembrane domain-predicting programs suggested that hMATE1 has 13 transmembrane domains. Essential amino acid residues were identified by the mutagenesis analyses of hMATE1 [23,42].

hmmtop/html/document.html). Most of the programs suggested 13TMDs for the human, rat, and rabbit MATE1 (Fig. 1C), except for TopPred/hMATE1/12TMDs and SOSUI/rbMATE1/11TMDs. Twelve and 13 TMDs were predicted for the mMATE1a and mMATE1b, respectively. Thirteen TMDs would mean that the C-terminus of MATE proteins is located on the extracellular face of the membranes, and this orientation of rbMATE1 was confirmed by evaluating the accessibility of the antibody to a C-terminal tag using permeabilized and non-permeabilized cells [27].

Human and rabbit MATE2-K consists of 566 and 601 amino acid residues, respectively [24,27]. Most of the TMD-predicting programs also suggested that these proteins possessed 13 putative transmembrane domains like the MATE1 proteins.

5. Tissue distribution and membrane localization

hMATE1 mRNA is primarily expressed in the kidney, and is also expressed in the adrenal grand, testis, skeletal muscle and liver [23,24]. Immunohistochemical analyses showed the hMATE1 protein to be localized at the apical region of the proximal [23,24] and distal convoluted tubules [23] of the kidney.

rMATE1 is also strongly expressed in the kidney by Northern blot analyses [25,26]. Real-time PCR analyses revealed that rMATE1 mRNA is highly expressed in the kidney and placenta, and slightly expressed in the pancreas, spleen, bladder, and lung. Using micro-dissected nephron segments, it was demonstrated that rMATE1 mRNA was primarily expressed in the proximal convoluted tubule and proximal straight tubule, where expression levels of OCT1 and OCT2 are abundant. Immunohistochemical analyses also showed that rMATE1 was abundant in the renal cortex, and was detected at the brush-border membranes of proximal tubules [33].

mMATE1 mRNA was predominantly expressed in the kidney, liver, and heart as a 3.8-kb transcript by Northern blot analysis [23], and was also detected in the brain, heart, stomach, small intestine, urinary bladder, thyroid gland, adrenal gland, and testis as well as kidney and liver by RT-PCR analyses. In Western blot analysis, mMATE1 protein was detected as a single band of 53 kDa in the membranes of the kidney and liver [23], and also in the heart, stomach, small intestine, bladder, thyroid gland, adrenal gland, and testis [32]. Immunohistochemical analyses revealed that mMATE1 protein was localized not only at the apical region of proximal convoluted tubules and the bile canaliculi but also in brain glia-like cells and capillaries, pancreatic duct cells, urinary bladder epithelium, adrenal gland cortex, alpha cells of the islets of Langerhans, Leydig cells, and vitamin A-storing Ito cells [32]. It should be noted that the antibody used in these immunochemical analyses was raised against the C-terminus of the original mMATE1a [23,32]. The amino acid sequence of these regions of the original mMATE1a is completely different from that of mMATE1b [31] described in the section of structures. Although Hiasa et al. [32] suggested that mMATE1 mediates the transport of physiologically important cationic transmitters, steroids, and hormones in endocrine cells, the reevaluation of the tissue distribution and membrane localization of mMATE1b may be necessary to elucidate the physiological and pharmacokinetic roles of mMATE family.

hMATE2-K is expressed only in the kidney, and is localized at the brush-border membranes of the renal proximal tubules [24]. The precise tissue distribution of rbMATE2-K was not examined,

but the cortical expression of rbMATE2-K mRNA appeared to be approximately 7-fold that of rbMATE1 mRNA [27].

As described above, rodent MATE2 is classified into the third member of MATE family, and the sites of its expression are clearly different from those of hMATE2-K and rbMATE2-K. Rodent MATE2 is predominantly expressed in the testis, and is localized to the Leydig cells [23,30].

