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REVIEW ARTICLE

Structure and function of multidrug and toxin extrusion proteins (MATEs) and their relevance to drug therapy and personalized medicine

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Abstract Multidrug and toxin extrusion (MATE; SLC47A) proteins are membrane transporters mediating the excretion of organic cations and zwitterions into bile and urine and thereby contributing to the hepatic and renal elimination of many xenobiotics. Transported substrates include creatinine as endogenous substrate, the vitamin thiamine and a number of drug agents with in part chemically different structures such as the antidiabetic metformin, the antiviral agents acyclovir and ganciclovir as well as the antibiotics cephalexin and cephradine. This review summarizes current knowledge on the structural and molecular features of human MATE transporters including data on expression and localization in different tissues, important aspects on regulation and their functional role in drug transport. The role of genetic variation of MATE proteins for drug pharmacokinetics and drug response will be discussed with consequences for personalized medicine.

Keywords Function · MATE · Metformin · Multidrug and toxin extrusion · Polymorphisms · SLC47

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Introduction

Human and mouse MATE1 were initially discovered in 2005 as mammalian orthologs of the bacterial MATE family conferring multidrug resistance (Otsuka et al. 2005). Subsequently, kidney-specific human MATE2K (Masuda et al. 2006) as well as MATE orthologs in rats and rabbits was identified (Terada et al. 2006; Ohta et al. 2006; Zhang et al. 2007) and intensely characterized. Knowledge regarding their tissue distribution, membrane localization and function has been summarized in several reviews (e.g., Moriyama et al. 2008; Damme et al. 2011; Nies et al. 2012; Motohashi and Inui 2013a).

MATE transporters mediate the efflux of organic cations across the luminal membrane of renal proximal tubule cells and the canalicular membrane of hepatocytes in exchange with protons and are therefore considered as the long-searched-for proton-coupled transporters of tubular epithelia (Otsuka et al. 2005). Transported substrates include endogenous compounds such as creatinine, the vitamin thiamine (vitamin B1) as well as several drug agents such as the frequently clinically used antidiabetic metformin and the antibiotics cephalexin and cephradine. An altered MATE function or expression may contribute to the interindividual variability of drug disposition with consequences for drug response. Therefore, in recent years, a number of pharmacokinetic and pharmacogenetic studies in healthy volunteers as well as patients have been conducted particularly to elucidate the impact of MATEs on interindividual variability of metformin response. Moreover, the potential role of MATE proteins in renal drug–drug interaction is of increasing interest (Hillgren et al. 2013).

Here, we summarize the current state of knowledge of molecular and functional characteristics of the human MATE transporters, with a particular focus on

tissue-specific expression, regulation, as well as substrate and inhibitor specificities. Furthermore, we summarize currently available data on the genetic variants of MATEs and discuss their potential functional impact on pharmacokinetics and drug therapy.

Gene organization

Human MATE genes

The human genome contains sequences for two distinct MATE genes, i.e., *SLC47A1* and *SLC47A2*, both being located in tandem on chromosome 17p11.2 (Otsuka et al. 2005) (Fig. 1a). The reference transcript with the NCBI accession number NM_018242 encodes MATE1, a functional protein of 570 amino acids (NP_060712) (Otsuka et al. 2005). Two transcript variants of *SLC47A1*, *SLC47A1_Δexon15* and *SLC47A1_Δexon15-16*, have been detected in liver, kidney and other tissues (Fig. 1b and see paragraph Tissue distribution and localization), which are predicted to encode proteins of 466 and 511 amino acids, respectively (Fig. 1c). The expression of the respective proteins has so far not been demonstrated. Moreover, the presence of further *SLC47A1* transcript variants has been postulated based on mRNA and EST alignments (ENSEMBL accession numbers: ENST00000395585, ENST00000436810, ENST00000571335, ENST00000575023), but again, corresponding proteins have not been identified yet.

For *SLC47A2*, four transcript variants are currently known, which give rise to proteins of different length and function (Fig. 1c): the originally identified MATE2 (isoform 1, 602 amino acids, NP_690872) (Otsuka et al. 2005), MATE2K lacking 36 amino acids due to alternative splicing of exon 7 (isoform 2, 566 amino acids, NP_001093116) (Masuda et al. 2006), MATE2B (219 amino acids, BAF37007) (Masuda et al. 2006) and MATE2 isoform 3 (580 amino acids, NP_001243592). MATE2 and MATE2K are both functional proteins, whereas MATE2B is not functional (Masuda et al. 2006; Tanihara et al. 2007; Asaka et al. 2007; Komatsu et al. 2011). No information is currently available for MATE2 isoform 3, whose existence has been inferred from sequencing of candidate full-ORF clones (Strausberg et al. 2002) but has not yet been experimentally proven.

MATE genes in other species

Orthologs of human MATE proteins have been found in many other species. In the current genome builds of the Ensemble project covering a total of 68 species (http://www.ensembl.org), 35 and 38 species have direct orthologs to human MATE1 and human MATE2, respectively.

Fig. 1 Organization of the human *SLC47A1* and *SLC47A2* genes. **a** ▶ Human *SLC47A1* and *SLC47A2* genes are located in tandem on chromosome 17. Chromosome banding is from Genecards (http://www.genecards.org); the reference tracks are from NCBI (http://www.ncbi.nlm.nih.gov/). **b** While cloning *SLC47A1*, two novel mRNAs expressed in human liver and kidney are identified that lead to alternatively spliced *SLC47A1* isoforms lacking exon 15 (predicted protein 466 amino acids) or lacking exon 15 and 16 (predicted protein 511 amino acids) (unpublished data). The gel picture shows DNA fragments after PCR of kidney or liver cDNA and of plasmids encoding *SLC47A1* reference sequence (MATE1 plasmid), *SLC47A1* isoform lacking exon 15 (MATE1_Δexon15 plasmid) and *SLC47A1* isoform lacking exon 15 and 16 (MATE1_Δexon15-16 plasmid). The same primer pair was used for all PCR reactions. **c** Sequence alignments of the already described *SLC47A1* and *SLC47A2* isoforms together with the two newly described *SLC47A1* isoforms. Sequence alignments were constructed with Clustal Omega (Sievers et al. 2011) and visualized using Jalview version 2.9.0b2 (http://www.jalview.org) (Waterhouse et al. 2009)

Figure 2a shows a phylogram of MATE proteins of species that are commonly used as preclinical models in drug development, i.e., mouse, rat, rabbit and the cynomolgus monkey.

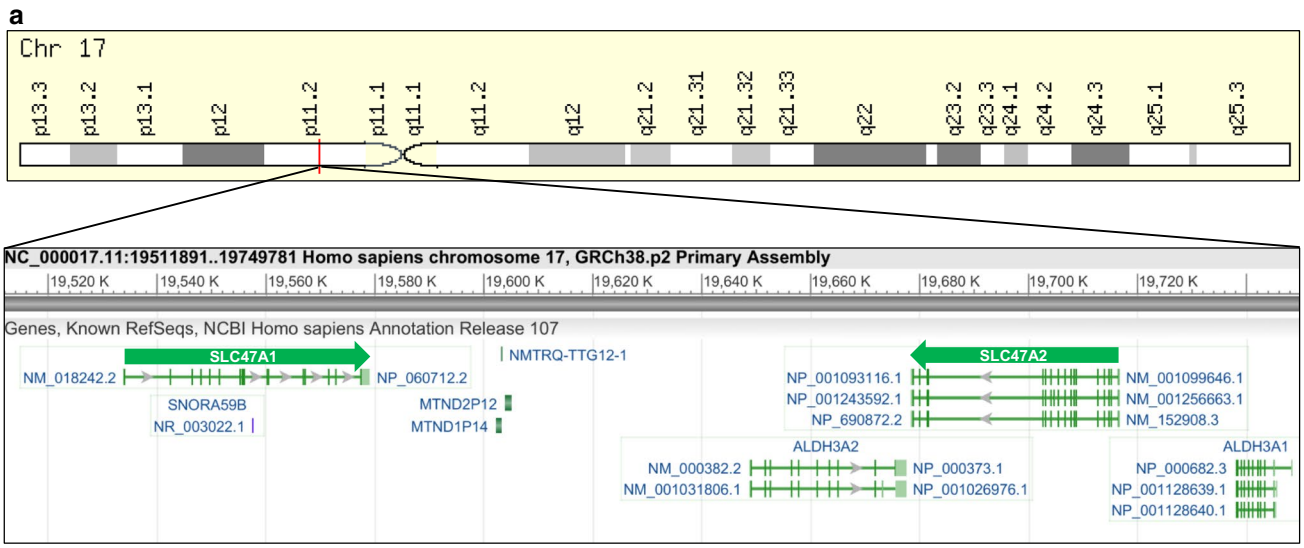
All MATE1 proteins are closely related and clustered in one group. Mouse Mate1 was originally cloned based on Genbank accession number AAH31436 (Otsuka et al. 2005; Hiasa et al. 2006) corresponding to cDNA clone BC031436. Mouse Mate1 was later designated as "mMate1a" because the novel variant mMate1b was identified as the true counterpart of human MATE1 (Kobara et al. 2008), which is now the validated reference sequence (NM_026183, Fig. 2b). At present, mMate1a is considered as nonexistent because the original cDNA clone apparently contained nucleotides, which are not present in the mouse C57BL/6J genome build 37 and resulted in frame-shift errors.

Of note, the so-called murine Mate2 proteins described by an independent research group are more closely related to human MATE1 than to human MATE2/2K. As previously suggested (Hiasa et al. 2007; Yonezawa and Inui 2011b), it would be reasonable to rename them, for example, as mouse Mate3 and rat Mate3. On the other hand, there are apparently no counterparts of human MATE2/2K in the mouse and the rat.