6. Functional aspects of MATEs

6.1. Driving force

MATE1 exhibited the pH-dependent transport of TEA in cellular uptake and efflux studies, and intracellular acidification through pretreatment with NH_4Cl stimulated TEA transport [23,25–28,31,32], suggesting that MATE1 utilized an oppositely directed H^+ gradient as a driving force. Uptake studies using plasma membrane vesicles from rMATE1-stably expressing cells definitively indicated that an oppositely directed H^+ gradient serves as a driving force for rMATE1 [34]. Namely, the transport of TEA exhibited the overshoot phenomenon only when there was an outwardly directed H^+ gradient, as observed in rat renal brush-border membrane vesicles (Fig. 2). The uptake of TEA stimulated by an H^+ gradient ($[H^+]_{in} > [H^+]_{out}$) was significantly reduced in the presence of a protonophore, carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone (FCCP). TEA uptake stimulated by an H^+ gradient was not changed in the presence of valinomycin-induced membrane potential, suggesting the electroneutral antiport of H^+ and TEA. Since the luminal pH is more acidic than the intracellular pH in the proximal tubules [35], due to the Na^+/H^+ exchanger (NHE) and/or ATP-driven H^+-pump, it is reasonable to assume that the inward H^+ gradient (luminal pH < intracellular pH) can drive the secretion of organic cations in the kidney *in vivo*.

6.2. Substrate specificity

MATE1 and MATE2-K can transport typical organic cations such as TEA [23–28,31,32,34], H_2-blocker cimetidine [24–28,34], neurotoxin 1-methyl-4-phenylpyridinium (MPP) [24,25,27,28,34], and antiarrhythmic drug procainamide [24,25,28,34], all demonstrated to be substrates for H^+/organic cation antiporters characterized by brush-border membrane vesicles [1–3]. In addition to these compounds, N^1-methylnicotinamide (NMN), metformin (antidiabetic drug) and creatinine, which are cationic compounds, were transported by these transporters [24,25,28,34]. Zwitterionic β-lactam antibiotics such as cephalexin and cephradine are effectively transported by MATE1 [25,28], consistent with the results of transport experiments using rat renal brush-border membrane vesicles [36]. On the other hand, a platinum anticancer agent, oxaliplatin, was a better substrate for hMATE2-K rather than hMATE1 [37,38]. The pharmacokinetic implications of oxaliplatin transport via hMATE2-K are discussed below (Section 8). Though there are a few exceptions, substrate specificity of MATE1 and MATE2-K is similar in general. Furthermore, species differences regarding to substrate specificity have not been reported in MATE family among human, mouse, rat, and rabbit.

6.3. Essential amino acid residues

In the NorM protein, the prototype of the bacterial MATE family, three conserved acidic amino acid residues, Asp32, Glu251, and Asp367, in the transmembrane region were demonstrated to be involved in the Na^+-dependent drug transport process [39]. Glu273 in the human MATE1 protein, the counterpart of Glu251 of NorM, is also conserved among species, and Otsuka et al. [23] demonstrated that the mutation of Glu273 reduced the transport activity.

Our studies using rat renal brush-border membrane vesicles have suggested the functional importance of cysteine (Cys) and histidine (His) residues of the H^+/organic cation antiport system [40,41]. As expected, rMATE1 has Cys and His residues essential for the transport activities. Namely, among the conserved Cys and His residues of rMATE1, Cys62, Cys126, and His385 were identified as essential [42]. Mutation of the corresponding residues in hMATE1 and hMATE2-K also diminished the transport activity. The PCMBS-induced inhibition of TEA transport was protected by an excess of various rMATE1 substrates, suggesting that Cys residues act as substrate-binding sites. Pelis et al. [43] have recently found that Cys474 of hOCT2, suggested to be located in the 11th transmembrane