Protein characteristics

Post-translational modifications

Several post-translational modifications have been predicted or experimentally proven for MATE1 and MATE2. The online tool PhosphoSite (Hornbeck et al. 2015) predicts two phosphorylation sites for MATE1 (Thr17-P, Tyr299-P) and four for MATE2 (Ser544-P, Ser586-P,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Chr 17
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p13.2
p13.1
p12
p11.2
p11.1
q11.1
q11.2
q12
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q21.31
q21.32
q21.33
q22
q23.2
q23.3
q24.1
q24.2
q24.3
q25.1
q25.3
NC_000017.11:19511891..19749781 Homo sapiens chromosome 17, GRCh38.p2 Primary Assembly
19,520 K
19,540 K
19,560 K
19,580 K
19,600 K
19,620 K
19,640 K
19,660 K
19,680 K
19,700 K
19,720 K
Genes, Known RefSeqs, NCBI Homo sapiens Annotation Release 107
SLC47A1
NM_018242.2
NP_060712.2
NMTRQ-TTG12-1
SNORA59B
NR_003022.1
MTND2P12
MTND1P14
SLC47A2
NP_001093116.1
NM_001099646.1
NP_001243592.1
NM_001256663.1
NP_690872.2
NM_152908.3
ALDH3A2
NM_000382.2
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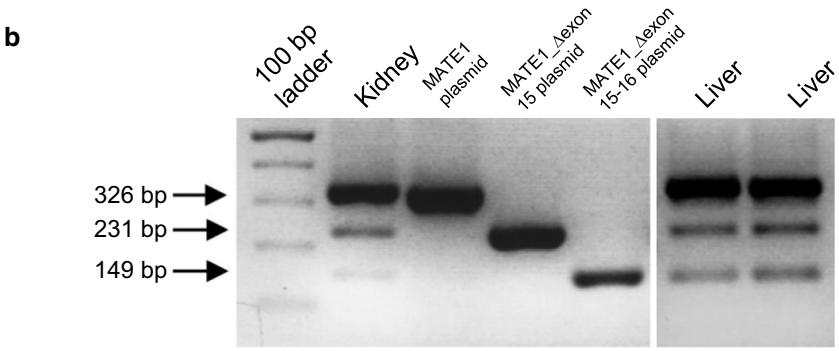
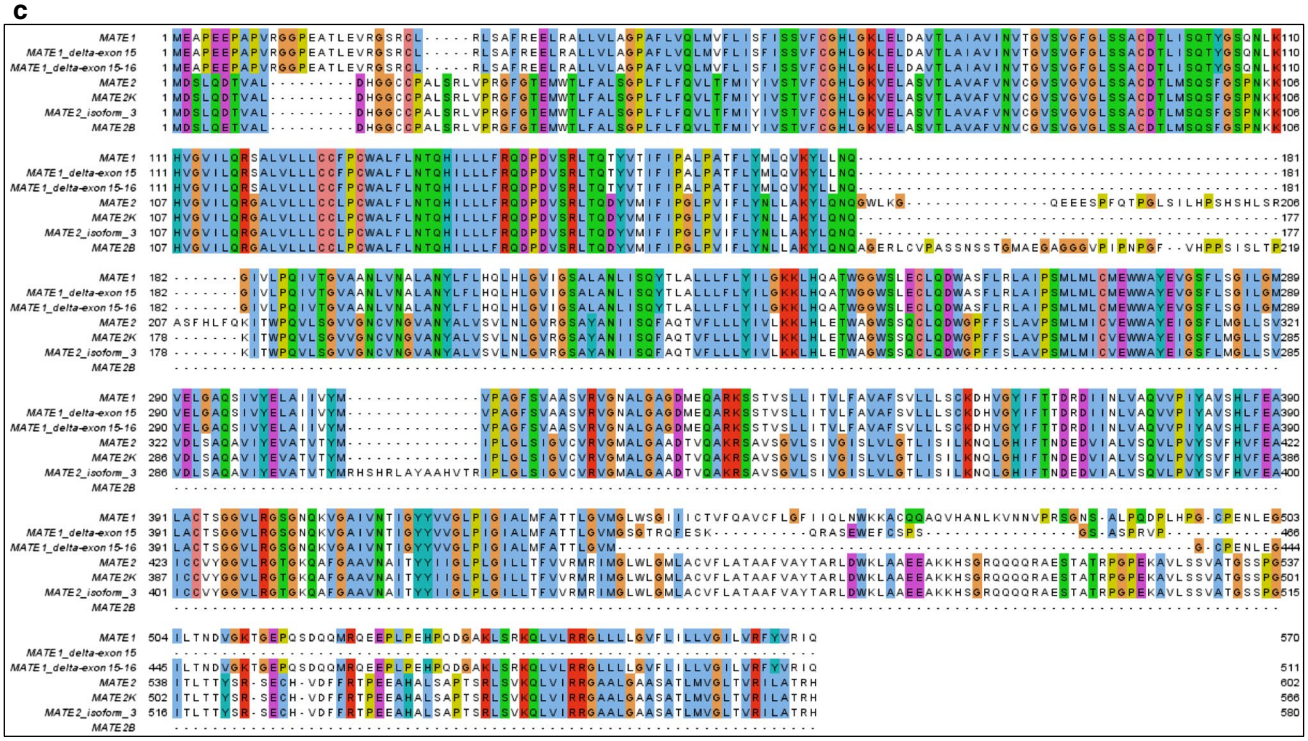
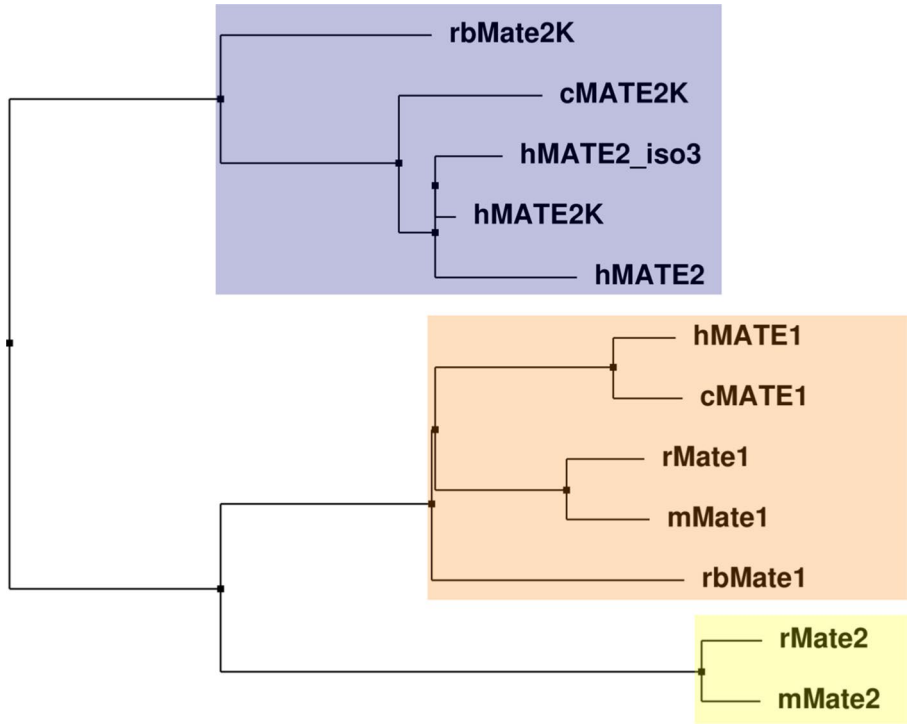

b
100 bp ladder
Kidney
MATE1 plasmid
MATE1_Δexon 15 plasmid
MATE1_Δexon 15-16 plasmid
Liver
Liver
326 bp
231 bp
149 bp


c
MATE1
MATE1_delta-exon 15
MATE1_delta-exon 15-16
MATE2
MATE2K
MATE2_isoform_3
MATE2B

a



b

Species	Common name	Designation	mRNA accession	Protein accession	Refseq status
Homo sapiens	Human	hMATE1	NM_018242.2	NP_060712.2	Validated
		hMATE2	NM_152908.3	NP_690872.2	Validated
		hMATE2K	NM_001099646.1	NP_001093116.1	Validated
		hMATE2 isoform 3	NM_001256663.1	NP_001243592.1	Validated
Macaca fascicularis	Cynomolgus monkey	cMATE1	NM_001319494.1	NP_001306423.1	Provisional
		cMATE2K	NM_001319593.1	NP_001306522.1	Provisional
Mus musculus	House mouse	mMate1	NM_026183.5	NP_080459.2	Validated
		mMate2	NM_001033542.2	NP_001028714.1	Provisional
Rattus norvegicus	Norway rat	rMate1	NM_001014118.2	NP_001014140.1	Provisional
		rMate2	NM_001191920.1	NP_001178849.1	Inferred
Oryctolagus cuniculus	Rabbit	rbMate1	NM_001109819.1	NP_001103289.1	Provisional
		rbMate2K	NM_001109820.2	NP_001103290.2	Provisional

Fig. 2 Phylogram of MATE proteins of different species. **a** Sequence alignments were constructed with Jalview version 2.9.0b2 (http://www.jalview.org) (Waterhouse et al. 2009) using the BLOSUM62 algorithm. **b** NCBI accession numbers of the sequences used to generate the sequence alignments in **a**. Refseq: reference sequence. See http://www.ncbi.nlm.nih.gov/books/NBK21091/table/ch18.T.refseq_status_codes/?report=objectonly for description of the status codes

Thr588-P, Thr594-P); the latter ones have also been identified by a high-throughput phosphoproteomics approach (Raijmakers et al. 2010). N-terminal acetylation was experimentally shown for MATE1 (Van Damme et al. 2012). The functional consequences of these post-translational modifications are currently unknown. Neither MATE1 nor MATE2/2K is apparently glycosylated as predicted by UniProt (UniProt Consortium 2015).

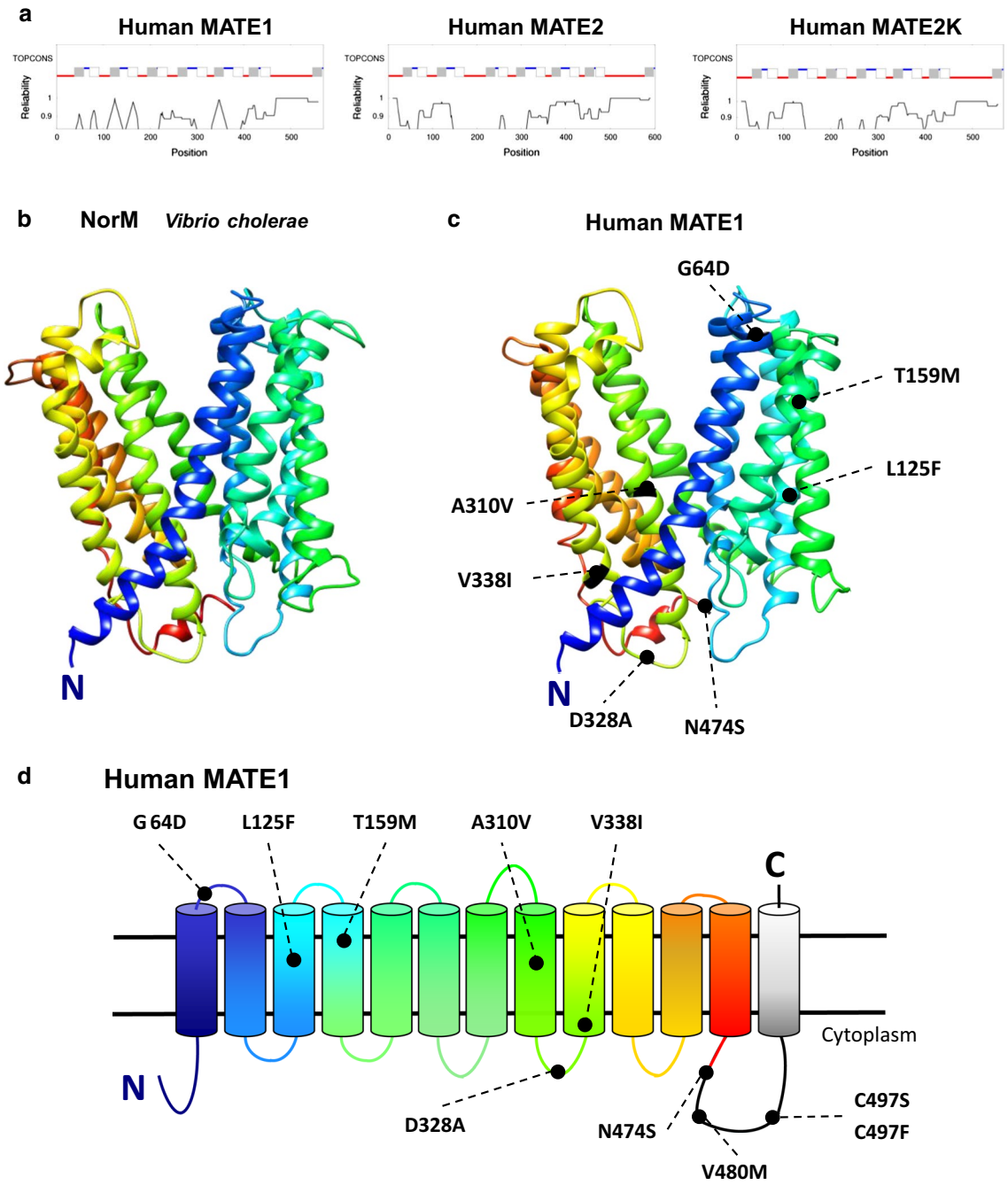


Fig. 3 Models of human MATE proteins. **a** Membrane topology was predicted using the web tool Topcons (http://topcons.net/) (Tsirigos et al. 2015). *Lower red* and *higher blue lines* indicate intracellular and extracellular regions of the proteins, respectively. *Grey and white boxes* indicate transmembrane helices. The Phyre2 server (Kelley et al. 2015) was used to model the three-dimensional structure of human MATE1. The highest scoring model for human MATE1 (**c**) was achieved when modeled on the bacterial MATE protein NorM from Vibrio cholerae (**b**). In **c** and **d**, genetic variants that have been identified in several ethnic populations and that have functional consequences are *highlighted* (color figure online)

Topology and structure

Because crystal three-dimensional structures of human MATE proteins are not available, their membrane topology can only be predicted by different computational methods. Commonly based on hydrophobicity of each amino acid, they calculate the probability for a stretch of amino acids being located in the membrane. These algorithms suggest that human MATE proteins have 13 transmembrane helices with an extracellular C-terminus (Zhang et al. 2007)

(Fig. 3a). This has been experimentally proven initially for rabbit Mate1 (Zhang and Wright 2009) and subsequently also for MATE1 from human and mouse (Zhang et al. 2012). The first 12 transmembrane helices constitute the functional core, while the 13th transmembrane helix is apparently not necessary for function, but may be important for turnover of the protein (Zhang and Wright 2009; Zhang et al. 2012). An experimental verification of MATE2/2K topology is still lacking.

Despite the lack of three-dimensional structures of human MATE proteins, structures can be predicted based on the homology modeling using available bacterial X-ray structures. When using the PHYRE2 server (Kelley et al. 2015), which enables a Web-based protein structure prediction, the highest scoring homology model of human MATE1 was achieved when modeled on the bacterial MATE protein NorM from *Vibrio cholerae* (He et al. 2010) (Fig. 3b, c). Missense variants leading to reduced or abolished function of human MATE1 (see paragraph Genetic variants in human MATEs and their clinical significance for drug pharmacokinetics and drug response) that have been described in different ethnic populations are shown on the predicted three-dimensional model (Fig. 3c) and topology model (Fig. 3d).

Tissue distribution and localization

In their initial description of human MATE1 and MATE2, Otsuka et al. (2005) analyzed expression of both transporters in 8 tissues by Northern blot analysis and identified kidney, liver, skeletal muscle and kidney, respectively, as the major sites of expression. A subsequent systematic quantitative real-time PCR analysis of 21 human tissues showed that MATE1 is ubiquitously expressed with additionally high MATE1 mRNA expression in the adrenal gland and testis (Masuda et al. 2006). More recently, MATE1 transcripts were also detected in synovial fibroblasts (Schmidt-Lauber et al. 2012) and bladder urothelium (Bexten et al. 2015). A systematic analysis of 48 human normal tissues (Fig. 4a) as well as of 20 normal human tissues with their corresponding tumor tissues (Fig. 4b) using tissue microarrays confirmed high MATE1 expression in adrenal gland, kidney and liver and showed a widespread expression in a large variety of additional tissues and tumors such as cervix, endometrium, uterus, testis and thyroid gland. Moreover, the transcript variant *SLC47A1_Δexon15* was also present in all investigated tissues although at about tenfold lower levels than the reference variant (Fig. 4c). The kidney is the major site of MATE2 (Otsuka et al. 2005; Komatsu et al. 2011) and MATE2K expression (Masuda et al. 2006), though MATE2K transcripts were detected in almost all other investigated 20 tissues at low abundance as well (Masuda et al. 2006).

Human MATE1 protein expression and localization have been studied in kidney, liver, placenta, adrenal gland, testis and prostate by different groups and techniques including immunoblotting, immunohistochemistry and quantitative proteomics (Otsuka et al. 2005; Masuda et al. 2006; Tanihara et al. 2007; Ha Choi et al. 2009; Kusuhara et al. 2011; Komatsu et al. 2011; Motohashi et al. 2013; Ahmadimoghaddam et al. 2013; Wang et al. 2015) (Fig. 5). In human kidney, MATE1 is localized together with MATE2 and MATE2K in the brush-border membrane of the proximal tubule epithelial cells (Otsuka et al. 2005; Masuda et al. 2006; Komatsu et al. 2011; Motohashi et al. 2013). All three MATE transporters are therefore considered to contribute to the renal tubular secretion of cationic drugs, which may enter the cells via organic cation transporter 2 (OCT2)-mediated uptake across the basolateral membrane (Fig. 5a). In human and murine hepatocytes, MATE1 is apparently localized on the canalicular (apical) membrane (Otsuka et al. 2005; Kusuhara et al. 2011). Recombinant human MATE1 is also localized in the apical membrane when expressed in vitro in polarized Madin–Darby canine kidney cells (Sato et al. 2008; König et al. 2011). Hepatic MATE1 protein levels have been recently quantified by a quantitative proteomics approach and varied about fivefold in a cohort of 55 individuals (Wang et al. 2015).

Methods to study MATE function

Cell models

In proximal tubule epithelial cells, MATE proteins are located on the apical membrane facing the tubular lumen (Fig. 5a). They are physiologically functioning as efflux transporters moving substances out of the cells in exchange with protons, which are secreted into the tubular lumen by sodium/proton exchangers. Yet, MATE function can easily be studied in vitro using cell lines stably expressing a respective recombinant MATE protein. Commonly, cells are prepulsed with ammonia to acidify the cytosol so that MATE function can be measured as uptake of the compounds of interest. Detailed descriptions of this method and other designs to measure MATE-mediated transport have been described in detail (Otsuka et al. 2005; Tanihara et al. 2007; Hillgren et al. 2013). Moreover, primary renal cell lines and polarized tubule cell monolayers are increasingly used as models to study tubular excretion of drugs (Fisel et al. 2014).

Knockout mouse models

Knockout mouse models are powerful tools for assessing the role of transporters in the context of multiple

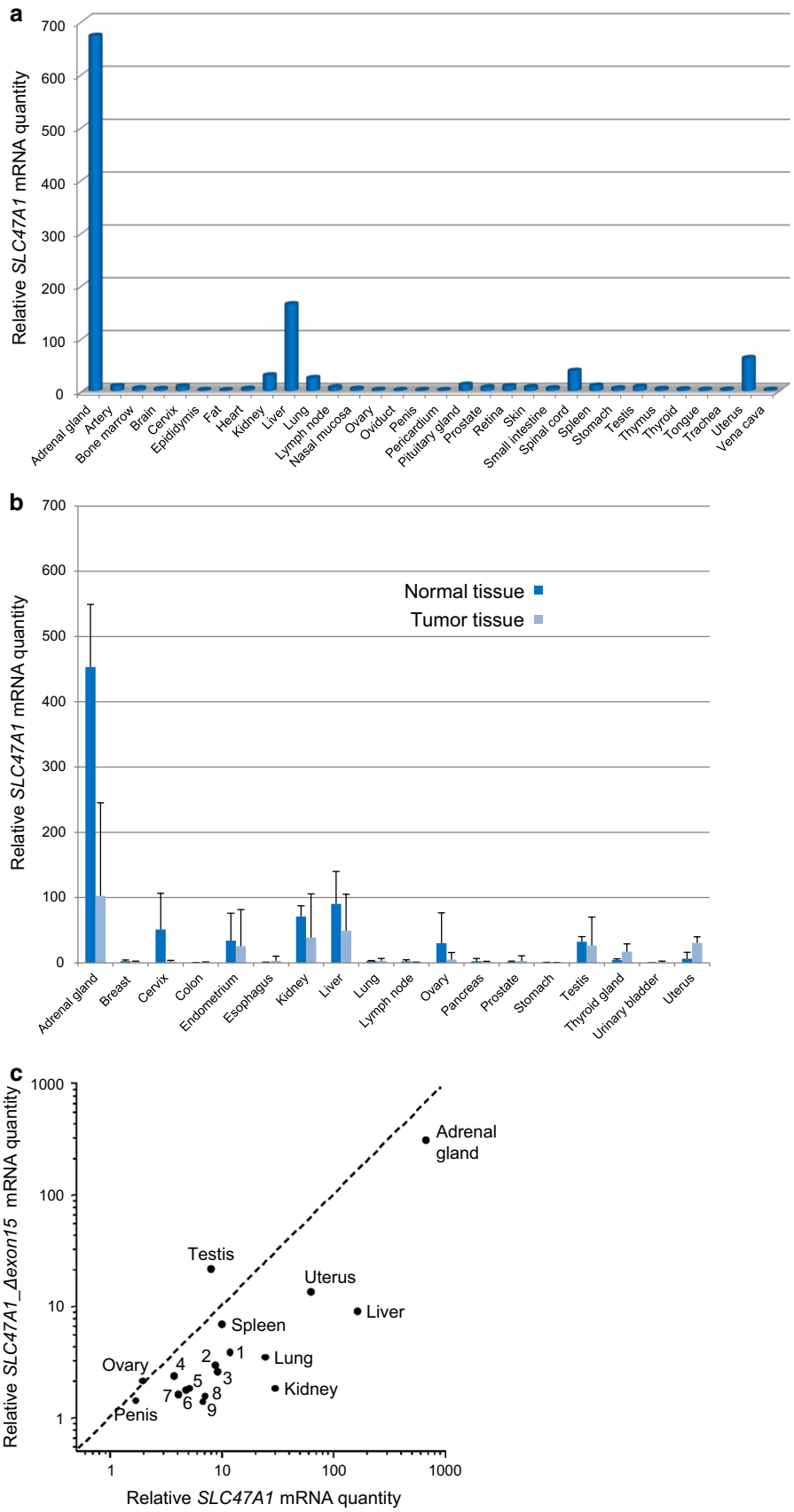


Fig. 4 Tissue distribution of *SLC47A1*. **a** Expression profiling of *SLC47A1* in 48 normal human tissues was performed using quantitative RT-PCR (TaqMan technology) and a commercial array comprising cDNAs from 48 normal human tissues normalized to glyceraldehyde-3-phosphate dehydrogenase (TissueScan RT-PCR array, Origene Technologies, Rockville, MD) as described (Nies et al. 2009 and unpublished data). Expression levels were below the detection limit in the following 16 tissues and cell types: colon, duodenum, esophagus, lymphocytes, mammary gland, muscle, optic nerve, pancreas, placenta, rectum, seminal vesicles, tonsil, ureter, urinary bladder, uvula, vagina. **b** Expression profiling of *SLC47A1* by TaqMan technology using a commercial array comprising cDNAs from 18 normal and corresponding tumor tissues normalized to β-actin (Origene Technologies) was performed as described (Schaeffeler et al. 2011 and unpublished data). **c** Comparison of the transcript levels of *SLC47A1* and the newly identified *SLC47A1_Δexon15* isoform in 18 normal human tissues by TaqMan technology using the commercial array described in **b** (unpublished data). *1* pituitary gland, *2* cervix, *3* retina, *4* thymus, *5* small intestine, *6* heart, *7* stomach, *8* skin, *9* lymph node