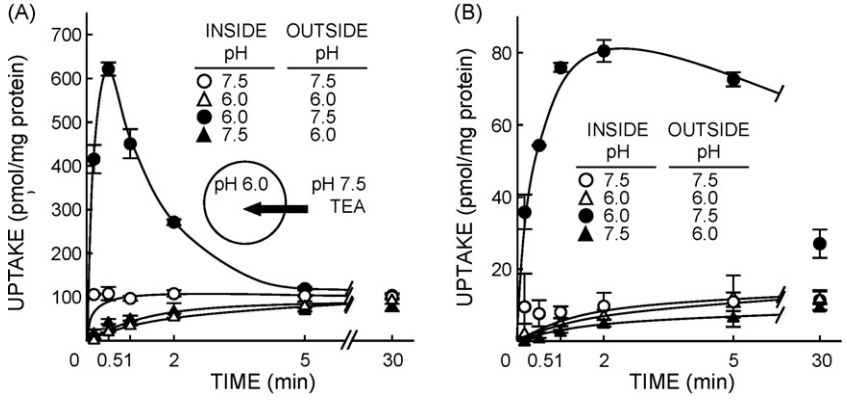

Fig. 2 – TEA uptake by rat renal brush-border membrane vesicles (A) and plasma membrane vesicles from rat MATE1-stably expressing cells (B). The transport of TEA exhibited the overshoot phenomenon only when there was an outwardly directed H^+ gradient in both systems.

helix which participates in the formation of the hydrophilic cleft, contributes to substrate–protein interaction. As OCTs and MATEs have similar substrate specificity, even if their driving forces are different, it is plausible that the same amino acid cysteine is involved in the recognition of substrates.

7. Regulational aspects of MATEs

7.1. *Comparison with OCTs*

In the case of the basolateral organic cation transporters (OCTs), it has been reported that various factors such as development [44], gender [45,46], chronic renal failure after 5/6 nephrectomy [47], and diabetes [48] affected the expression of OCTs in the kidney. For example, the expression level of rat OCT2, but not OCT1 or OCT3, in the kidney was much higher in males than females [45]. The treatment of male and female rats with testosterone significantly increased rOCT2 expression in the kidney [46]. Indeed, functional reporter assays revealed that androgen response elements in the rat OCT2 promoter region play important roles in the enhancement of transcription by testosterone [49]. Recently, as a basal transcriptional regulator of the hOCT2 gene, upstream stimulatory factor 1 was identified [50].

In contrast to OCTs, there is little information available about the regulation of MATEs, and similar approaches for MATEs have been carried out. A gender difference was not observed in rMATE1 protein [33] and rbMATE1 and rbMATE2-K mRNA [27]. The level of basolateral rOCT2 was changed in male nephrectomized rats, but was not changed in female nephrectomized rats [33]. Based on these findings, female rats were used to evaluate the roles of luminal rMATE1 in nephrectomized rats, avoiding the influence of basolateral side [33]. The tubular secretion of cimetidine was markedly decreased in female nephrectomized rats. Although the protein expression of rOCT2 was not changed, the level of rMATE1 was significantly decreased in the remnant kidney. The protein level of rMATE1, but not of rOCT2, correlated well with the tubular secretion of cimetidine. The level of NHE3 was also markedly depressed in both the male and female nephrectomized rats. These results suggested that the secretion of cimetidine was decreased by the reduced expression of rMATE1 but also by the functional loss of this transporter due to a lowered H^+-gradient at the brush-border membrane, caused by a decrease in NHE3.

7.2. *Promoter and rSNP analyses of the MATE1 gene*

Functional promoter analyses of the human and rat MATE1 genes were recently characterized [51]. Deletion analyses suggested that the region spanning −65/−25 was essential for the basal transcriptional activity of human MATE1, and this region lacked a canonical TATA box, but possessed two putative Sp1-binding sites. The functional involvement of Sp1 was confirmed by the overexpression of Sp1, a mutational analysis of Sp1-binding sites, mithramycin A treatment, and an electrophoretic mobility shift assay. Interestingly, a single nucleotide polymorphism (SNP) was discovered in the Sp1-binding site (G-32A) of the hMATE1 promoter, and it was