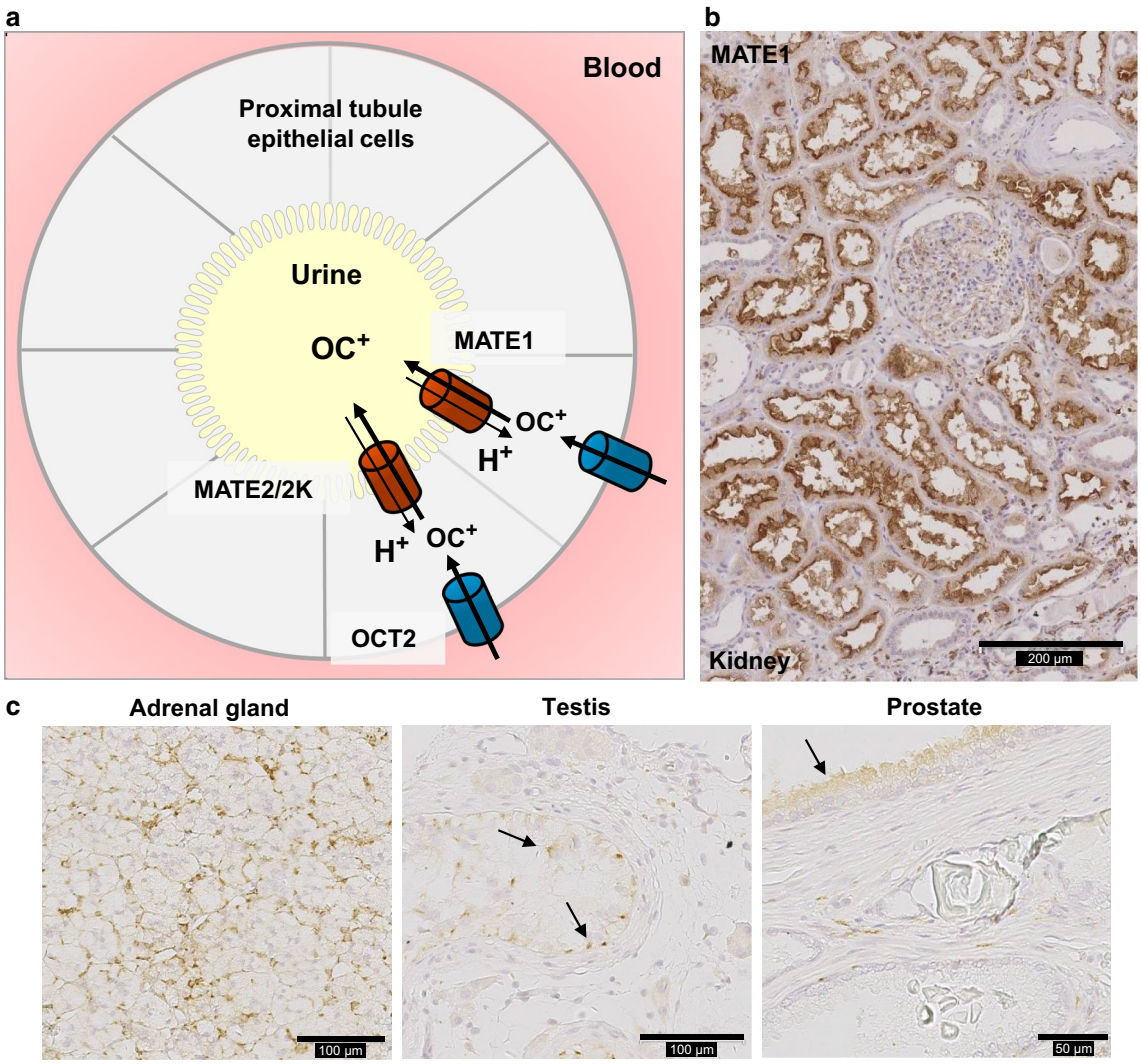


Fig. 5 Localization of MATE1 in different human tissues. **a** Scheme of the localization of OCT2 and MATEs on the basolateral and luminal membranes, respectively, of proximal tubule epithelial cells. **b**, **c** Immunolocalization of MATE1 in the brush-border membrane of kidney, in cells of the adrenal gland, in Sertoli cells of the testis (*arrows*), and the glandular epithelial cells of the prostate (*arrow*) using a MATE1-specific rabbit antibody (HPA021987, Sigma-Aldrich) (unpublished data). OC^+, organic cation

transporters, metabolizing enzymes, plasma protein binding and blood flow (Degorter and Kim 2011). Because neither Mate2 nor Mate2K is expressed in mouse kidney (Hiasa et al. 2007) (Fig. 2a), but renal expression of mouse Mate1 is high, Mate1 knockout mice can be considered as a model to study MATE1 and MATE2/2K deficiency in humans (Tsuda et al. 2009a; Yonezawa and Inui 2011b). Mate1 knockout mice are viable and fertile without any overt phenotypical or histological alterations suggesting that other transporters may compensate for Mate1 function in the kidney (Tsuda et al. 2009a; Li et al. 2011). Mate1 knockout mice have been used to elucidate the pharmacokinetics and particularly renal elimination of MATE substrates such as endogenous compounds and xenobiotics, including the antidiabetic drug metformin, the anticancer agents cisplatin and flutamide, the antibacterial drug cephalexin and the herbicide paraquat (Tsuda et al. 2009a; Watanabe et al. 2010; Nakamura et al. 2010; Li et al. 2011; Toyama et al. 2012; Li et al. 2013a; Nakano et al. 2015). For example, treatment of Mate1 knockout mice with metformin resulted in significantly increased hepatic levels of metformin and led to lactic acidosis suggesting that homozygous variant or compound heterozygous carriers of MATE polymorphisms resulting in significantly reduced or even abolished transporter function may be at risk to develop metformin-induced lactic acidosis (Toyama et al. 2010, 2012). Despite the usefulness of the Mate1 knockout mouse model, species differences in substrate affinity between mouse and human MATE1 need to be considered (Hillgren et al. 2013).

Cynomolgus monkey

In a recent study, cynomolgus monkey was evaluated as a surrogate model for studying human organic cation transporters, including MATE1 and MATE2K. This animal model was suggested to have some utility for in vitro–in vivo extrapolations involving the inhibition of renal OCT2 and MATEs and may be a promising tool for the risk assessment of human drug–drug interactions (Shen et al. 2016).

Substrates and inhibitors

So far, more than 1000 compounds have been investigated whether they interact with human MATE1 and MATE2K. In contrast, similar comprehensive analyses have not been performed for MATE2, and the prototypical probe substrate tetraethylammonium (TEA) is currently the only known transported substrate (Komatsu et al. 2011). Several structure–activity relationship models have been proposed to predict whether a certain compound is a substrate, an inhibitor or both of MATE1 and MATE2K (Kido et al. 2011; Astorga et al. 2012; Wittwer et al. 2013; Morrissey et al. 2016). Moreover, recently a quantitative structure–pharmacokinetic relationship model was developed to predict renal clearance of MATE substrates (Dave and Morris 2015). In general, MATE substrates are cationic by nature or positively charged at physiological pH 7.4, hydrophilic, and have a low molecular weight. Examples include the endogenous substrate creatinine, the vitamin thiamine, the prototypical probe substrates 1-methyl-4-phenylpyridinium (MPP) and TEA, the antidiabetic drug metformin and the histamine H_2 receptor antagonist cimetidine as well as the herbicide paraquat (Fig. 6). The substrate specificity of MATE is similar to OCT2 (encoded by *SLC22A2*), localized on the basolateral membrane of kidney proximal tubule cells (Fig. 5a), thereby supporting the concept that OCT2 and MATE transporters work in concert in the renal elimination of endogenous compounds and xenobiotics (Otsuka et al. 2005; Masuda et al. 2006; Tanihara et al. 2007; Damme et al. 2011; Morrissey et al. 2013; Hillgren et al. 2013; Motohashi and Inui 2013a, b; Chu et al. 2016). A similar functional vectorial transport can be assumed for the antiviral drugs acyclovir and ganciclovir, which are taken up from blood into the proximal tubule epithelial cells via the organic anion transporter 1 (OAT1, encoded by *SLC22A6*) and then excreted into the tubular lumen via MATE1 (Takeda et al. 2002). A functional interplay between the organic anion transporter 3 (OAT3, encoded by *SLC22A8*), another basolateral membrane transporter of renal proximal tubule cells, and MATE1 leading to extensive renal secretion and insufficient drug exposure was probably the reason for failure of a novel oxazolidinone antibiotic in phase I clinical trials (Lai et al. 2010).

Zwitterionic compounds (e.g., cephalexin, cephradine, oxaliplatin) and anionic compounds (e.g., estrone sulfate) are also transported by MATEs indicating a broader substrate range than OCT2. While the transport capacity of several substrates for MATE1 and MATE2K is quite similar, some drug agents are preferentially transported by MATE1 (e.g., cephalexin, cephradine, fexofenadine) or by MATE2K (e.g., oxaliplatin and verapamil). Table 1 gives an overview of MATE1 and MATE2K substrates and their selectivities toward the MATE transporters.

Inhibitors of MATE1 and MATE2K are generally characterized by a positive charge at pH 7.4, a high LogP value and a median molecular weight of 349 (range 284–558) (Astorga et al. 2012; Wittwer et al. 2013). Table 2 summarizes inhibitor selectivities for MATE1 and MATE2K. A higher selectivity of inhibitors for MATEs over OCT2, as is the case for the H_2 receptor antagonist cimetidine and the antimalarial agent pyrimethamine (Yonezawa and Inui 2011b), may explain clinically relevant drug–drug interactions (see also paragraph Role of MATEs for toxicity and drug–drug interactions).

Of interest, the recent development of ^{11}C-labeled metformin as positron electron tomography tracer and its application in mice will enable the noninvasive testing of physiological MATE function and MATE-mediated drug–drug interactions in future clinical investigations (Hume et al. 2013; Shingaki et al. 2015; Jensen et al. 2016).

Regulation

Transcriptional regulation

The 5′ regions of the rat and human *SLC47A1* genes contain, instead of a TATA box, two GC-rich regions. These are critical for basal transcriptional activity due to binding of Sp1 as a general transcription factor (Kajiwara et al. 2007). Additionally, the rate of human *SLC47A1* transcription is also regulated by AP-1 and AP2-rep, both of which bind in the 5′ UTR close to the transcriptional start site (Ha Choi et al. 2009). Finally, Nkx-2.5, SREBP-1 and USF-1 were identified to bind in the 5′ gene region of the *SLC47A1* gene; they may also function as possible regulators of transcription (Kim et al. 2013). Of note, genetic variants in either of these transcription factor binding sites result in altered promoter activity in vitro and partially also in altered MATE1 mRNA expression levels (see Paragraph Genetic variants in human MATEs and their clinical significance for drug pharmacokinetics and drug response).

The role of nuclear receptors, i.e., ligand-activated transcription factors, in regulation of human *SLC47A1* and *SLC47A2* is still poorly understood, and limited data are available for mice. Studies using hepatocyte nuclear

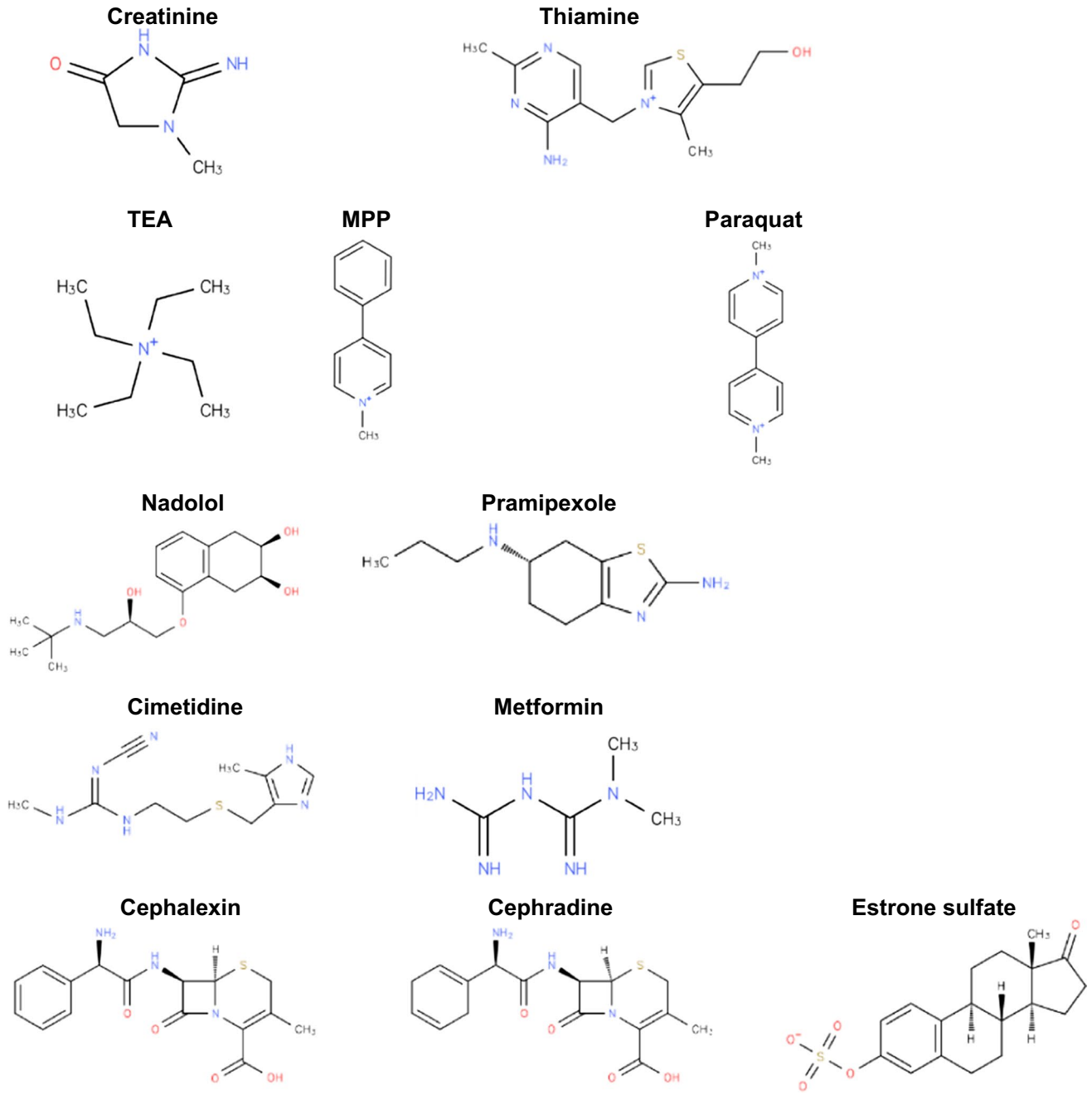


Fig. 6 Structures of selected MATE substrates were downloaded from the publicly available ChEBI database (https://www.ebi.ac.uk/chebi/init.do)

factor 4α (Hnf4α) knockout mice showed that hepatic Mate1 expression depends on the presence of Hnf4α (Lu et al. 2010). Similar results were obtained for renal Mate1 expression (Martovetsky et al. 2013). Whether HNF4α is also important for human MATE1 expression is currently unknown. The nuclear factors aryl hydrocarbon receptor (Ahr), constitutive androstane receptor (Car), nuclear factor erythroid-2-related factor 2 (Nrf2), peroxisome proliferator-activated receptor alpha (Pparα) and pregnane X receptor (Pxr) are not involved in the hepatic regulation of mouse Mate1 (Lickteig et al. 2008).

The observation that the pro-inflammatory cytokines TNFa, IL-1b and IL-6 may decrease MATE1 mRNA and protein expression in human rheumatoid arthritis synovial fibroblasts suggests additional and as yet unexplored signaling pathways of MATE1 regulation (Schmidt-Lauber et al. 2012).

Moreover, MATE proteins may also be post-transcriptionally regulated as recently suggested by in vitro studies

Table 1 Overview of substrates for human MATE1 and MATE2K

Compound	Function/use	MW (g/mol)	Charge at pH 7.4	MATE1	MATE2K	References
6β-Hydroxycortisol	Metabolite	378	0	**+**	+	Imamura et al. (2013)
Acyclovir	Antiviral	225	+1	+ (2640)	+ (4320)	Tanihara et al. (2007)
Asymmetric dimethylarginine (ADMA)	Metabolite	202	+1 (+2, − 1)	+	+	Strobel et al. (2013)
Agmatine	Metabolite	130	+2	+ (240)		Winter et al. (2011)
L-Arginine	Amino acid	174	0 (+1, − 1)	+	+	Strobel et al. (2013)
4-(4-(Dimethylamino)styryl) -N-methylpyridinium (ASP)	Fluorescent dye	366	+1	+ (23)	+ (10)	Kido et al. (2011)
Atenolol	Antihypertensive	266	+1	+ (32)	+ (76)	Yin et al. (2015)
Atecegatran	Thrombin inhibitor	496	0	+		Matsson et al. (2013)
N-Butylpyridinium, 1-butyl-1 -methyl-pyrrolidinium, 1-butyl-3 -methylimidazolium	Cationic liquids	136, 142, 139	All +1	+	+	Martinez-Guerrero and Wright (2013)
Cephalexin	Antibacterial	347	0 (+1, − 1)	**+ (5900)**	–	Masuda et al. (2006), Tanihara et al. (2007) and Watanabe et al. (2010)
Cephradine	Antibacterial	349	0 (+1, − 1)	**+**	–	Masuda et al. (2006) and Tanihara et al. (2007)
Chloroquine	Antimalarial	319	+2	+		Müller et al. (2011)
Cimetidine	Antiulcerative	252	0	+ (7–170)	+ (18–370)	Masuda et al. (2006), Tanihara et al. (2007), Sato et al. (2008), Matsumoto et al. (2008) and Ohta et al. (2009)
Cisplatin	Antineoplastic	299	+2 (+4, − 2)	±	±	Yonezawa et al. (2006) and Yokoo et al. (2007)
Creatinine	Metabolite	113	0	+ (>2000)	+ (>2000)	Masuda et al. (2006), Tanihara et al. (2007), Sato et al. (2008), Lepist et al. (2014), Shen et al. (2015)
4′,6-Diamino-2-phenylindole (DAPI)	Fluorescent dye	277	0	+ (1)	+ (3)	Yasujima et al. (2010)
Estrone 3-sulfate	Metabolite	350	−1	+ (470)	+ (850)	Tanihara et al. (2007)
Fexofenadine	Antihistaminic	502	0 (+1, − 1)	**+**	+	Matsushima et al. (2009)
Ganciclovir	Antiviral	255	+1	+ (5120)	+ (4280)	Tanihara et al. (2007)
Guanidine	Metabolite	59	+1	+ (2100)	+ (4200)	Tanihara et al. (2007) and Sato et al. (2008)
Imatinib	Tyrosine kinase inhibitor	494	+1	+		Schmidt-Lauber et al. (2012)
Lamivudine	Antiretroviral	229	0	+	**+**	Müller et al. (2013)
2-Sulfanylethane sulfonate (Mesna)	Antineoplastic	141	−1	+		Cutler et al. (2012)
Metformin	Antidiabetic	129	+2	+ (227–780)	+ (1050–1980)	Masuda et al. (2006), Tanihara et al. (2007), Sato et al. (2008), Kajiwara et al. (2009), Chen et al. (2009) and Meyer zu Schwabedissen et al. (2010)
Methyl-4-phenylpyridinium (MPP)	Model Cation	170	+1	+ (100)	+ (94–110)	Masuda et al. (2006), Tanihara et al. (2007), Sato et al. (2008), Matsumoto et al. (2008) and Han et al. (2010)

Table 1 continued

Compound	Function/use	MW (g/mol)	Charge at pH 7.4	MATE1	MATE2K	References
N-Methylnicotinamide (NMN)	Metabolite	136	0		+	Masuda et al. (2006) and Ito et al. (2012)
Nadolol	Antihypertensive	309	+1	+ (531)	+ (372)	Misaka et al. (2016)
Nitidine	Experimental antineoplastic	348	+1	+		Li et al. (2014)
Oxaliplatin	Antineoplastic	397	+1 (+2, − 1)	+	**+**	Yonezawa et al. (2006) and Yokoo et al. (2007)
Paraquat	Herbicide	186	+2	+ (169–212)		Chen et al. (2007), (2009)
Pramipexole	Antiparkinson	211	+1	+	+	Knop et al. (2015)
Procainamide	Antiarrhythmic	235	+1	+ (1230)	+ (1580–4100)	Masuda et al. (2006), Tanihara et al. (2007) and Sato et al. (2008)
Quercetin	Plant flavonoid	302	−1	+		Lee et al. (2014)
Tetraethyl ammonium (TEA)	Model cation	130	+1	+ (220–580)	+ (375–1390)	Otsuka et al. (2005), Masuda et al. 2006, Tanihara et al. (2007), Asaka et al. (2007), Sato et al. (2008), Matsumoto et al. (2008), Kajiwara et al. (2009), Chen et al. 2009 and Ohta et al. (2009)
Thiamine	Vitamin	265	+1	+ (3.5)	+ (3.9)	Masuda et al. (2006), Tanihara et al. (2007) and Kato et al. (2014)
Topotecan	Antineoplastic	421	+1	+ (70)	+ (60)	Tanihara et al. (2007)
Varenicline	Antinicotine addiction	211	+1	+	+	Kajiwara et al. (2012)
Verapamil	Antiarrhythmic	454	+1	–	**+**	Masuda et al. (2006) and Tanihara et al. (2007)