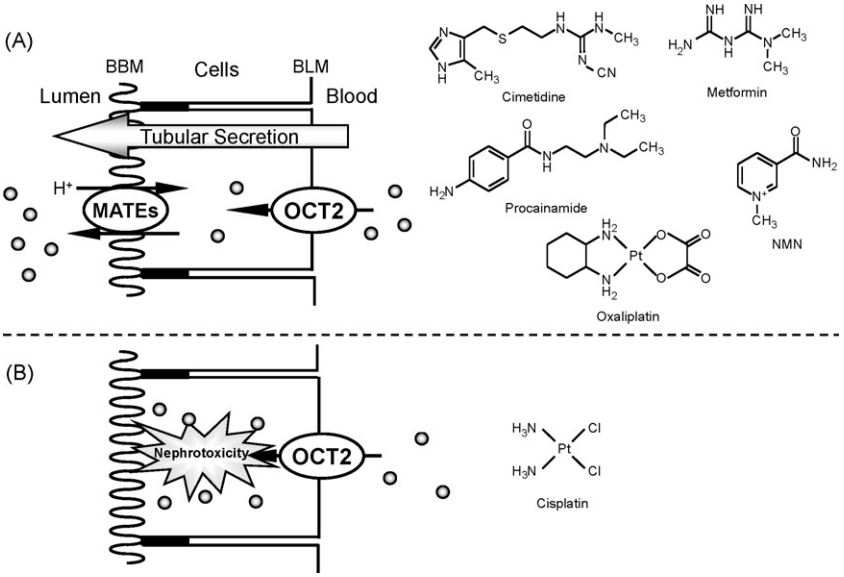

Fig. 3 – Organic cation transport systems in human renal proximal tubular cells and chemical structures of typical substrates. Cellular uptake of organic cations across the basolateral membranes (BLM) is mediated by membrane potential-dependent organic cation transporter 2 (OCT2). In human proximal tubular cells, there is little expression of other isoforms such as OCT1 and OCT3. The exit of cellular organic cations across the brush-border membranes (BBM) is mediated principally by H^+/organic cation antiporters (MATE1 and MATE2-K). (A) Cimetidine, metformin, procainamide, and NMN recognized by both transporters are mainly excreted into the urine. Oxaliplatin is transported by both transporters, and could not be accumulated in the renal proximal tubular cells. (B) Cisplatin is transported by hOCT2, but not by hMATE family. These transport properties may induce the accumulation of cisplatin in the renal proximal tubular cells and nephrotoxicity.

Table 1 – Characteristics of MATE family

	hMATE1/SLC47A1 [23,24,28,37,38,42,51]	hMATE2-K/SLC47A2 [24,28,37,38,42]	MATEs of other species [23,25–27,30–34,38,42,51]
Amino acids	570	566	566 (r), 532 (m1a), 567 (m1b), 573 (m2), 568 (rb1), 601 (rb2-K)
Tissue distribution	Kidney, adrenal grand ≫ testis > skeletal muscle, liver, uterus	Kidney	Kidney, placenta > pancreas, spleen, bladder, lung (r); kidney, liver, brain, heart, stomach, small intestine, urinary bladder, thyroid gland, adrenal gland, testis (m1a); kidney (m1b, rb1, rb2-K); testis (m2)
Membrane localization	Brush-border membranes	Brush-border membranes	Brush-border membranes
Driving force	Oppositely directed H^+ gradient	Oppositely directed H^+ gradient	Oppositely directed H^+ gradient
Substrates	TEA, cimetidine, MPP, procainamide, metformin, creatinine, cephalexin, cephradine, etc.	TEA, cimetidine, MPP, procainamide, NMN, metformin, creatinine, oxaliplatin, etc.	TEA (r, m1a, m1b, m2, rb1, rb2-K), cimetidine (r, rb1, rb2-K), MPP (r, rb1, rb2-K), procainamide (r), NMN (r), metformin (r), creatinine (r), cephalexin (r), oxaliplatin (r), etc.
Essential amino acid residues	Cys63, Cys127, Glu273, His386	Cys59, Cys123, His382	Cys62 (r), Cys126 (r), His385 (r)
Transcription factor	Sp1		Sp1 (r)

The abbreviations in the MATEs of other species are as follows: r, rat MATE1; m1a, mouse MATE1a; m1b, mouse MATE1b; m2, mouse MATE2; rb1, rabbit MATE1; rb2-K, rabbit MATE2-K.

demonstrated that this substitution affects hMATE1 promoter activity by disrupting the binding of Sp1 (an approximately 50% reduction relative to the control), suggesting that this SNP influences the mRNA level of MATE1.