Transport is indicated by a plus symbol (+) and, if available, the Michaelis–Menten constant is given in parentheses (μM). Compounds with controversial results are shown with a ± symbol. Bold indicate a higher selectivity of the compound for the respective MATE transporter. Structures were downloaded as SMILES from the PubChem Compound library (http://www.ncbi.nlm.nih.gov/pccompound/) and imported into MarvinSketch 15.9.14 to calculate the major microspecies at pH 7.4

Neither transported by MATE1 or MATE2K are: adefovir, captopril, carboplatin, carnitine, choline, cidofovir, dehydroepiandrosterone sulfate, 17α-ethinylestradiol-3-sulfate, glycylsarcosine, indomethacin, levofloxacin, nedaplatin, nicotine, ochratoxin A, para-aminohippuric acid, prostaglandin F2α, quinidine, quinine, salicylic acid, tenofovir, tetracycline, uric acid, valproic acid, verapamil (Yonezawa et al. 2006; Masuda et al. 2006; Tanihara et al. 2007; Yokoo et al. 2007; Han et al. 2010)

Table 2 Selected inhibitors of human MATE1 and MATE2K and their selectivity for either transporter

	Inhibitor	IC_{50} or K_i (μM)		References
		MATE1	MATE2K	
Equal affinity to MATE1 and MATE2K	Chlorhexidine	0.7	0.5	Wittwer et al. (2013)
	MPP	4.7	3.3	Yee et al. (2010)
	Procainamide	217	178	Tsuda et al. (2009b)
	Pyrimethamine*	0.08	0.05	Ito et al. (2010)
	Quinidine	29	23	Tsuda et al. (2009b)
	Ranitidine	5.4	10.0	Astorga et al. (2012)
Higher affinity to MATE1 than to MATE2K	Cimetidine*	1.1	7.3	Tsuda et al. (2009b)
	Clonidine	8	54	Astorga et al. (2012)
	Diltiazem	12.5	117	Tsuda et al. (2009b)
	Imatinib	0.05	0.5	Minematsu and Giacomini (2011)
	Imipramine	42	183	Tsuda et al. (2009b)
	Topotecan	1.3	8.6	Wittwer et al. (2013)
	Vecuronium	1.9	25.2	Wittwer et al. (2013)
	Zafirlukast	1.3	7.6	Wittwer et al. (2013)
Higher affinity to MATE2K than to MATE1	Nizatidine			Morrissey et al. (2016)
	Pramipexole	141.4	24.1	Tsuda et al. (2009b)
	TEA	40.6	14.4	Yee et al. (2010)

* For comparison, the IC_{50} values of cimetidine and pyrimethamine for OCT2 are 70 μM and 10 μM, respectively (Suhre et al. 2005; Ito et al. 2010). Tsuda et al. (2009b) reported K_i values

using mouse Mate1, whose transport activity was negatively regulated by ischemia/reperfusion-inducible protein (Li et al. 2013b).

Effects of gender

The effect of gender on Mate1 expression was systematically studied in mice, rats and rabbits. In mice, Mate1 mRNA levels were significantly higher in female than male livers but, on the contrary, significantly lower in female kidneys than in males (Lickteig et al. 2008). This gender difference is apparently not caused by different estrogen levels (Meetam et al. 2009). No gender differences were observed in rats (Nishihara et al. 2007; Ma et al. 2015) and rabbits (Zhang et al. 2007) for renal Mate1 expression. Of interest, in a preliminary analysis of *SLC47A1* and *SLC47A2* mRNA levels using the publicly available TCGA data set (http://cancergenome.nih.gov/; (Cancer Genome Atlas Research Network 2013), we identified no gender differences in non-tumor human kidney (unpublished data).

Ontogeny

Although the critical importance of membrane transporters in pharmacotherapy of adults has been recognized in recent years, much less is known about the ontogeny of transporters from birth to adulthood (Mooij et al. 2015; Brouwer et al. 2015; Elmorsi et al. 2015). While availability of human data is limited, studies have been performed in mice and rats where increasing levels of renal Mate1 mRNA expression from the fetus through the postnatal–juvenile period were observed, finally reaching adult levels (Sweeney et al. 2011; Ahmadimoghaddam et al. 2013). Summaries of rodent studies on hepatic and renal Mate1 expression are given in several recent reviews (Klaassen and Aleksunes 2010; Brouwer et al. 2015; Elmorsi et al. 2015). However, it is unclear whether these data are transferable and predictive for the human situation. Only one human study comprising only a very small set of samples showed increasing hepatic MATE1 mRNA expression levels from neonates to older children up to adults (Klaassen and Aleksunes 2010).

MATE expression under pathophysiological conditions

Given the important role of MATEs in the renal excretion of endogenous compounds and drugs, altered expression of MATEs under pathophysiological conditions may be clinically relevant. In rat models of chronic renal failure or acute kidney injury, induced by ischemia/reperfusion, Mate1 protein levels are decreased in the proximal tubules (Nishihara et al. 2007; Matsuzaki et al. 2008). Because liver diseases may result in altered expression of renal transporters in different animal models (Ikemura et al. 2009), the effect of

Table 3 Clinical studies investigating potential MATE-mediated drug–drug interactions

Interacting drug	Affected drug/compound	Clinical effect on affected drug	References
Cimetidine	Cephalexin	27 % decrease in CL_{ren} of cephalexin	van Crugten et al. (1986)
Cimetidine	Dofetilide	33 % decrease in CL_{ren} of dofetilide, 48 % increase in AUC	Abel et al. (2000)
Cimetidine	Fexofenadine	39 % decrease in CL_{ren} of metformin	Yasui-Furukori et al. (2005)
Cimetidine	Glycopyrronium	23 % decrease in CL_{ren} of glycopyrronium, 22 % increase in AUC	Dumitras et al. (2013)
Cimetidine	Metformin	27 % decrease in CL_{ren} of metformin, 50 % increase in AUC	Somogyi et al. (1987)
Cimetidine	Procainamide	44 % decrease in CL_{ren} of procainamide, 35 % increase in AUC	Somogyi et al. (1983)
Cimetidine	Ranitidine	40 % decrease in CL_{ren} of ranitidine	van Crugten et al. (1986)
Pyrimethamine	Creatinine	37 % decrease in CL_{ren} of creatinine	Opravil et al. (1993)
Pyrimethamine	Creatinine	20 % decrease in CL_{ren} of creatinine	Kusuhara et al. (2011)
Pyrimethamine	Metformin	158 % increase in AUC of metformin	Oh et al. (2016)
Pyrimethamine	Metformin	35 % decrease in CL_{ren} of metformin, 39 % increase in AUC	Kusuhara et al. (2011)
Quinine	Ritonavir	21 % increase in AUC of ritonavir	Soyinka et al. (2010)
Trimethoprim	Metformin	32 % decrease of CL_{ren} of metformin, 37 % increase in AUC	Grün et al. (2013)
Trimethoprim	Metformin	26.4 % decrease of CL_{ren} of metformin, 29.5 % increase in AUC	Müller et al. (2015)

AUC, area under the plasma concentration–time curve, CL_{ren}, renal clearance

cholestasis, induced by bile duct ligation, on renal organic cation transporters was studied in rats. In contrast to increased levels of the uptake transporter Oct2, the expression of Mate1 protein was not affected by acute cholestasis (Kurata et al. 2010). The observed increased renal tubular secretion of cimetidine was, therefore, attributed to elevated levels of Oct2 rather than Mate1. In contrast, in a rat model of acute liver injury, induced by ischemia/reperfusion, renal Oct2 and Mate1 levels were both decreased resulting in decreased systemic and tubular secretory clearances of cimetidine (Ikemura et al. 2013). Moreover, renal Mate1 and Oct2 mRNA levels were decreased in a diabetic mouse model and a mouse model of nonalcoholic steatohepatitis leading to increased plasma half-life and decreased oral clearance of metformin (Clarke et al. 2015). These studies show that MATE expression may change under different pathological conditions with consequences on drug disposition. Clinical studies are necessary to investigate whether these changes also occur in humans.

Role of MATEs for toxicity and drug–drug interactions

Cisplatin nephrotoxicity

MATEs, together with OCT2, play a key role in the renal elimination of platinum drugs (Yonezawa and Inui 2011a). Because cisplatin is efficiently transported by OCT2 into the proximal tubule epithelial cells but not effluxed into urine by MATEs, it may accumulate within the cells increasing the risk of nephrotoxicity (Yokoo et al. 2007; Terada and Inui 2008; Nakamura et al. 2010; Fisel et al. 2014). This is apparently not the case for oxaliplatin because this is a substrate for MATEs (Table 1). However, only ~30 % of patients treated with cisplatin develop nephrotoxicity suggesting the involvement of additional transporters such as copper transporters (SLC31A1) in cisplatin disposition (Harrach and Ciarimboli 2015).

MATE-mediated drug–drug interactions

Because the H_2 receptor antagonist cimetidine and the antimalarial agent pyrimethamine inhibit MATEs >tenfold more potent than OCT2, they may cause drug–drug interactions when co-administered with other MATE substrates such as metformin (Hillgren et al. 2013). Table 3 summarizes clinical studies investigating pharmacokinetic consequences on interacting drugs with MATE. In general, the renal clearance of the affected drug decreases, while drug exposure is increased. However, further clinical studies are warranted whether mostly moderate changes in plasma levels subsequently result in clinically relevant pharmacodynamic consequences.

Genetic variants in human MATEs and their clinical significance for drug pharmacokinetics and drug response

Identification of genetic variants and their effects in vitro

Pharmacokinetic studies with the Mate1 knockout mouse model clearly show an important role of Mate1 for renal drug elimination. It is therefore obvious to elucidate

Table 4 Allele frequencies of *SLC47A1* and *SLC47A2* sequence variants in different ethnic populations and functional consequences

Genetic variant	Nucleotide change	Location	Consequence type	Consequence in vitro	Consequence in vivo	Minor allele frequency (%) in population						References
						African-Americans	Caucasians/European Americans	Chinese Americans	Japanese	Koreans	Mexican Americans	
A. *SLC47A1* (MATE1, NM_018242)												
rs2453579	C > A	5′ Gene region	Regulatory region variant	Increased promoter activity, increased binding of Nkx-2.5, SREBP-1, USF-1						36.5		Kim et al. (2013)
rs72466470	G > A	5′ Gene region	Regulatory region variant	Decreased promoter activity, decreased binding of Sp1					1.9			Kajiwara et al. (2007)
rs2252281	T > C	5′ UTR	Regulatory region variant	Decreased promoter activity, decreased binding of AP-1	See Table 5A	44.5	32.1	23.1			28.9	Ha Choi et al. (2009)
rs78572621	C > G	5′ UTR	Regulatory region variant	Increased promoter activity		1.7	5.4	3.1			7.8	Ha Choi et al. (2009)
rs111427955	C > T	5′ UTR	Regulatory region variant	Increased promoter activity		1.5	1.5	2.9			0.8	Ha Choi et al. (2009)
rs555657341	G > T	Exon	Missense variant (Val10Leu)	Normal transport function					2.2			Kajiwara et al. (2009)
rs2453580	T > C	Intron			See Table 5A	39.8	42.0	23.2	16.3		26.5	Pattaro et al. (2012) and HapMap data

Table 4 continued

Genetic variant	Nucleotide change	Location	Consequence type	Consequence in vitro	Consequence in vivo	Minor allele frequency (%) in population						References
						African-Americans	Caucasians/ European Americans	Chinese Americans	Japanese	Koreans	Mexican Americans	
rs77630697	G > A	Exon	Missense variant (Gly64Asp)	Loss of transport function	See Table 5A	0	0	0.7	0.6	0.5	0	Kajiwara et al. (2009) and Chen et al. (2009) and Yoon et al. 2013
rs77474263	C > T	Exon	Missense variant (Leu125Phe)	Reduced transport function	See Table 5A	0	0	0.7		0.5	5.1	Chen et al. 2009 and Yoon et al. (2013)
rs35646404	C > T	Exon	Missense variant (Thr159Met)	Loss of transport function		0	0		1.0			Meyer zu Schwabedissen et al. (2010)
rs2289669	G > A	Intron			See Table 5A	10.4	42.7–45.6	46.4	37.6		49.0	Tzvetkov et al. 2009 and Becker et al. (2009) and HapMap data
rs111060526	C > T	Exon	Missense variant (Ala310Val)	Reduced transport function					2.2	0		Kajiwara et al. (2009) and Yoon et al. (2013)
rs111060527	A > C	Exon	Missense variant (Asp328Ala)	Reduced transport function	See Table 5A				0.6	0		Kajiwara et al. (2009) and Yoon et al. (2013)
rs35790011	G > A	Exon	Missense variant (Val338Ile)	Reduced transport function		5.0–5.1	0–0.4	0	1.0		0	Chen et al. (2009) and Meyer zu Schwabedissen et al. (2010)
rs8065082	C > T	Intron			See Table 5A	23.5	48.7	47.6	37.2		54.0	HapMap data

Table 4 continued

Genetic variant	Nucleotide change	Location	Consequence type	Consequence in vitro	Consequence in vivo	Minor allele frequency (%) in population						References
						African-Americans	Caucasians/European Americans	Chinese Americans	Japanese	Koreans	Mexican Americans	
rs111653425	C > T	Exon	Missense variant (Ala465Val)		See Table 5A		1.8					Sveinbjornsson et al. (2014)
rs111060528	A > G	Exon	Missense variant (Asn474Ser)	Reduced transport function					0.6	0		Kajiwara et al. (2009) and Yoon et al. (2013)
rs76645859	G > A	Exon	Missense variant (Val480Met)	Loss of transport function		0	0	0.8			0	Chen et al. (2009)
rs35395280	G > T/C	Exon	Missense variant (Cys497Phe/Ser)	Changes in substrate specificity		2.4 (C)	0 (C)	0 (C)			0 (C)	Chen et al. (2009) and Meyer zu Schwabedissen et al. (2010)
rs78700676	G > C	Exon	Missense variant (Gln519His)	Normal transport function		0.8	0	0			0	Chen et al. (2009)
B. *SLC47A2* (MATE2K, NM_001099646)												
rs758427	A > G	5′ gene region	Regulatory region variant	Increased promoter activity	See Table 5B	38.8	26.3	59.4	46.4	29.2	41.0	Chung et al. (2013) and HapMap data
rs34834489	G > A	5′ Gene region	Regulatory region variant	Increased promoter activity	See Table 5B					27.1		Chung et al. (2013)
rs12943590	G > A	5′ UTR	Regulatory region variant	Increased promoter activity, reduced binding of MZF-1	See Table 5B	27.7	26.2	48.5		45.8	34.1	Choi et al. (2011) and Yoon et al. (2013)
rs111060529	G > T	Exon	Missense variant (Lys64Asn)	Reduced transport function					0.6	0		Kajiwara et al. (2009) and Yoon et al. (2013)

Table 4 continued

Genetic variant	Nucleotide change	Location	Consequence type	Consequence in vitro	Consequence in vivo	Minor allele frequency (%) in population						References
						African-Americans	Caucasians/ European Americans	Chinese Americans	Japanese	Koreans	Mexican Americans	
rs146901447	C > T	Exon	Missense variant (Pro162Leu)	Reduced transport function		0.5–5.6	0	0	0		0	Choi et al. (2011) and Nishimura et al. (2014)
rs562968062	GC > TT	Exon	Missense variant (Gly211Val) and splice region variant	Loss of transport function	See Table 5B	0	0		1.7–2.1	0		Kajiwara et al. (2009), Yoon et al. (2013), Nishimura et al. (2014)
rs373244724	A > G	Exon	Missense variant (Tyr273Cys)	Reduced transport function		0.5	0		1.6			Nishimura et al. (2014)
rs34399035	G > A	Exon	Missense variant (Gly393Arg)	Reduced transport function		0	0.9	0			0.8	Choi et al. (2011)

HapMap data accessed via ENSEMBL genome browser (http://www.ensembl.org)

Table 5 Genotype–phenotype correlations of *SLC47A1* and *SLC47A2* sequence variants

	SLC47A1 variant	Population (*n*)	Results	References
A. *SLC47A1* (MATE1, NM_018242)				
Kidney function				
eGFRcrea eGFRcys	rs2453580 (intron)	26 Population-based studies of individuals of European ancestry ($n = 6271$)	Meta-analyses of GWAS identified positive association of C allele with eGFRcrea and eGFRcys in non-diabetic individuals ($p = 2.1 \times 10^{-9}$)	Pattaro et al. (2012)
Serum creatinine	rs111653425 (Ala465Val)	Icelanders ($n = 194{,}286$)	GWAS identified the T allele to be associated with increased serum creatinine ($p = 9.5 \times 10^{-14}$)	Sveinbjornsson et al. (2014)
Susceptibility				
Chronic kidney disease	rs111653425 (Ala465Val)	Icelanders ($n = 15{,}594$ cases, $n = 291{,}420$ controls)	GWAS identified the T allele to be associated with increased risk of chronic kidney disease (OR = 1.24, $p = 0.00041$)	Sveinbjornsson et al. (2014)
Tissue expression				
Kidney Liver	rs2252281 (5′UTR)	Surgical kidney samples ($n = 38$), postmortem liver samples ($n = 34$)	mRNA levels in TC ($n = 21$) or CC ($n = 5$) kidneys were significantly lower ($p = 0.015$) compared to TT genotype ($n = 12$); no effect in human liver	Ha Choi et al. (2009)
Pharmacokinetics/pharmacodynamics				
Metformin (twice daily, 1000 mg, for 9 months)	rs2252281 (5′ UTR)	Caucasian T2DM patients ($n = 159$)	No effect on metformin steady-state concentration	Christensen et al. (2011)
Metformin (two doses, total 1850 mg)	rs2252281 (5′ UTR)	Healthy male and female Asian ($n = 18$), African-American ($n = 33$) and Caucasian ($n = 6$) volunteers	Variant rs2252281 had no significant effect on the pharmacokinetics of metformin. However, after metformin administration, volunteers homozygous for the variant rs2252281 had significantly lower glucose AUC (greater response) after the oral glucose tolerance test than volunteers carrying at least one reference allele ($p = 0.002$)	Stocker et al. (2013)
Metformin (single dose, 500 mg)	rs2252281 (5′ UTR)	Healthy male and female Caucasians ($n = 50$)	Heterozygous carriers of rs2252281 had reduced CL_{ren} when also carrying the minor allele of *SLC22A2* rs316019 compared to rs2252281 reference TT genotype and minor allele of *SLC22A2* rs316019 ($p < 0.028$)	Christensen et al. (2013)

Table 5 continued

	SLC47A1 variant	Population (*n*)	Results	References
Metformin (single dose, 250 mg, 375 mg or 500 mg)	rs77630697 (Gly64Asp)	Japanese T2DM patients ($n = 48$)	No effect on oral metformin clearance in heterozygous carriers	Toyama et al. (2010)
Metformin (single dose, 250 mg, 375 mg or 500 mg)	rs77474263 (Leu125Phe)	Japanese T2DM patients ($n = 48$)	No effect on oral metformin clearance in heterozygous carriers	Toyama et al. (2010)
Metformin (various settings)	13 SNPs including rs2453580 (intron), rs2289669 (intron)	Population pharmacokinetic study of pooled data from Australian patients with T2DM ($n = 120$), healthy Caucasian subjects ($n = 16$) and healthy Malaysian subjects ($n = 169$)	No effect on metformin clearance of investigated variants	Duong et al. (2013)
Metformin (twice daily, 1000 mg, for 9 months)	rs2289669 (intron)	Caucasian T2DM patients ($n = 159$)	No effect on metformin steady-state concentration	Christensen et al. (2011)
Metformin (single dose, 500 mg)	rs2289669 (intron)	Healthy male Caucasians ($n = 103$)	No significant association between CL_{ren} and the rs2289669 G > A variant	Tzvetkov et al. (2009)
Metformin (single dose, 500 mg)	rs2289669 (intron)	Chinese T2DM patients ($n = 30$)	Significant reduction in CL_{ren} in homozygous carriers of the AA allele ($p = 0.001$)	He et al. (2015)
Metformin	rs2289669 (intron)	Healthy Koreans ($n = 26$)	CL_{ren} of metformin significantly higher after ranitidine treatment in the MATE1 GG group compared with the MATE1 GA + AA group when demographic data and *SLC22A2* rs316019 were included in the model ($p \leq 0.05$)	Cho and Chung (2016)
Memantine (at least 1 month at a stable dose)	rs2289669 (intron)	Population pharmacokinetic study of Swiss patients ($n = 108$)	No significant effect on memantine clearance	Noetzli et al. (2013)
Metformin (single dose, 250 mg, 375 mg or 500 mg)	rs111060527 (Asp328Ala)	Japanese T2DM patients ($n = 48$)	No effect on oral metformin clearance in heterozygous carriers	Toyama et al. (2010)
Treatment outcome				
Metformin (twice daily, 1000 mg, for 24 months)	rs2252281 (5′ UTR)	Caucasian T2DM patients ($n = 159$)	No effect on absolute decrease of HbA1c levels over 24 months	Christensen et al. (2011)
Metformin	rs2252281 (5′ UTR)	Caucasian ($n = 185$) and African-American ($n = 64$) T2DM patients receiving metformin monotherapy	When patients carrying one or more *SLC22A1* reduced-function variants were removed from the analysis, patients homozygous for the rs2252281 variant C allele had a significantly larger relative change in HbA1c levels (i.e., greater response to metformin) than patients carrying at least one reference rs2252281 T allele ($p = 0.01$)	Stocker et al. (2013)