To date, many large-scale screenings of SNPs of SLC drug transporters have been carried out to identify genetic factors involved in the interindividual differences of pharmacokinetics. Recently, it has been demonstrated that OCT1 genotype is a determinant of the therapeutic action and pharmacokinetics of metformin [52,53]. Because MATE1 plays pivotal roles in the renal handling of metformin, the SNP in the promoter region of the *MATE1* gene may affect the pharmacokinetic properties of metformin. Further studies of the relationship between gene polymorphisms of *MATE1* and the pharmacokinetics of MATE1 substrate drugs including metformin may clarify the clinical implications of this SNP.

8. Pharmacokinetic and toxicological roles

In general, efficient renal secretion of organic cations could be achieved by the efficient interplay between OCT2 and MATE1 and/or MATE2-K in human renal tubular epithelial cells. Cationic drugs such as cimetidine, metformin, and procainamide, and endogenous organic cations such as NMN recognized by both transporters were mainly excreted into the urine (Fig. 3A). These transporters also control the exposure of renal cells to nephrotoxic drugs and thereby are responsible for xenobiotic-induced nephrotoxicity.

Cisplatin, carboplatin, oxaliplatin, and nedaplatin are currently used to treat solid tumors. Among them, only cisplatin induces nephrotoxicity with a higher accumulation in the kidney. *In vitro* and *in vivo* studies indicated that a kidney-specific OCT2 was the determinant of cisplatin-induced nephrotoxicity, mediating the renal uptake of cisplatin [37,54]. In addition, low-nephrotoxic platinum agents, carboplatin and nedaplatin, were not transported by OCT2. However, oxaliplatin was revealed to be a good substrate of OCT2 although it was not nephrotoxic. We hypothesized that hMATE1 and/or hMATE2-K protect against oxaliplatin-induced nephrotoxicity by effluxing this agent from the intracellular compartment. As expected, marked transport of oxaliplatin by hMATE2-K, but not hMATE1, was observed [37,38]. On the other hand, cisplatin, carboplatin, and nedaplatin were not transported by either transporter [37,38]. These results clearly account for the relationship between the renal pharmacokinetics and nephrotoxicity of platinum agents; (i) cisplatin was accumulated in the kidney via hOCT2 and induced nephrotoxicity (Fig. 3B), (ii) oxaliplatin was transported by hMATE2-K as well as hOCT2 and therefore, its renal cellular concentration was lowered (Fig. 3A), and (iii) carboplatin and nedaplatin were not accumulated in the kidney via organic cation transporters. The MATE family is proposed to play an important role in protecting the kidney from cationic toxins.

9. Summary and perspective

In this commentary, we described recent findings about the MATE/SLC47A family regarding their structure, expression,

transport function, and regulation (Table 1). Most of the molecular characteristics of MATEs are consistent with the biochemical properties of renal H^+/organic cation antiport systems assessed by classical assays using *in vitro* brush-border membrane vesicles and cultured renal epithelial cells. With respect to the roles of MATEs, their pharmacokinetic significance including renal secretion has been emphasized. In human proximal tubular cells, the renal tubular secretion of clinically important cationic drugs is mediated by the interplay of basolateral OCT2 and brush-border MATE1/MATE2-K (Fig. 3). Thus, the establishment of OCT/MATE double transfectants could be useful for the evaluation and prediction for the renal handling of cationic drugs, drug–drug interactions, and drug toxicity. Although there is little information available about the regulational aspects of MATEs, similar evidences have been accumulated for other renal drug transporters [55]. An understanding of the mechanisms for the regulation of MATEs will help us to evaluate the intra- and interindividual variability in the renal handling of cationic drugs. Finally, regarding the classification of the mammalian MATE family, we recommend that mouse and rat MATE2 could be renamed mouse and rat MATE3, respectively.

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