Table 5 continued

	SLC47A1 variant	Population (*n*)	Results	References
Metformin	12 Tagging SNPs including rs2289669 (intron)	Incident metformin users ($n = 116$, Rotterdam study)	Only the rs2289669 G > A variant was associated with metformin response. For each A allele, the reduction in HbA1c levels was 0.3 % larger ($p = 0.005$, $p = 0.045$ after Bonferroni correction)	Becker et al. (2009)
Metformin	rs2289669 (intron)	Incident metformin users ($n = 98$, Rotterdam study)	The effect of the rs2289669 G > A variant on HbA1c levels was larger in patients with the *SLC22A1* rs622342 CC genotype than in the patients with the rs622342 AA genotype ($p = 0.005$)	Becker et al. (2010)
Metformin	rs2289669 (intron)	Caucasian T2DM patients ($n = 148$)	Significantly higher reduction in HbA1c levels after 6 months treatment with metformin in homozygous carriers of rs2289669 A allele in comparison with common G allele carriers ($p = 0.008$, $p = 0.018$ adjusted for covariates)	Tkac et al. (2013)
Metformin	rs2289669 (intron)	Caucasian T2DM patients ($n = 135$)	No effect of the rs2289669 G > A variant on HbA1c levels, but significant effect of the rs2289669 G > A variant on the total cholesterol levels ($p = 0.018$), in patients treated with a combination of metformin and sulphonylurea for at least 6 months	Klen et al. (2014)
Metformin (twice daily, 1000 mg, for 24 months)	rs2289669 (intron)	Caucasian T2DM patients ($n = 159$)	No effect on absolute decrease of HbA1c levels over 24 months	Christensen et al. (2011)
Metformin (1-year follow up)	rs2289669 (intron)	Chinese T2DM patients ($n = 220$)	Significantly lower ΔHbA1c levels (1 year later HbA1c minus baseline HbA1c) in carriers of variant AA genotype compared to carriers of GG or GA genotype ($p = 0.02$)	He et al. (2015)
Metformin intolerance	rs2289669 (intron)	Latvian T2DM patients ($n = 246$)	No effect on metformin gastrointestinal side effects	Tarasova et al. (2012)
Metformin intolerance	rs2289669 (intron)	Swiss patients ($n = 44$) with castration-resistant prostate cancer receiving single-agent metformin 1000 mg two times a day until disease progression or unwanted toxicity	No effect on metformin gastrointestinal and nervous system side effects	Joerger et al. (2015)
Prostate cancer progression	rs2289669 (intron)	Swiss patients ($n = 44$) with castration-resistant prostate cancer receiving single-agent metformin 1000 mg two times a day until disease progression or unwanted toxicity	Disease progression was more frequent in carriers of at least one A allele (44 %) as compared to homozygous carriers of the G allele (12.5 %) ($p = 0.07$)	Joerger et al. (2015)

Table 5 continued

	SLC47A1 variant	Population (*n*)	Results	References
Ability of metformin to lower T2DM incidence	rs8065082 (intron)	Participants of the American Diabetes Prevention Program ($n = 2994$, different ethnicities)	T allele associated with reduced metformin response ($p = 0.006$)	Jablonski et al. (2010)
	Genetic variant	Population (*n*)	Results	References
B. *SLC47A2* (MATE2K, NM_001099646)				
Pharmacokinetics/pharmacodynamics				
Metformin (two doses, total 1750 mg)	Variant haplotype 1 including rs12943590 (5' UTR) Variant haplotype 2 including rs758427 and rs34834489 (both 5′ gene region)	Healthy male and female Korean volunteers ($n = 45$)	Volunteers with variant haplotype 1 or 2 showed a significant increase in metformin CL_{ren} and secretion clearance compared with reference haplotype ($p = 0.006$). However, the glucose-lowering effect of metformin after the oral glucose tolerance test was not different between the reference and variant haplotypes	Chung et al. (2013)
Metformin (two doses, total 1850 mg)	rs12943590 (5′ UTR)	Healthy male and female Asian ($n = 18$), African-American ($n = 33$) and Caucasian ($n = 6$) volunteers	Volunteers with at least one variant allele had a significantly increased renal clearance of metformin ($p = 0.02$). Volunteers with two variant alleles had a higher glucose AUC (reduced response) after the oral glucose tolerance test than volunteers with at least one reference allele ($p < 0.05$)	Stocker et al. (2013)
Metformin (various settings)	3 Variants including 12943590	Population pharmacokinetic study of pooled data from Australian patients with T2DM ($n = 120$), healthy Caucasian subjects ($n = 16$) and healthy Malaysian subjects ($n = 169$)	No effect on metformin clearance of investigated variants	Duong et al. (2013)
Metformin (single dose, 500 mg)	rs12943590 (5′ UTR)	Korean healthy male volunteers ($n = 96$)	No effect on metformin AUC_{inf} and C_{max}	Yoon et al. (2013)
Metformin (single dose, 250 mg, 375 mg or 500 mg)	rs562968062 (Gly211Val)	Japanese T2DM patients ($n = 48$)	No effect on oral metformin clearance in heterozygous carriers	Toyama et al. (2010)
Metformin (twice daily, 1000 mg, for 9 months)	rs34399035 (Gly393Arg)	Caucasian T2DM patients ($n = 159$)	No effect on trough steady-state metformin concentration	Christensen et al. (2011)

Table 5 continued

	Genetic variant	Population (*n*)	Results	References
Treatment outcome				
Metformin	rs12943590 (5′ UTR)	Caucasian ($n = 189$) and African-American ($n = 64$) T2DM patients receiving metformin monotherapy	Patients homozygous for the variant had a significantly poorer response to metformin treatment (lower relative change in HbA1c levels) as compared to carriers of the reference allele ($p = 0.002$)	Choi et al. (2011)
Metformin (twice daily, 1000 mg, for 24 months)	rs34399035 (Gly393Arg)	Caucasian T2DM patients ($n = 159$)	Patients with the heterozygous genotype had a lower decrease in HbA1c levels over 24 months than patients with the reference genotype ($p = 0.05$)	Christensen et al. (2011)

AUC_{inf}, area under the plasma concentration–time curve from 0 to infinity; C_{max}, maximal plasma concentration; CL_{ren}, renal clearance; eGFRcrea, estimated glomerular filtration rate based on serum creatinine; eGFRcys, estimated glomerular filtration rate based on cystatin C; GWAS, genome-wide association studies; HbA1c, glycosylated hemoglobin; OR, odds ratio; T2DM, type 2 diabetes mellitus

the impact of genetic variants in human MATEs on drug response and/or the development of adverse drug reactions. Due to a variety of large-scale next-generation sequencing projects, such as the 1000 Genomes project (The 1000 Genomes Consortium et al. 2012) and the NHLBI-GO Exome Sequencing Project (http://evs.gs.washington.edu/EVS), the number of *SLC47A1* and *SLC47A2* genetic variants is increasing and in particular rare variants are discovered. For example, the Exome Aggregation Consortium (ExAC) strives to aggregate exome sequencing data from a variety of large-scale exome sequencing projects and currently covers data from >60,000 unrelated individuals (Exome Aggregation Consortium et al. 2015). The ExAC database lists 207 and 206 missense variants for MATE1 and MATE2K, respectively, most of them with minor allele frequencies <0.01 % (http://exac.broadinstitute.org). In general, the allele frequencies of missense variants are low and usually do not exceed 2 % in different ethnic populations. Several regulatory region and missense variants have been analyzed for their functional consequences in luciferase assays and transport assays in vitro, respectively (Table 4). The altered promoter activity of some regulatory variants could be explained by altered binding of transcription factors such as Sp1, AP-1, Nkx-2.5, SREBP-1 and USF-1, to the *SLC47A1* gene promoter (Kajiwara et al. 2007; Ha Choi et al. 2009; Kim et al. 2013) and MZF-1 to the *SLC47A2* gene promoter (Choi et al. 2011). Several missense variants showed a complete loss of function in vitro, i.e., MATE1-Gly64Asp, MATE1-Val480Met and MATE2K-Gly211Val, which was attributed to an abolished plasma membrane expression of the respective transporter (Kajiwara et al. 2009; Chen et al. 2009). By mapping the missense MATE1 variants on the three-dimensional structure and topology models of human MATE1 (Fig. 3c, d), it becomes evident that most of them are located within the transmembrane regions or in the last intracellular loop. These locations are apparently crucial for a proper MATE1 function. This has also been shown by site-directed mutagenesis studies, in which cysteine, histidine and glutamate residues in the transmembrane regions of human MATE1 and MATE2K have been identified being essential for substrate binding and transport activity (Asaka et al. 2007; Matsumoto et al. 2008; Damme et al. 2011).

Genotype–phenotype correlations and clinical consequences of genetic variants

Because some MATE1 and MATE2K variants altered metformin transport function in in vitro experiments (Table 4) and the lack of Mate1 changed metformin pharmacokinetics in the knockout mouse model (Tsuda et al. 2009a), several studies addressed the association of *SLC47A1* and *SLC47A2* genotypes with pharmacokinetic/pharmacodynamic

parameters and treatment outcome of metformin (Table 5). In most studies, the variants had no effects on the pharmacokinetic parameters of metformin. However, the *SLC47A1* regulatory region variant rs2252281 and the intronic variants rs2289669 and rs8065082 were repeatedly associated with reduced metformin response (Becker et al. 2009; Jablonski et al. 2010; Stocker et al. 2013; Tkac et al. 2013; He et al. 2015), while the common *SLC47A2* promoter variant rs12943590 was associated with greater metformin response (Choi et al. 2011; Stocker et al. 2013) in some studies. Yet, in other studies, the effect of the *SLC47A1* variant rs2289669 could not be replicated (Christensen et al. 2011; Klen et al. 2014), indicating that other metformin transporters (Becker et al. 2010; Stocker et al. 2013; Christensen et al. 2013) and/or non-genetic factors (Maruthur et al. 2014; Emami Riedmaier et al. 2015) need to be considered as well.

Notably, the *SLC47A1* missense variant rs111653425 (MATE1-Ala465Val), which occurs at a low allele frequency of 1.8 % in Icelanders (Table 4) and whose in vitro functional studies are missing, has been significantly associated with increased serum creatinine levels.

Conclusions

Since their initial discovery in 2005 (Otsuka et al. 2005), there is an increasing interest to elucidate the functional role of MATE1 and MATE2K as important transport proteins for renal and hepatic organic cation excretion. Both MATE transporters are now considered as the long-searched-for proton-coupled transporters in the luminal membrane of proximal tubule epithelial cells. Intensive functional studies by several groups have revealed the partial overlapping substrate and inhibitor specificities of MATE1 and MATE2K as they are capable of transporting a wide range of organic cations including a number of clinically relevant drugs. Since several clinical studies have suggested that MATEs may be involved in clinically relevant drug–drug interactions, both transporters are recommended to be tested during the drug development process for clinically relevant drug–drug interactions (Hillgren et al. 2013). However, despite the convincing functional evidence of MATE transporters in in vitro and in knockout mouse experiments, the role of genetic variation for drug pharmacokinetics and for drug therapy in humans, particularly for response to the intensely studied antidiabetic agent metformin, appears to be limited and does not resemble major effects observed in Mate1 knockout mouse models. The reason for this discrepancy may be that other factors may contribute substantially to the expression and function of MATE proteins in human such as epigenetic regulation (e.g., DNA methylation, microRNAs; Ivanov et al. 2014; Fisel et al. 2016). Moreover, in addition to MATEs, other drug transporters may affect drug pharmacokinetics as well. Thus, comparable to most intensively studied membrane transporters from the ABC family (e.g., P-glycoprotein/ABCB1; Wolking et al. 2015), a more comprehensive view needs to be considered to fully understand the role of MATEs for drug therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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